South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

March 8, 2019

DSS

Strong Families - South Dakota's Foundation and Our Future

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Strong Families - South Dakota's Foundation and Our Future

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

March 8, 2019
1:00 – 3:00 PM

DDN Locations:
Sioux Falls
University Center
DDN Room FADM145
4801 North Career Avenue

Pierre
Capitol Building
DDN Room CAP A
500 East Capitol

Rapid City
Black Hills State University
DDN Room UC113
4300 Cheyenne Boulevard

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs/PMPM

Old business
- **CGRP utilization**
- **CiproDex utilization**
- **Antiasthmatic monoclonal antibodies fax forms**
- **Antipsychotic PA reviews**

New business
- **ADD/ADHD utilization review**
- **Consensi**
- **Orlissa**
- **Immunomodulators**

Public comment accepted after individual topic discussion

Next meeting date 6/21/19 & adjournment

South Dakota Department of Social Services, Division of Medicaid Services
Pharmacy & Therapeutics (P&T) Committee Meeting Minutes

Friday, December 7, 2018
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	X	Kelley Oehlke, PharmD	X
Dana Darger, RPh, Chair	X	Lenny Petrik, PharmD	X
James Engelbrecht, MD	X	Timothy Soundy, MD	
Deidre Van Gilder, PharmD	X	Mike Jockheck, DSS Staff	X
Mikal Holland, MD	X	Sarah Akers, DSS Staff	X
Richard Holm, MD	X	Bill Snyder, DSS Staff	
Bill Ladwig, RPh	X		

Administrative Business
Darger called the meeting to order at 1:05 PM. The minutes of the June meeting were presented. Engelbrecht made a motion to approve. Oehlke seconded the motion. Motion was approved unanimously.

Prior Authorization Update (PA) and Statistics
The committee reviewed the PA activity report from July 1, 2018 to September 30, 2018. A total of 1,468 PAs were reviewed of which 286 requests (20%) were received via telephone and 1,182 requests (80%) were received via fax. Darger requested system capabilities to approve antipsychotic PAs more via electronic review. An in-depth review process for antipsychotics will be provided for the next meeting.

Analysis of the Top 15 Therapeutic Classes and Drug Spend
The committee reviewed the top 15 therapeutic classes by total cost of claims from July 1, 2018 to September 30, 2018. The top five therapeutic classes were atypical antipsychotics, insulins, respiratory and CNS stimulants, amphetamines, and disease-modifying anti-rheumatic agents. The top 15 therapeutic classes make up 27.70% of total claims. The committee also reviewed the top 50 drugs based on total claims cost and number of claims. The top 50 drugs by claims cost make up 12.11% of total claims. Darger commented on CiproDex utilization hitting the top 50 drug spend. Baack replied CiproDex is the preferred topical for ear tubes; Baack questioned its use for more otitis media or otitis external. Darger requested utilization data on Ciprodex specifically prescriber information and member age. Baack will review literature.

Old Business
Committee reviewed CGRP utilization and fax form. Committee requested to review utilization again at the next meeting.

Committee reviewed Onfi utilization and Darger commented member count and utilization were appropriate.

Committee reviewed the PPI utilization and based on utilization data decided to revise the PPI PA/step therapy. Lansoprazole and omeprazole suspension will be removed from PA and they are to be used first before other PPI packets/suspensions/solutab for children less than 13 years old and members with

dysphagia. Prilosec pack (delayed release granules) will be added to step therapy. Holm made a motion to approve. Baack seconded the motion. Motion was approved unanimously. Engelbrecht suggested sending the updated PPI step therapy protocol information to all PPI prescribers.

The committee reviewed the estimated PDL savings. Darger was satisfied with the review.

New business
The committee reviewed utilization for respiratory drug utilization and were asked if other classes warranted in-depth review. Baack replied other classes had been reviewed in the past.

Committee was notified of the SUPPORT ACT. Jockheck commented he wanted to get it on the committee's radar and discuss it more in depth at future meetings.

Committee reviewed the anticonvulsant class, specifically Epidiolex and Diacomit. Both drugs are approved for Dravet Syndrome of which there are few options on the market. Committee recommended adding a similar PA to Onfi for Epidiolex. Engelbrecht made a motion to approve and Baack seconded the motion. The motion was approved unanimously.

The committee reviewed the anti-asthmatic monoclonal antibodies class and current PA for Nucala and Xolair. After reviewing the PA fax forms for Nucala and Xolair, committee recommended amending the criteria to add specialty consultation. Nucala requires prescribed or in consultation by rheumatologist, pulmonologist, allergist, or immunologist. Xolair requires prescribed or in consultation by dermatologist, rheumatologist, pulmonologist, allergist, or immunologist. Baack made a motion to approve and Ladwig seconded the motion. The motion was approved unanimously.
Committee recommended adding PA to Fasenra. Enbelbrecht made a motion to approve and Holm seconded the motion. The motion was approved unanimously.

Akers discussed the DSS Boards Code of Conduct & Conflict of Interest to the committee. During the 2016 legislative session, the legislature developed the State Board of Internal Controls for all boards under DSS. The committee is being asked to review, discuss, and plan to adopt at this meeting or next meeting the DSS Boards Code of Conduct and Conflict of Interest. After review and discussion, Holm moved to accept the DSS Boards Code of Conduct and Conflict of Interest. Ladwig seconded the motion. All committee members were in favor and accepted.

The next meeting is scheduled on March 8, 2018. Tentative meeting date for June 2019 is June 21, 2019. Ladwig made a motion to adjourn. Holm seconded the motion. The meeting adjourned at 2:19 PM.

PA Report

10/1/2019 to 12/31/2018

Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
URGENT	60	59	1	98.3%	1.7%
STANDARD	1446	1446	0	100.0%	0.0%
GRAND TOTAL	**1506**	**1505**	**1**	99.9%	0.1%

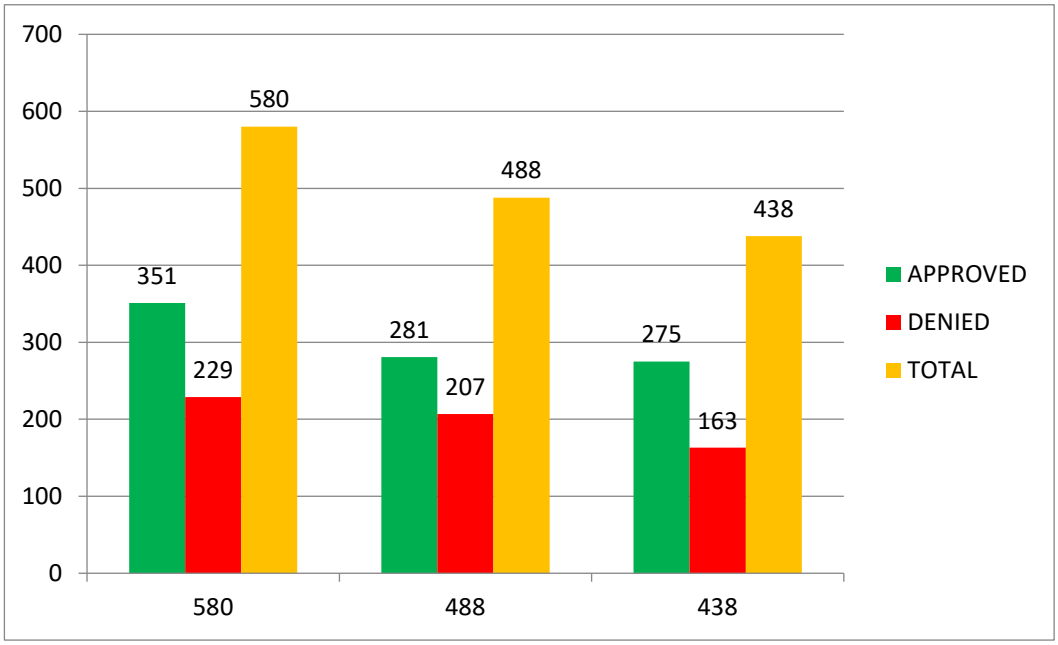
Request type Summary

Drug Class	# of Requests	Phone Requests		Fax Requests	
		#	%	#	%
OPIATE AGONISTS	388	123	32%	265	68%
ATYPICAL ANTIPSYCHOTICS	116	23	20%	93	80%
ANTICONVULSANTS, MISCELLANEOUS	101	17	17%	84	83%
PROTON-PUMP INHIBITORS	78	13	17%	65	83%
OPIATE PARTIAL AGONISTS	65	27	42%	38	58%
SCABICIDES AND PEDICULICIDES	60	16	27%	43	72%
ANTIPRURITICS AND LOCAL ANESTHETICS	49	4	8%	45	92%
ANTIMIGRAINE AGENTS, MISCELLANEOUS	45	3	7%	42	93%
SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	44	8	18%	36	82%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	40	7	18%	33	83%
SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	40	3	8%	37	93%
GI DRUGS, MISCELLANEOUS	40	6	15%	34	85%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	30	4	13%	26	87%
SELECTIVE SEROTONIN AGONISTS	22	3	14%	19	86%
ANTIBACTERIALS (SKIN, MUCOUS MEMBRANE)	19	0	0%	19	100%
ANTIALLERGIC AGENTS	19	2	11%	17	89%
BENZODIAZEPINES (ANTICONVULSANTS)	18	3	17%	15	83%
RESPIRATORY AND CNS STIMULANTS	18	3	17%	15	83%
DIRECT FACTOR XA INHIBITORS	18	5	28%	13	72%
ANTIHISTAMINES (GI DRUGS)	18	2	11%	16	89%
SELECTIVE BETA-3-ADRENERGIC AGONISTS	18	2	11%	16	89%
ANTIMUSCARINICS	17	2	12%	15	88%
AMPHETAMINES	16	3	19%	13	81%
HEPARINS	14	8	57%	6	43%
SOMATOTROPIN AGONISTS	12	3	25%	9	75%
HCV PROTEASE INHIBITOR ANTIVIRALS	12	2	17%	10	83%
CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	12	1	8%	11	92%
SEROTONIN MODULATORS	10	1	10%	9	90%
RESPIRATORY TRACT AGENTS, MISCELLANEOUS	10	3	30%	6	60%
INCRETIN MIMETICS	10	1	10%	9	90%
WAKEFULNESS-PROMOTING AGENTS	9	0	0%	9	100%
RIFAMYCIN ANTIBIOTICS	8	0	0%	8	100%
ANTINEOPLASTIC AGENTS	8	3	38%	5	63%

ANTIDEPRESSANTS, MISCELLANEOUS	8	1	13%	7	88%
BETA-ADRENERGIC BLOCKING AGENTS	5	0	0%	5	100%
DIHYDROPYRIDINES	5	3	60%	2	40%
VESICULAR MONOAMINE TRANSPORT2 INHIBITOR	5	1	20%	4	80%
OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	4	0	0%	4	100%
1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	4	1	25%	3	75%
SECOND GENERATION ANTIHISTAMINES	4	1	25%	3	75%
HCV POLYMERASE INHIBITOR ANTIVIRALS	4	0	0%	4	100%
ANXIOLYTICS,SEDATIVES,AND HYPNOTICS,MISC	4	1	25%	3	75%
IMMUNOMODULATORY AGENTS	4	0	0%	4	100%
MUCOLYTIC AGENTS	4	3	75%	1	25%
CORTICOSTEROIDS (EENT)	4	1	25%	3	75%
REPLACEMENT PREPARATIONS	4	1	25%	3	75%
CELL STIMULANTS AND PROLIFERANTS	3	0	0%	3	100%
CONTRACEPTIVES	3	1	33%	2	67%
PCSK9 INHIBITORS	3	0	0%	3	100%
PROGESTINS	3	0	0%	3	100%
ANTIGOUT AGENTS	3	0	0%	3	100%
CYSTIC FIBROSIS (CFTR) CORRECTORS	3	0	0%	3	100%
OTHER MACROLIDE ANTIBIOTICS	3	2	67%	1	33%
RAPID-ACTING INSULINS	3	0	0%	3	100%
VASODILATING AGENTS (RESPIRATORY TRACT)	2	1	50%	1	50%
INSULINS	2	0	0%	2	100%
ANGIOTENSIN II RECEPTOR ANTAGONISTS	2	0	0%	2	100%
OTHER MISCELLANEOUS THERAPEUTIC AGENTS	2	1	50%	1	50%
LEUKOTRIENE MODIFIERS	2	1	50%	1	50%
PHARMACEUTICAL AIDS	2	1	50%	1	50%
GLYCOPEPTIDE ANTIBIOTICS	2	1	50%	1	50%
IMMUNOSUPPRESSIVE AGENTS	2	1	50%	1	50%
ESTROGENS	1	0	0%	1	100%
ANOREXIGENIC AGENTS, MISCELLANEOUS	1	1	100%	0	0%
HEMOSTATICS	1	0	0%	1	100%
AMPHETAMINE DERIVATIVES	1	0	0%	1	100%
GONADOTROPINS	1	0	0%	1	100%
NUCLEOSIDE AND NUCLEOTIDE ANTIVIRALS	1	1	100%	0	0%
CYCLOOXYGENASE-2 (COX-2) INHIBITORS	1	0	0%	1	100%
PITUITARY	1	0	0%	1	100%
CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1	0	0%	1	100%
BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	1	0	0%	1	100%
HMG-COA REDUCTASE INHIBITORS	1	0	0%	1	100%
ANTIEMETICS, MISCELLANEOUS	1	1	100%	0	0%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	1	0	0%	1	100%
PARASYMPATHOMIMETIC (CHOLINERGIC AGENTS)	1	0	0%	1	100%
DIGESTANTS	1	0	0%	1	100%
HEMATOPOIETIC AGENTS	1	0	0%	1	100%
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	1	0	0%	1	100%
AZOLES (SKIN AND MUCOUS MEMBRANE)	1	0	0%	1	100%
HISTAMINE H2-ANTAGONISTS	1	0	0%	1	100%
LONG-ACTING INSULINS	1	0	0%	1	100%
ANTITOXINS AND IMMUNE GLOBULINS	1	1	100%	0	0%
CYSTIC FIBROSIS (CFTR) POTENTIATORS	1	0	0%	1	100%
DIABETES MELLITUS	1	0	0%	1	100%
TOTALS	1506	327	22%	1177	78%

PA Initial Requests Summary

Month	Approved	Denied	Total
Oct-18	351	229	580
Nov-18	281	207	488
Dec-18	275	163	438
4Q18	907	599	1506
Percent of Total	60.23%	39.77%	



Top 5 Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
OPIATE AGONISTS	254	134	388	65.46%	25.76%	TRAMADOL, HYDROCODONE/APAP
ATYPICAL ANTIPSYCHOTICS	89	27	116	76.72%	7.70%	ARIPIPRAZOLE, LATUDA
ANTICONVULSANTS, MISC	49	52	101	48.51%	6.71%	LYRICA, FELBATOL
PROTON PUMP INHIBITORS	43	35	78	55.13%	5.18%	ESOMEPRAZOLE MAGNESIUM, DEXILANT
OPIATE PARTIAL AGONISTS	53	12	65	81.54%	4.32%	SUBOXONE, BUPRENORPHINE
Others -	413	345	758	54.49%	50.33%	
4Q18	901	605	1506	59.83%		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
ATYPICAL ANTIPSYCHOTICS	89	27	116	76.72%
CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	7	5	12	58.33%
SCABICIDES AND PEDICULICIDES	44	16	60	73.33%
OPIATE AGONISTS	254	134	388	65.46%
ANTIMUSCARINICS	5	12	17	29.41%
SELECTIVE SEROTONIN AGONISTS	4	18	22	18.18%
AMPHETAMINES	7	9	16	43.75%
OPIATE PARTIAL AGONISTS	53	12	65	81.54%
ANTICONVULSANTS, MISCELLANEOUS	49	52	101	48.51%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	18	12	30	60.00%
GI DRUGS, MISCELLANEOUS	21	19	40	52.50%
DIHYDROPYRIDINES	1	4	5	20.00%
ANTIMIGRAINE AGENTS, MISCELLANEOUS	18	27	45	40.00%
RIFAMYCIN ANTIBIOTICS	5	3	8	62.50%
LEUKOTRIENE MODIFIERS	2	0	2	100.00%
CONTRACEPTIVES	3	0	3	100.00%
SOMATOTROPIN AGONISTS	7	5	12	58.33%
PROTON-PUMP INHIBITORS	43	35	78	55.13%
SECOND GENERATION ANTIHISTAMINES	3	1	4	75.00%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	32	8	40	80.00%
SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	24	16	40	60.00%
ANTIHISTAMINES (GI DRUGS)	15	3	18	83.33%
OTHER MISCELLANEOUS THERAPEUTIC AGENTS	1	1	2	50.00%
AMPHETAMINE DERIVATIVES	0	1	1	0.00%
HEPARINS	12	2	14	85.71%
ANTIPRURITICS AND LOCAL ANESTHETICS	0	49	49	0.00%
SELECTIVE BETA-3-ADRENERGIC AGONISTS	6	12	18	33.33%
HCV POLYMERASE INHIBITOR ANTIVIRALS	2	2	4	50.00%
INCRETIN MIMETICS	7	3	10	70.00%
BETA-ADRENERGIC BLOCKING AGENTS	4	1	5	80.00%
ANTIBACTERIALS (SKIN, MUCOUS MEMBRANE)	5	14	19	26.32%
DIRECT FACTOR XA INHIBITORS	15	3	18	83.33%
RESPIRATORY TRACT AGENTS, MISCELLANEOUS	6	4	10	60.00%
WAKEFULNESS-PROMOTING AGENTS	6	3	9	66.67%
ANTIDEPRESSANTS, MISCELLANEOUS	4	4	8	50.00%
DIABETES MELLITUS	1	0	1	100.00%
CYCLOOXYGENASE-2 (COX-2) INHIBITORS	0	1	1	0.00%
BENZODIAZEPINES (ANTICONVULSANTS)	14	4	18	77.78%
ANTIALLERGIC AGENTS	3	16	19	15.79%
RESPIRATORY AND CNS STIMULANTS	11	7	18	61.11%
SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	32	12	44	72.73%
REPLACEMENT PREPARATIONS	1	3	4	25.00%

RAPID-ACTING INSULINS	3	0	3	100.00%
VESICULAR MONOAMINE TRANSPORT2 INHIBITOR	3	2	5	60.00%
PARASYMPATHOMIMETIC (CHOLINERGIC AGENTS)	1	0	1	100.00%
CYSTIC FIBROSIS (CFTR) CORRECTORS	3	0	3	100.00%
INSULINS	2	0	2	100.00%
ANTINEOPLASTIC AGENTS	6	2	8	75.00%
ANXIOLYTICS,SEDATIVES,AND HYPNOTICS,MISC	2	2	4	50.00%
CORTICOSTEROIDS (EENT)	3	1	4	75.00%
OTHER MACROLIDE ANTIBIOTICS	2	1	3	66.67%
HCV PROTEASE INHIBITOR ANTIVIRALS	3	9	12	25.00%
ANTIGOUT AGENTS	3	0	3	100.00%
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	0	1	1	0.00%
1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	3	1	4	75.00%
SEROTONIN MODULATORS	9	1	10	90.00%
NUCLEOSIDE AND NUCLEOTIDE ANTIVIRALS	1	0	1	100.00%
IMMUNOMODULATORY AGENTS	2	2	4	50.00%
CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1	0	1	100.00%
CELL STIMULANTS AND PROLIFERANTS	0	3	3	0.00%
PCSK9 INHIBITORS	2	1	3	66.67%
OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	1	3	4	25.00%
ANOREXIGENIC AGENTS, MISCELLANEOUS	0	1	1	0.00%
IMMUNOSUPPRESSIVE AGENTS	2	0	2	100.00%
MUCOLYTIC AGENTS	0	4	4	0.00%
GONADOTROPINS	1	0	1	100.00%
VASODILATING AGENTS (RESPIRATORY TRACT)	2	0	2	100.00%
PROGESTINS	0	3	3	0.00%
CYSTIC FIBROSIS (CFTR) POTENTIATORS	1	0	1	100.00%
HEMOSTATICS	1	0	1	100.00%
ANGIOTENSIN II RECEPTOR ANTAGONISTS	2	0	2	100.00%
DIGESTANTS	1	0	1	100.00%
HMG-COA REDUCTASE INHIBITORS	1	0	1	100.00%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	0	1	1	0.00%
HISTAMINE H2-ANTAGONISTS	1	0	1	100.00%
PHARMACEUTICAL AIDS	0	2	2	0.00%
GLYCOPEPTIDE ANTIBIOTICS	0	2	2	0.00%
ANTIEMETICS, MISCELLANEOUS	1	0	1	100.00%
ANTITOXINS AND IMMUNE GLOBULINS	1	0	1	100.00%
LONG-ACTING INSULINS	1	0	1	100.00%
HEMATOPOIETIC AGENTS	1	0	1	100.00%
BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	0	1	1	0.00%
PITUITARY	0	1	1	0.00%
ESTROGENS	1	0	1	100.00%
AZOLES (SKIN AND MUCOUS MEMBRANE)	0	1	1	0.00%
4Q18	901	605	1506	
Percent of Total	59.83%	40.17%		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Oct	14	66.67%	7	33.33%	21
Nov	18	66.67%	9	33.33%	27
Dec	14	87.50%	2	12.50%	16
4Q18	46	71.88%	18	28.13%	64

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
ANTICONVULSANTS, MISCELLANEOUS	8	1	9	88.89%
OPIATE PARTIAL AGONISTS	1	0	1	100.00%
OPIATE AGONISTS	14	2	16	87.50%
HCV PROTEASE INHIBITOR ANTIVIRALS	0	5	5	0.00%
IMMUNOMODULATORY AGENTS	1	0	1	100.00%
GI DRUGS, MISCELLANEOUS	4	3	7	57.14%
PROGESTINS	0	2	2	0.00%
AMPHETAMINES	1	0	1	100.00%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	1	0	1	100.00%
MUCOLYTIC AGENTS	0	1	1	0.00%
WAKEFULNESS-PROMOTING AGENTS	1	0	1	100.00%
SELECTIVE BETA-3-ADRENERGIC AGONISTS	1	0	1	100.00%
PROTON-PUMP INHIBITORS	1	1	2	50.00%
RIFAMYCIN ANTIBIOTICS	0	1	1	0.00%
BENZODIAZEPINES (ANTICONVULSANTS)	1	0	1	100.00%
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	1	0	1	100.00%
ANTIMIGRAINE AGENTS, MISCELLANEOUS	4	0	4	100.00%
SCABICIDES AND PEDICULICIDES	1	0	1	100.00%
RESPIRATORY TRACT AGENTS, MISCELLANEOUS	1	0	1	100.00%
BETA-ADRENERGIC BLOCKING AGENTS	1	0	1	100.00%
ANTINEOPLASTIC AGENTS	1	0	1	100.00%
ANTIMUSCARINICS	1	0	1	100.00%
HCV POLYMERASE INHIBITOR ANTIVIRALS	0	1	1	0.00%
INCRETIN MIMETICS	0	1	1	0.00%
SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	2	0	2	100.00%
4Q18	46	18	64	

South Dakota Medicaid

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 10/01/2018 - 12/31/2018				
AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/ Rx	%Total Claims
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	11,816	$284,693.01	$24.09	5.09%
MISCELLANEOUS ANTICONVULS	11,576	$1,286,036.61	$111.10	4.99%
AMINOPENICILLIN ANTIBIOTICS	10,928	$916,196.87	$83.84	4.71%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	10,255	$1,299,377.94	$126.71	4.42%
ATYPICAL ANTIPSYCHOTICS	7,695	$1,746,625.69	$226.98	3.32%
ADRENALS	7,508	$780,657.35	$103.98	3.24%
SECOND GENERATION ANTIHIS	7,351	$199,727.61	$27.17	3.17%
OPIATE AGONISTS	7,343	$418,520.73	$57.00	3.16%
RESPIRATORY AND CNS STIMULANTS	6,978	$1,116,941.30	$160.07	3.01%
AMPHETAMINES	6,612	$1,137,267.89	$172.00	2.85%
PROTON-PUMP INHIBITORS	6,609	$356,169.32	$53.89	2.85%
OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	4,779	$388,130.28	$81.22	2.06%
OTHER MACROLIDE ANTIBIOTICS	4,502	$345,907.39	$76.83	1.94%
THYROID AGENTS	3,981	$147,564.90	$37.07	1.72%
ANGIOTENSIN-CONVERTING EN	3,835	$203,407.20	$53.04	1.65%
TOTAL TOP 15 THERAPEUTIC CLASSES	111,768	$10,627,224.09	$95.08	48.17%

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 10/01/2018 - 12/31/2018				
AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/ Rx	%Total Claims
ATYPICAL ANTIPSYCHOTICS	7,695	$1,746,625.69	$226.98	3.32%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	10,255	$1,299,377.94	$126.71	4.42%
MISCELLANEOUS ANTICONVULS	11,576	$1,286,036.61	$111.10	4.99%
AMPHETAMINES	6,612	$1,137,267.89	$172.00	2.85%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	279	$1,125,440.22	$4,033.84	0.12%
RESPIRATORY AND CNS STIMULANTS	6,978	$1,116,941.30	$160.07	3.01%
AMINOPENICILLIN ANTIBIOTICS	10,928	$916,196.87	$83.84	4.71%
ADRENALS	7,508	$780,657.35	$103.98	3.24%
ANTINEOPLASTIC AGENTS	375	$563,606.26	$1,502.95	0.16%
SKIN AND MUCOUS MEMBRANE	450	$497,904.13	$1,106.45	0.19%
INSULINS	1,298	$478,361.34	$368.54	0.56%
HEMOSTATICS	32	$471,189.34	$14,724.67	0.01%
RAPID-ACTING INSULINS	1,031	$432,030.63	$419.04	0.44%
OPIATE AGONISTS	7,343	$418,520.73	$57.00	3.16%
LONG-ACTING INSULINS	1,158	$393,820.99	$340.09	0.50%
TOTAL TOP 15 THERAPEUTIC CLASSES	73,518	$12,663,977.29	$172.26	31.69%

Total Rx Claims from 10/01/2018 - 12/31/2018	232,020

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 10/01/2018 - 12/31/2018					
Drug Brand Name	**AHFS Description**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/ Rx**	**%Total Claims**
AMOXICILLIN	AMINOPENICILLIN ANTIBIOTICS	8,560	$664,441.26	$77.62	3.69%
METHYLPHENIDATE HYDROCHLO	RESPIRATORY AND CNS STIMULANTS	5,152	$855,867.52	$166.12	2.22%
GABAPENTIN	MISCELLANEOUS ANTICONVULS	4,039	$268,377.72	$66.45	1.74%
AZITHROMYCIN	OTHER MACROLIDE ANTIBIOTICS	4,015	$200,112.46	$49.84	1.73%
SERTRALINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,850	$112,103.43	$29.12	1.66%
FLUOXETINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,848	$61,366.88	$15.95	1.66%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	3,593	$114,316.55	$31.82	1.55%
MONTELUKAST SODIUM	LEUKOTRIENE MODIFIERS	3,547	$59,439.30	$16.76	1.53%
VYVANSE	AMPHETAMINES	3,368	$903,477.75	$268.25	1.45%
LISINOPRIL	ANGIOTENSIN-CONVERTING EN	3,351	$180,292.83	$53.80	1.44%
LEVOTHYROXINE SODIUM	THYROID AGENTS	3,204	$62,365.34	$19.46	1.38%
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	3,184	$268,066.33	$84.19	1.37%
CETIRIZINE HCL	SECOND GENERATION ANTIHIS	3,181	$50,632.98	$15.92	1.37%
AMPHETAMINE/DEXTROAMPHETA	AMPHETAMINES	3,010	$189,611.79	$62.99	1.30%
TRAZODONE HYDROCHLORIDE	SEROTONIN MODULATORS	2,961	$36,533.73	$12.34	1.28%
PROAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,919	$471,394.65	$161.49	1.26%
HYDROCODONE/ACETAMINOPHEN	OPIATE AGONISTS	2,743	$146,731.04	$53.49	1.18%
AMOXICILLIN/CLAVULANATE P	AMINOPENICILLIN ANTIBIOTICS	2,358	$247,897.01	$105.13	1.02%
CLONIDINE HCL	CENTRAL ALPHA-AGONISTS	2,257	$64,776.49	$28.70	0.97%
GUANFACINE ER	MISC. CENTRAL NERVOUS SYS	2,172	$51,347.73	$23.64	0.94%
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	2,145	$220,802.76	$102.94	0.92%
PREDNISONE	ADRENALS	2,073	$66,276.83	$31.97	0.89%
VENTOLIN HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,007	$122,910.35	$61.24	0.87%
ESCITALOPRAM OXALATE	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	1,964	$46,066.55	$23.46	0.85%
CEPHALEXIN	1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	1,917	$171,261.83	$89.34	0.83%
FLUTICASONE PROPIONATE	CORTICOSTEROIDS	1,884	$44,629.09	$23.69	0.81%
ATORVASTATIN CALCIUM	HMG-COA REDUCTASE INHIBIT	1,877	$50,628.02	$26.97	0.81%
LORATADINE	SECOND GENERATION ANTIHIS	1,855	$37,248.17	$20.08	0.80%
CEFDINIR	3RD GENERATION CEPHALOSPORIN ANTIBIOTICS	1,855	$81,606.39	$43.99	0.80%
ARIPIPRAZOLE	ATYPICAL ANTIPSYCHOTICS	1,736	$46,470.87	$26.77	0.75%
CLONAZEPAM	BENZODIAZEPINES (ANTICONV	1,605	$36,951.57	$23.02	0.69%
MUPIROCIN	ANTIBACTERIALS (SKIN & MU	1,584	$156,585.68	$98.85	0.68%
PREDNISOLONE SODIUM PHOSP	ADRENALS	1,584	$98,228.69	$62.01	0.68%
TRIAMCINOLONE ACETONIDE	CORTICOSTEROIDS (SKIN, MUCOUS MEMBRANE)	1,545	$65,093.16	$42.13	0.67%
COMPOUND	-	1,523	$74,250.47	$48.75	0.66%
RISPERIDONE	ATYPICAL ANTIPSYCHOTICS	1,513	$28,697.35	$18.97	0.65%
TRAMADOL HCL	OPIATE AGONISTS	1,495	$46,661.00	$31.21	0.64%
ONDANSETRON ODT	5-HT3 RECEPTOR ANTAGONIST	1,492	$95,103.61	$63.74	0.64%
POLYETHYLENE GLYCOL 3350	CATHARTICS AND LAXATIVES	1,489	$29,154.78	$19.58	0.64%
QUETIAPINE FUMARATE	ATYPICAL ANTIPSYCHOTICS	1,399	$30,937.51	$22.11	0.60%
LAMOTRIGINE	MISCELLANEOUS ANTICONVULS	1,391	$20,439.73	$14.69	0.60%
SULFAMETHOXAZOLE/TRIMETHO	SULFONAMIDES (SYSTEMIC)	1,351	$67,932.68	$50.28	0.58%
AMLODIPINE BESYLATE	DIHYDROPYRIDINES	1,310	$84,993.62	$64.88	0.56%
LEVETIRACETAM	MISCELLANEOUS ANTICONVULS	1,308	$44,558.69	$34.07	0.56%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYT	1,253	$57,923.12	$46.23	0.54%
TOPIRAMATE	MISCELLANEOUS ANTICONVULS	1,212	$16,440.68	$13.56	0.52%
MIRTAZAPINE	ANTIDEPRESSANTS, MISCELLANEOUS	1,199	$23,921.16	$19.95	0.52%
FUROSEMIDE	LOOP DIURETICS	1,187	$42,353.59	$35.68	0.51%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,182	$152,417.53	$128.95	0.51%
BUPROPION HCL XL	ANTIDEPRESSANTS, MISCELLANEOUS	1,155	$22,504.81	$19.48	0.50%
TOTAL TOP 50 DRUGS		**118,402**	**$7,092,203.08**	**$59.90**	**51.03%**

Drug Brand Name	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/ Rx	%Total Claims
VYVANSE	AMPHETAMINES	3,368	$903,477.75	$268.25	1.45%
METHYLPHENIDATE HYDROCHLO	RESPIRATORY AND CNS STIMULANTS	5,152	$855,867.52	$166.12	2.22%
AMOXICILLIN	AMINOPENICILLIN ANTIBIOTICS	8,560	$664,441.26	$77.62	3.69%
HUMIRA PEN	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	92	$511,715.50	$5,562.13	0.04%
PROAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,919	$471,394.65	$161.49	1.26%
LATUDA	ATYPICAL ANTIPSYCHOTICS	419	$468,785.05	$1,118.82	0.18%
INVEGA SUSTENNA	ATYPICAL ANTIPSYCHOTICS	211	$424,157.92	$2,010.23	0.09%
GABAPENTIN	MISCELLANEOUS ANTICONVULS	4,039	$268,377.72	$66.45	1.74%
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	3,184	$268,066.33	$84.19	1.37%
KALYDECO	CYSTIC FIBROSIS (CFTR) POTENTIATORS	11	$262,949.04	$23,904.46	0.00%
AMOXICILLIN/CLAVULANATE P	AMINOPENICILLIN ANTIBIOTICS	2,358	$247,897.01	$105.13	1.02%
PULMOZYME	MUCOLYTIC AGENTS	64	$244,058.00	$3,813.41	0.03%
ENBREL SURECLICK	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	55	$233,983.76	$4,254.25	0.02%
LYRICA	MISCELLANEOUS ANTICONVULS	467	$230,335.60	$493.22	0.20%
ORKAMBI	CYSTIC FIBROSIS (CFTR) CORRECTORS	11	$230,227.03	$20,929.73	0.00%
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	2,145	$220,802.76	$102.94	0.92%
NOVOLOG FLEXPEN	RAPID-ACTING INSULINS	572	$215,567.44	$376.87	0.25%
FLOVENT HFA	ADRENALS	980	$213,437.50	$217.79	0.42%
AZITHROMYCIN	OTHER MACROLIDE ANTIBIOTICS	4,015	$200,112.46	$49.84	1.73%
ADVAIR DISKUS	SELECTIVE BETA-2-ADRENERGIC AGONISTS	530	$197,367.78	$372.39	0.23%
ONFI	BENZODIAZEPINES (ANTICONV	142	$193,790.56	$1,364.72	0.06%
AMPHETAMINE/DEXTROAMPHETA	AMPHETAMINES	3,010	$189,611.79	$62.99	1.30%
STELARA	SKIN AND MUCOUS MEMBRANE	12	$189,315.19	$15,776.27	0.01%
LISINOPRIL	ANGIOTENSIN-CONVERTING EN	3,351	$180,292.83	$53.80	1.44%
CEPHALEXIN	1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	1,917	$171,261.83	$89.34	0.83%
EPCLUSA	HCV POLYMERASE INHIBITOR ANTIVIRALS	7	$170,470.32	$24,352.90	0.00%
MUPIROCIN	ANTIBACTERIALS (SKIN & MU	1,584	$156,585.68	$98.85	0.68%
ARISTADA	ATYPICAL ANTIPSYCHOTICS	69	$152,672.20	$2,212.64	0.03%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,182	$152,417.53	$128.95	0.51%
AFINITOR DISPERZ	ANTINEOPLASTIC AGENTS	7	$152,253.77	$21,750.54	0.00%
ADVATE	HEMOSTATICS	6	$147,668.18	$24,611.36	0.00%
HYDROCODONE/ACETAMINOPHEN	OPIATE AGONISTS	2,743	$146,731.04	$53.49	1.18%
NORDITROPIN FLEXPRO	SOMATOTROPIN AGONISTS	46	$142,191.57	$3,091.12	0.02%
VIMPAT	MISCELLANEOUS ANTICONVULS	196	$142,149.95	$725.25	0.08%
BANZEL	MISCELLANEOUS ANTICONVULS	70	$131,888.10	$1,884.12	0.03%
LANTUS SOLOSTAR	LONG-ACTING INSULINS	397	$131,414.53	$331.02	0.17%
JANUVIA	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	361	$129,540.22	$358.84	0.16%
VRAYLAR	ATYPICAL ANTIPSYCHOTICS	129	$129,032.36	$1,000.25	0.06%
ZITHROMAX	OTHER MACROLIDE ANTIBIOTICS	379	$128,100.00	$337.99	0.16%
VENTOLIN HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,007	$122,910.35	$61.24	0.87%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	3,593	$114,316.55	$31.82	1.55%
SERTRALINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,850	$112,103.43	$29.12	1.66%
ADVAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	306	$111,774.60	$365.28	0.13%
RECOMBINATE	HEMOSTATICS	3	$110,226.60	$36,742.20	0.00%
INGREZZA	-	19	$109,868.51	$5,782.55	0.01%
NOVOLOG FLEXPEN	INSULINS	289	$107,300.05	$371.28	0.12%
HUMIRA	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	21	$106,674.97	$5,079.76	0.01%
IMBRUVICA	ANTINEOPLASTIC AGENTS	9	$104,811.96	$11,645.77	0.00%
LEVEMIR FLEXTOUCH	LONG-ACTING INSULINS	406	$103,327.00	$254.50	0.17%
PREDNISOLONE SODIUM PHOSP	ADRENALS	1,584	$98,228.69	$62.01	0.68%
TOTAL TOP 50 DRUGS		**66,847**	**$11,471,952.44**	**$171.62**	**28.81%**

South Dakota Medicaid

Fiscal Year PMPM

Year	FY11*	FY12	FY13	FY14	FY15	FY16	FY17	FY18
Total $	$62,708,015	$65,712,352	$64,227,335	$70,961,816	$81,744,966	$85,732,737	$90,787,929	$81,556,647
Brand $	$43,750,598	$45,044,905	$41,635,288	$47,023,090	$53,317,423	$54,287,460	$61,855,369	$57,915,840
Generic $	$18,957,415	$20,667,445	$22,592,047	$23,938,723	$28,427,549	$31,445,276	$28,932,564	$23,640,806
Brand % of $	69.80%	68.50%	64.80%	66.30%	65.20%	63.30%	68.10%	71.00%
Generic % of $	30.20%	31.50%	35.20%	33.70%	34.80%	36.70%	31.90%	29.00%
Avg $ per Brand Rx	$189.10	$209.25	$241.42	$299.64	$324.36	$369.40	$431.26	$478.15
Avg $ per Generic Rx	$25.11	$26.98	$29.09	$31.13	$34.70	$37.20	$34.45	$32.76
Avg $ per Rx	$63.58	$66.97	$67.67	$76.63	$83.10	$86.40	$92.42	$96.77
Total # of Rx	986,210	981,288	949,179	926,035	983,673	992,251	982,323	842,794
Brand Rx	231,358	215,269	172,459	156,930	164,377	146,960	143,429	121,125
Generic Rx	754,852	766,019	776,720	769,105	819,296	845,291	839,894	721,669
Brand % of Rx	23.50%	21.90%	18.20%	16.90%	16.70%	14.80%	14.60%	14.40%
Generic % of Rx	76.50%	78.10%	81.80%	83.10%	83.30%	85.20%	85.50%	85.60%
Rx per Recipient	0.718	0.707	0.681	0.669	0.7	0.7	0.68	0.6
PMPM	$45.68	$47.32	$46.09	$51.28	$58.05	$60.20	$63.25	$57.43
Rx per User	3	3	3.2	3.3	3.4	3.6	3.5	3.1
$ per User	$190.53	$202.07	$214.91	$250.27	$280.11	$306.76	$321.10	$300.47
% Users of Total Recips.	24.00%	23.40%	21.40%	20.50%	20.70%	19.60%	19.70%	19.10%

* FY 11 = 7/1/10 - 6/30/11

Utilization and PA Information

Time frame: 10/1/2018 – 12/31/2018
Red font denotes drug is on prior authorization

CGRP Inhibitors (PA)

	3Q 2018					4Q 2018				
Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Aimovig	16	$9,355.06	$584.69	9	31-57	32	$17,502.21	$546.94	18	18-49
Ajovy	0					4	$2,332.1	$583.03	3	18-31
Emgality	0					0				

PA Request Summary

Drug Class	# of Requests	Phone Requests		Fax Requests	
		#	%	#	%
ANTIMIGRAINE AGENTS, MISCELLANEOUS	45	3	7%	42	93%

PA Summary	Approved	Denied	Total	Approval Rate
ANTIMIGRAINE AGENTS, MISCELLANEOUS	14	27	41	34%
AIMOVIG	13	20	33	39%
AJOVY	1	7	8	12.5%

Appeals Detail	Approved	Denied	Total	Approval Rate
ANTIMIGRAINE AGENTS, MISCELLANEOUS	4	0	4	100%
AIMOVIG	2	0	2	
AJOVY	2	0	2	

CiproDex

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
CiproDex	760	$156,582.14	$206.03	651	0 – 64

CiproDex

Provider Specialty	Prescriber Count	Utilization	Paid Amount	Member Count	Age Range	Prescriber City	Pharmacy City
Chiropractor	1	1	$219.98	1	11	Sioux Falls	Tea
Critical Care, Pediatrics	1	7	$1,540.45	7	0-16	Aberdeen	Aberdeen
Dentist, General Practice	1	1	$219.98	1	5	**West Des Moines IA**	Sioux Falls
Emergency Medicine	7	7	$1,585.04	7	4-36	Mitchell, Rapid City, Sioux Falls, Watertown, Yankton	Mitchell, Rapid City, Sioux Falls, Watertown, Yankton
Family Practice	40	64	$13,622.54	55	0-55	**Columbia MO**, **Omaha NE**, **South Sioux City NE**, **Lusk WY**, plus 16 SD cities	**Sioux City IA**, plus 16 SD cities
General Practice	3	8	$854.00	7	1-30	Eagle Butte, Pine Ridge, **San Juan PR**	Eagle Butte, Pine Ridge, Wagner
Hematology & Oncology	1	1	$232.63	1	55	**Bismarck ND**	**Bismarck ND**
Internal Medicine	2	4	$718.50	4	1-48	Aberdeen, Pierre	Aberdeen, Pierre
Licensed Practical Nurse	1	1	$220.57	1	1	Chamberlain	Chamberlain
Nephrology/Renal Medicine	1	2	$263.19	2	18, 36	Sioux Falls	Sioux Falls
Nurse Practitioner	8	20	$4,217.13	20	0-57	Aberdeen, Huron, Madison, Mission, Rapid City, Sioux Falls, Sturgis	Aberdeen, Huron, Madison, Rapid City, Sioux Falls, Sturgis, **Valentine NE**
Nurse Practitioner, Family Health	45	75	$16,556.60	74	0-55	**Browns Valley MN, Ortonville MN**, **Bismarck ND**, plus 25 SD cities	**Browns Valley MN**, **Bismarck ND**, plus 28 SD cities
Nurse Practitioner, Pediatric Care	3	11	$2,483.62	11	1-16	Aberdeen, Brookings, Pierre	Aberdeen, Brookings Pierre
Otolaryngology	14	118	$23,281.93	101	0-60	**Omaha NE**, plus 27 SD cities	26 SD cities
Otolaryngology, Facial Plastic Surgery	1	6	$1,128.80	5	1-54	Mitchell	Huron, Mitchell, Platte
Otolaryngology, Otolaryngology/Facial Plastic Surgery	1	47	$11,040.15	42	0-19	Rapid City	Faith, **Hettinger ND**, Mission, Pine Ridge, Spearfish, Sturgis, **Valentine NE**, Wanblee, White River
Pediatrics	44	141	$28,930.98	127	0-19	**Bismarck ND**, **Columbus NE**, plus 11 SD cities	**Bismarck ND**, plus 19 SD cities
Pediatrics, Pediatric Emergency Medicine	1	1	$219.98	1	2	**San Antonio TX**	Sioux Falls
Pharmacist	1	1	$0.00	1	26	Kyle	Kyle
Physician Assistant	47	113	$22,860.78	106	0-53	**Payette ID, Miles City MT,** plus 23 SD cities	27 SD cities
Physician Assistant, Medical	11	61	$12,568.63	55	0-64	Aberdeen, **Peridot AZ**, Rapid City, Sioux Falls, Sisseton, Vermillion, Wagner, Watertown, Yankton	**Wheaton MN**, plus 17 SD cities
Physician Assistant, Surgical	2	4	$427.00	4	9-49	**Dickson TN**, **Tampa FL**	Kyle, Pine Ridge
Plastic Surgery, Facial	2	9	$1,357.06	6	1-18	Sioux Falls, Watertown	Mitchell, Sioux Falls, Tea, Watertown

Specialist	1	1	$58.56	1	11	**South Sioux City NE**	Dakota Dunes
Student in an Organized Health Care Education/Training Program/Student, Health Care	31	56	$11,974.04	54	0-57	Brookings, **Durham NC**, Hartford, Huron, **Oshkosh WI**, Pierre, Rapid City, Sioux Falls, Watertown, Yankton	Aberdeen, Brookings, Canton, DeSmet, Huron, Pierre, Rapid City, Scotland, Sioux Falls, Sisseton, Yankton

Antipsychotics PA reviews

Drug Name	Total PA Reviews	PA Status	Denial Reasons
ABILIFY MAINTENA	5	5 Approvals	
ARIPIPRAZOLE (QLL)	21	10 Approvals 11 Denials	9 – exceed qty limit 2 – tried/failed two different antidepressants
ARIPIPRAZOLE ODT (QLL)	1	1 Approval	
ARISTADA	6	6 Approvals	
CLOZAPINE ODT (QLL)	3	2 Approvals 1 Denial	1 – did not have approved diagnosis
INVEGA SUSTENNA (QLL)	12	9 Approvals 3 Denials	3 – did not fail a standard dosage form from this drug class in the last 30 days
INVEGA TRINZA	2	2 Approvals	
LATUDA	20	18 Approvals 2 Denials	2 – did not have approved diagnosis
OLANZAPINE (QLL)	1	1 Approval (qty)	
OLANZAPINE ODT (QLL)	5	4 Approvals 1 Denial	1 – did not fail a standard dosage form from this drug class in the last 30 days
PALIPERIDONE ER (QLL)	10	9 Approvals 1 Denial	1 – exceed qty limits
REXULTI	3	2 Approvals 1 Denial	1 – did not have approved diagnosis
RISPERDAL (QLL)	1	1 Approval	1 – brand approved
RISPERDAL CONSTA	4	4 Approvals	
RISPERIDONE (QLL)	12	9 Approvals (qty) 3 Denials (qty)	3 – exceed qty limits
RISPERIDONE ODT (QLL)	1	1 Approval	
VRAYLAR	6	5 Approvals 1 Denial	1 – did not have approved diagnosis
ZIPRASIDONE HCL (QLL)	1	1 Denial	1 – exceed qty limits

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Atypical Antipsychotics Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)

Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Continuation of therapy:
Is this for a continuation of a second generation atypical antipsychotic agent? ❑ **Yes** ❑ **No**

What is the patient's diagnosis for the medication being requested? (Mandatory)

_____

ICD-10 Code(s) [Mandatory]: _____

Clinical information:
For patients with a diagnosis of depression, has the patient tried and failed 2 different antidepressants? ❑ **Yes** ❑ **No**
For patients younger than 6 years of age, is a psychiatrist, developmental pediatrician, child/adolescent psychiatrist or pediatric neurologist involved in care? ❑ **Yes** ❑ **No**

For alternative dosage forms (e.g., rapid dissolve tablets, injectables, extended-release), also answer the following:
Is the patient unable to swallow? ❑ **Yes** ❑ **No**
Has the patient failed a standard dosage form from this drug class in the last 30 days? ❑ **Yes** ❑ **No**

Quantity limit requests:
What is the quantity requested per DAY? _____
What is the reason for exceeding the plan limitations?
❑ Titration or loading dose purposes
❑ Patient is on a dose-alternating schedule (e.g., one tablet in the morning and two tablets at night, one to two tablets at bedtime)
❑ Requested strength/dose is not commercially available
❑ Other: _____

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: AtypicalAntipsychotics_SouthDakotaMedicaid_2017May-P

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Dupixent® Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)		
Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:

❑ Atopic dermatitis

❑ Other diagnosis: _____ ICD-10 Code(s): _____

Clinical information:

Has the patient had a documented trial of topical corticosteroid within the last 120 days? ❑ **Yes** ❑ **No**

Was the medication prescribed by or in consultation with a dermatologist or allergist/immunologist? ❑ **Yes** ❑ **No**

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: Dupixent_SouthDakotaMedicaid_2017Nov-P

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Fasenra™ Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)		
Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:

❑ Severe asthma with an eosinophilic phenotype

❑ Other diagnosis: _____ ICD-10 Code(s): _____

Clinical information:

Has the patient experienced inadequate control of asthmatic symptoms after a minimum of three months use of a high-dose inhaled corticosteroid (ICS) and controlled medication (long-acting beta2 agonist (LABA) or high-dose LABA/ICS combination product or leukotriene receptor antagonist)? ❑ **Yes** ❑ **No**

Is Fasenra prescribed by or in consultation with a rheumatologist, pulmonologist, allergist, or immunologist? ❑ **Yes** ❑ **No**

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

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_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: Fasenra_SouthDakotaMedicaid_2019Jan-W

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Nucala® Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)		
Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:

❑ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)
❑ Severe asthma with an eosinophilic phenotype
❑ Other diagnosis: _____ ICD-10 Code(s): _____

Clinical information:

Is Nucala prescribed by or in consultation with a rheumatologist, pulmonologist, allergist, or immunologist? ❑ **Yes** ❑ **No**

For severe asthma with an eosinophilic phenotype, also answer the following:

Has the patient experienced inadequate control of asthmatic symptoms after a minimum of three months use of a high dose corticosteroid and controller medication? ❑ **Yes** ❑ **No**

Has the patient had at least two asthma exacerbations requiring medical intervention within the past 12 months? ❑ **Yes** ❑ **No**

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: Nucala_SouthDakotaMedicaid_2019Jan-P

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Xolair® Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)

Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:
❑ Asthma
❑ Chronic idiopathic urticaria (CIU)
❑ Other diagnosis: _____ ICD-10 Code(s): _____

For asthma, answer the following:
Does the patient have a positive skin test or in vitro reactivity to a perennial aeroallergen? ❑ **Yes** ❑ **No**
Does the patient have an elevated serum IgE level? ❑ **Yes** ❑ **No**
Are the patient's symptoms inadequately controlled with inhaled corticosteroids? ❑ **Yes** ❑ **No**
Is Xolair prescribed by or in consultation with a pulmonologist, allergist, or immunologist? ❑ **Yes** ❑ **No**

For chronic idiopathic urticaria, answer the following:
Does the patient remain symptomatic despite H1 antihistamine treatment? ❑ **Yes** ❑ **No**
Is Xolair prescribed by or in consultation with a dermatologist, rheumatologist, pulmonologist, allergist, or immunologist? ❑ **Yes** ❑ **No**

Quantity limit requests:
What is the quantity requested per MONTH? _____
What is the reason for exceeding the plan limitations?
❑ Titration or loading dose purposes
❑ Patient is on a dose-alternating schedule (e.g., one tablet in the morning and two tablets at night, one to two tablets at bedtime)
❑ Requested strength/dose is not commercially available
❑ Other: _____

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: Xolair_SouthDakotaMedicaid_2019Jan-P

ADD/ADHD Drugs Utilization

Time frame: 10/1/2018 – 12/31/2018

Summary

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Amphetamines	25,516	$4,665,654,60	$182.85	3,463	3 – 64
Central Alpha-Agonists	299	$46,042.71	$153.99	52	4 – 32
Misc Central Nervous System	12,609	$715,112.13	$56.71	1,729	4 – 85
Respiratory & CNS Stimulants	26,817	$4,614,496.59	$172.07	3,587	0 – 62
Wakefulness-Promoting Agents	264	$67,361.47	$255.16	40	4 – 64

Amphetamine

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Amphetamine	**37**	**$13,766.66**	**$372.07**	**9**	
• Adzenys XR tab/ER susp	32	$13,098.06	$409.31	8	5-14
• Dyanavel XR suspension	5	$1720.01	$133.72	1	7
Amphetamine sulfate					
• Evekeo	8	$1,720.01	$215.00	2	16, 40
Amphetamine-dextroamphetamine	**11,891**	**$933,625.21**	**$78.52**	**1,931**	
• Adderall tab	4	$1,577.59	$394.40	3	15 – 34
• Adderall XR cap	107	$21,935.98	$205.01	11	5 – 39
• amphet/dextr tab	4,025	$134,253.42	$33.35	1,404	3 – 63
• amphet/dextr cap ER	7,650	$747,87782	$97.76	492	3 – 63
• Mydavis	105	$27,980.40	$266.48	21	10 – 57
Dextroamphetamine sulfate	**456**	**$59,497.31**	**$130.48**	**79**	
• dextroamphetamine tab	95	$6,513.60	$68.56	24	7 – 58
• dextroamphetamine cap ER	361	$52,983.71	$146.77	55	3 – 58
Lisdexamfetamine dimesylate	**13,124**	**$3,657,045.41**	**$278.65**	**1,961**	
• Vyvanse cap	12,947	$3,607,637.50	$278.65	1,921	3 – 64
• Vyvanse chew	177	$49,407.91	$279.14	40	6 – 12

Misc Central Nervous System

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Clonidine hcl (ADHD)					
• clonidine tab ER	299	$46,042.71	$153.99	52	4 – 32

Central Alpha-Agonists

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Atomoxetine					
• atomoxetine cap	101	$472,290.98	$136.54	590	4 – 56
• Strattera	43	$17,855.64	$415.25	17	6 – 23
Guanfacine tab ER					
• guanfacine tab ER	9,082	$219,303.69	$24.15	1,220	4 – 85
• Intuniv tab	25	$5,661.82	$226.47	4	7 – 16

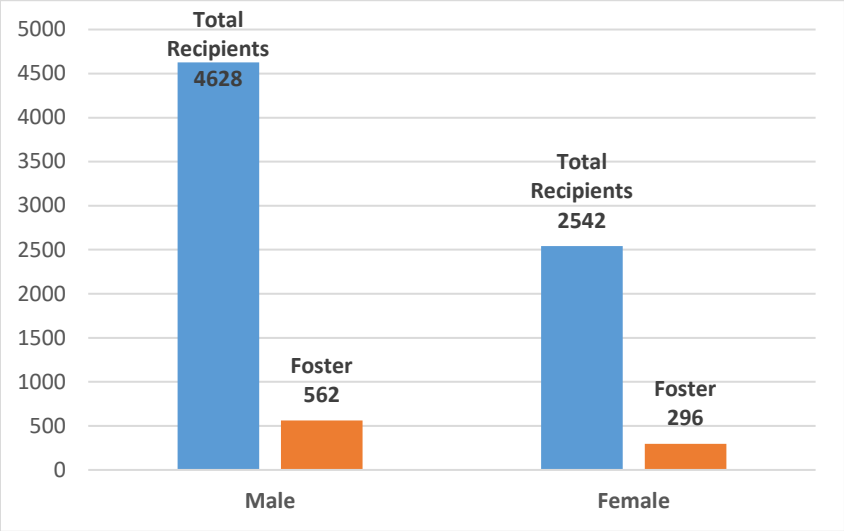
Respiratory & CNS Stimulants

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Caffeine citrate					
• Caffeine citrate solution	134	$90,534.62	$675.63	70	0
Dexmethylphenidate					
• dexmethylphenidate tab	1,178	$53,582.60	$45.49	209	4 – 60
• dexmethylphenidate cap ER	4,869	$834,205.49	$171.33	693	4 – 59
• Focalin tab 5mg	2	$854.00	$427.00	1	12
• Focalin cap XR	26	$8,818.74	$339.18	6	6 – 14
Methylphenidate					
• Cotempla tab	62	$23,205.24	$374.28	12	6 – 13
• Daytrana patch	144	$41,251.71	$286.47	29	5 – 19
Methylphenidate hcl					
• Aptensio cap XR	24	$5,194.58	$216.44	5	5 – 8
• Concerta tab	93	$15,570.66	$167.43	16	7 – 29
• Metadate tab ER 20mg	4	$264.15	$66.04	2	8, 16
• methylphenidate chew	212	$47,649.94	$224.76	50	3 – 13
• methylphenidate solution	76	$10,762.55	$141.61	24	4 – 16
• Methylin solution	14	$578.31	$41.31	3	4 – 8
• methylphenidate cap	1,632	$163,344.90	$100.09	282	4 – 55
• methylphenidate cap ER	549	$78,684.71	$143.32	101	5 – 56
• methylphenidate tab	3,094	$69,762.61	$22.55	622	3 – 62
• methylphenidate tab ER	14,238	$3,014,252.45	$211.70	2136	3 – 59
• Quillichew chew ER & susp	421	$140,945.39	$334.79	86	4 – 13
• Ritalin LA cap	44	$14,709.97	$334.32	21	5 – 40
• methylphenidate cap LA 60mg	1	$323.97	$323.97	1	1

Wakefulness-Promoting Agents

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Modafinil	**146**	**46,315.27**			
• modafinil 100 & 200mg tab	128	$7,477.91	$58.42	25	4 – 64
• Provigil 200mg tab	18	$38,837.36	$2,157.63	2	40, 41
Armodafinil					
• armodafinil tab	**118**	**$21,046.20**	$178.36	15	14 – 64

Utilizing members: 7,170 recipients (aged 0 – 85 years old) of which 858 were identified as foster care (aged 0 to 25 years old)



Concomitant therapy:

Anti-manic agent – 6 recipients (aged 11 – 58 years old)

Atypical antipsychotics – 79 recipients (aged 4 – 20 years old)

Benzodiazepines – 334 recipients (aged 5 – 65 years old)

Haloperidol tab – 3 recipients (aged 27 – 32 years old) – all prescribed by psychiatry

Buprenorphine/naloxone combination – 22 recipients (aged 24 – 57 years old)

Opioids – 593 recipients (aged 3 to 64 years old)

INTRODUCTION

- Approximately 92.1 million American adults are living with some form of cardiovascular disease or the after-effects of stroke according to the American Heart Association Heart Disease and Stroke Statistics 2018 update. Cardiovascular disease accounts for nearly 836,546 deaths in the United States (US) annually; about 1 of every 3 deaths. (*Benjamin et al 2018*).
- Calcium channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance. In addition, calcium channel blocking agents (also called calcium channel blockers) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload (*Kannam et al 2017, Dobesh PP 2017, Michel T 2011*).
- The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue (*Micromedex 2.0 2018, Kannam et al 2017*).
- The calcium channel blocking agents include dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally heterogeneous group. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The non-dihydropyridines also block the T-type calcium channel in the atrioventricular (AV) node (*Micromedex 2.0 2018, Kannam et al 2017, Dobesh PP 2017, Michel T 2011, Saseen 2017*).
- Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle. They have little effect on cardiac muscle contractility or conduction (*Micromedex 2.0 2018, Kannam et al 2017*).
  - All available dihydropyridine calcium channel blocking agents can be used in the treatment of hypertension, with the exception of nimodipine and immediate release nifedipine capsules. Although not a first-line treatment in all hypertensive patients, the dihydropyridines are generally effective but differ somewhat in other properties and effects.
  - Amlodipine, oral nicardipine, and long-acting nifedipine are effective treatment options for chronic stable angina. Short-acting agents, such as short-acting nifedipine, should be avoided due to increased cardiovascular and mortality risks in some patients as well as significant adverse effects, such as reflex tachycardia. Amlodipine is also indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease (CAD).
  - Amlodipine is the only calcium channel blocker that is Food and Drug Administration (FDA)-approved in combination with a nonsteroidal anti-inflammatory drug (NSAID). Consensi (amlodipine/celecoxib) was FDA-approved on May 31, 2018 (although not yet available) for the treatment of hypertension and osteoarthritis.
- The non-dihydropyridine calcium channel blocking agents include diltiazem and verapamil and both agents are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action (*Micromedex 2.0 2018*). Non-dihydropyridines dilate the arteries somewhat less than dihydropyridines, but they also reduce heart rate and contractility (*Micromedex 2.0 2018, Kannam et al 2017, Weber et al 2014*).
  - The non-dihydropyridine calcium channel blocking agents are indicated for use in the treatment of angina, arrhythmias, and hypertension. Diltiazem is a potent coronary vasodilator but is only a mild arterial vasodilator. Although it decreases AV node conduction, diltiazem does not have negative inotropic properties. Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node and has negative inotropic and chronotropic effects (*Micromedex 2.0, 2018*).
  - Guidelines stipulate that a non-dihydropyridine calcium channel blocker may be prescribed in certain patients, often with co-morbid indications. Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure *(Yancy et al 2013, Yancy et al 2016, Yancy et al 2017)*. Caution is also advised in elderly patients. Guidelines generally reserve non-dihydropyridine calcium channel blockers for patients with high risk cardiovascular diseases and

arrhythmias; therefore, they are usually reserved for progressive cardiovascular and heart disease (*Al-Khatib et al 2017, American Geriatrics Society 2015, Amsterdam et al 2014, Fihn et al 2014, Go et al 2014, January et al 2014, KDIGO 2012, Williams et al 2018, Montalescot et al 2013, Page et al 2016, Rosendorff et al 2015, Weber et al 2014*).

- Calcium channel blockers are also included in various combination products (eg, amlodipine-benazepril); however, these combination agents are not included in this review.
- Since there are several branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review encompasses all dosage forms and strengths with the exception of injectable indications and formulations used primarily in an institutional setting.
- Medispan Therapeutic Class: Calcium Channel Blockers

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Dihydropyridines	
Adalat CC (nifedipine extended-release)	✔
Afeditab CR (nifedipine extended-release)	✔
Consensi** (amlodipine/celecoxib)	-
Felodipine extended-release	✔
Isradipine	✔
Nicardipine	✔
Nimodipine	✔
Nisoldipine extended-release	✔
Norvasc (amlodipine)	✔
Nymalize (nimodipine)	-
Procardia (nifedipine)	✔
Procardia XL (nifedipine extended-release)	✔
Sular (nisoldipine extended-release)	✔
Non- dihydropyridines	
Calan (verapamil) tablet	✔
Calan SR (verapamil extended-release) tablet	✔
Cardizem (diltiazem) tablet	✔
Cardizem CD* (diltiazem extended-release) capsule	✔
Cardizem LA† (diltiazem extended-release) tablet	✔
Dilacor XR‡ (diltiazem extended-release) capsule	✔
Tiazac§ (diltiazem extended-release) capsule	✔
Verelan (verapamil sustained-release) capsule	✔
Verelan PM (verapamil extended-release) capsule	✔

*Cartia XT is a branded generic of Cardizem CD.
**Consensi was FDA-approved in May 2018; however, it is not yet available.
†Matzim LA is the branded generic of Cardizem LA.
‡Dilacor XR is no longer manufactured, but included in this review because its branded generic, DILT-XR, is still on the market.
§Taztia XT and Diltzac are branded generics of Tiazac.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Dihydropyridines

Indication	Amlodipine	Consensi (amlodipine/ Celecoxib)	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Angina Pectoris								
Treatment of chronic stable angina	✔ *		-	-	✔ †	-	-	-

Indication	Amlodipine	Consensi (amlodipine/ Celecoxib)	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Treatment of chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents	-		-	-	-	✔ (capsule, ER tablet [Procardia XL])	-	-
Treatment of vasospastic angina	✔ ‡		-	-	-	✔ (capsule, ER tablet [Procardia XL])§	-	-
CAD								
Reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction < 40%	✔		-	-	-	-	-	-
Hypertension								
Treatment of hypertension	✔ ‖	✔ **	✔ ‖	✔ ¶	✔ ‖	✔ (ER tablet)‖	-	✔ ‖
Treatment of hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions	✔ ‖		✔ ‖	-	-	✔ (ER tablet [Procardia XL])‖	-	-
Miscellaneous								
Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V)	-		-	-	-	-	✔	-
Management of the signs and symptoms of osteoarthritis		✔ **						

*Alone or in combination with other antianginal agents.
**Consensi was FDA-approved in May 2018, however, it is not yet available.
†Alone or in combination with beta blockers.
‡Confirmed or suspected vasospastic angina. Alone or may be used in combination with other antianginal agents.
§Vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm.
‖Alone or in combination with other antihypertensive agents.
¶Alone or in combination with thiazide-type diuretics.

(Prescribing information: Adalat CC 2016, Afeditab CR 2014, Consensi 2018, felodipine ER 2014, isradipine 2014, nicardipine capsule 2016, nimodipine 2012, nisoldipine extended-release tablet 2017, Norvasc 2017, Nymalize 2018, Procardia 2016, Procardia XL 2016, Sular 2017)

Table 3. Food and Drug Administration Approved Indications – Non-Dihydropyridines

Indication	Diltiazem	Verapamil
Angina Pectoris		
Angina due to coronary artery spasm or vasospastic angina	✔ (tablet [Cardizem], extended-release capsule [Cardizem CD])	✔ (Calan)
Chronic stable angina	✔	✔ (Calan)
Unstable angina	-	✔ (Calan)
Arrhythmias		

Indication	Diltiazem	Verapamil
Control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation in association with digitalis	-	✔ (Calan)
Prophylaxis of repetitive paroxysmal supraventricular tachycardia	-	✔ (Calan)
Hypertension		
Hypertension	✔ *(with the exception of Cardizem)	-
Hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.	✔ *(Cardizem LA)	✔

*May be used alone or in combination with other antihypertensive agents.

(Prescribing Information: Calan 2017, Calan SR 2017, Cardizem 2016, Cardizem CD 2017, Cardizem LA 2016, DILT-XR 2017, Tiazac 2016, Verelan 2016, Verelan PM 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Dihydropyridines

- Clinical trials have demonstrated the efficacy of these agents for their respective indications.
- In a crossover study for the treatment of angina, amlodipine and felodipine have been shown to be more effective than placebo, though no significant difference between the 2 active treatment groups was observed (*Koenig 1997*).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established (*Sheehy et al 2000, Mounier-Vehier et al 2002, Kes et al 2003, Ryuzaki et al 2007, Saito et al 2007, Pepine et al 2003, Whitcomb et al 2000, White et al 2003b, Lenz et al 2001, Drummond et al 2007, Mazza et al 2002, Hollenberg et al 2003, White et al 2003a, Jordan et al 2007, Messerli et al 2002, Chrysant et al 2012, Messerli et al 2000, Jamerson et al 2004, Neutel et al 2005, Chrysant et al 2007, Chrysant et al 2004, Minami et al 2007, Jamerson et al 2007, Malacco et al 2002, Kereiakes et al 2007, Tatti et al 1998, Miranda et al 2008, Fogari et al 2007, Ribeiro et al 2007, Chrysant et al 2008, Chrysant et al 2009, Oparil et al 2009, Braun et al 2009, Littlejohn et al 2009a, Littlejohn et al 2009b, Sharma et al 2007, Neutel et al 2012, Maciejewski et al 2006, Ichihara et al 2006, Karpov et al 2012, Philipp et al 2007, Philipp et al 2011, Schunkert et al 2009, Ke et al 2010, Destro et al 2008, Flack et al 2009, Schrader et al 2009, Sinkiewicz et al 2009, Fogari et al 2009, Poldermans et al 2007, Calhoun et al 2009a, Calhoun et al 2009b, Crikelair et al 2009, Pareek et al 2010, Gustin et al 1996, Karotsis et al 2006, Lindholm et al 2005, Van Bortel et al 2008, Wiysonge et al 2007, Baguet et al 2007*).
  - In-class comparisons for the treatment of hypertension have found better compliance and a higher response rate with amlodipine compared to felodipine, though van der Krogt and colleagues found similar decreases in overall systolic and diastolic blood pressures between groups (*Sheehy et al 2000, Van der Krogt et al 1996*).
  - The most clinical trial experience has been with amlodipine and nifedipine, which have been shown to have beneficial effects on cardiovascular and stroke outcomes in hypertension trials (*Rahman et al 2012, Black et al 2008, ALLHAT 2002, Julius et al 2004, Zanchetti et al 2006, Nissen et al 2004, Ogihara et al 2008, Jamerson et al 2008, Weber et al 2010, Weber et al 2013, Brown et al 2000*).
- The dihydropyridines have been shown to have favorable effects on cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) in select diseases (*Pitt et al 2000, Dahlöf et al 2005, Chapman et al 2007, Nissen et al 2004, ALLHAT 2002, Black et al 2008, Rahman et al 2012, Ogihara et al 2008, Julius et al 2004, Zanchetti et al 2006, Jamerson et al 2008, Bakris et al 2010, Weber et al 2010, Weber et al 2013, Hansson et al 1999, National Intervention Cooperative Study 1999, Brown et al 2000, Estacio et al 1998*).
  - In the ALLHAT study, ACE inhibitors had a 51% higher rate (relative risk [RR], 1.51; 95% confidence interval [CI], 1.22 to 1.86) of stroke in patients of African or Caribbean descent (Black) when used as initial therapy compared to

calcium channel blockers. ACE inhibitors were also less effective in reducing blood pressure in Black patients compared to a calcium channel blocker (*Rahman et al 2012, Black et al 2008, ALLHAT 2002*).

- An unpublished phase III randomized controlled trial compared amlodipine/celecoxib (Consensi) with its individual components and matching placebo in 152 patients with hypertension *(Smith et al, 2018)*. After 2 weeks of treatment, the primary endpoint of change in mean daytime ambulatory systolic blood pressure was noninferior with amlodipine/celecoxib vs amlodipine (-10.6 vs -8.8 mmHg; p < 0.001), and the secondary endpoint of mean 24-hour diastolic blood pressure was superior with amlodipine/celecoxib vs amlodipine (-7.1 vs -4.8 mmHg; p = 0.38).

Non-dihydropyridines

- The non-dihydropyridine calcium channel blockers are indicated to treat hypertension and angina, in addition to slowing ventricular rate in patients with atrial fibrillation/atrial flutter. Clinical trials demonstrate the efficacy of these agents for their respective indications.
- For the treatment of angina, diltiazem and verapamil have been shown to be effective in improving exercise tolerance and reducing heart rate, angina frequency and nitroglycerin use *(De Rosa et al 1998, Chugh et al 2001, van Kesteren et al 1998, Frishman et al 1999).*
  - A direct comparison between diltiazem and verapamil found no significant differences between the agents in exercise tolerance; however, resting heart rate, angina frequency and nitroglycerin use were all significantly lower in the diltiazem group *(De Rosa et al 1998).*
- Both diltiazem and verapamil have shown efficacy in the treatment of hypertension, but comparisons with other classes of medications have not consistently demonstrated "superiority" of either agent (*Wright et al 2004, Rosei et al 1997*).
  - Wright and colleagues compared diltiazem and amlodipine in African American patients with hypertension and demonstrated significantly greater reductions in diastolic blood pressure during the first 4 hours after awakening in addition to greater reductions in heart rate with diltiazem; however, mean 24-hour systolic blood pressure reductions were significantly greater with amlodipine *(Wright et al 2004).*
- Studies evaluating the efficacy of the non-dihydropyridine calcium channel blockers for various cardiovascular outcomes generally demonstrated no significant difference between verapamil or diltiazem compared to other agents including beta blockers and diuretics *(Hansson et al 2000, Pepine et al 2003, Mancia et al 2007, Bangalore et al 2008, Black et al 2003).*

CLINICAL GUIDELINES

- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of calcium channel blocking agents. Most recommend that the selection of an antihypertensive agent be based on compelling indications for use:
  - Most guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a calcium channel blocker as first-line therapy (*Go et al 2014, James et al 2014, Williams et al 2018, Weber et al 2014, Carey et al 2018*). The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline generally recommends that combination therapy include an ACE inhibitor or ARB with a calcium channel blocker and/or a thiazide-type diuretic *(Williams et al 2018)*.
  - In Black hypertensive patients, thiazide-type diuretics or calcium channel blockers are recommended specifically as first-line therapy *(James et al 2014, Williams et al 2018, Weber et al 2014*).
  - In patients with chronic kidney disease, calcium channel blockers are generally recommended after ACE inhibitors or ARBs (*KDIGO 2012, Go et al 2014, Williams et al 2018, Weber et al 2014*).
  - Consensus guidelines recommend calcium channel blockers as an option in pregnant patients with severe hypertension to prevent stroke; nifedipine is one of the only dihydropyridines tested in these patients *(Bushnell et al 2014, Williams et al 2018).*
  - A long-acting dihydropyridine calcium channel blocker may be added to a basic hypertensive regimen, particularly after a beta blocker and ACE inhibitor, in hypertensive patients with CAD and stable angina *(Rosendorff et al 2015).*
  - A non-dihydropyridine calcium channel blocker may be prescribed for hypertensive patients with CAD who have an intolerance or contraindication to a beta blocker; however, a combination of a beta blocker and a non-dihydropyridine calcium channel blocker may increase the risk of bradyarrhythmias and heart failure *(Rosendorff et al 2015)*.
  - Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure *(Yancy et al 2016, Yancy et al 2017).*

- The 2018 ESC/ESH guidelines recommend calcium channel blockers, ACE inhibitors, and ARBs over beta-blockers or diuretics in patients with left ventricular (LV) hypertrophy *(Williams et al 2018)*. However, in general, calcium channel blocking agents are not recommended for the routine treatment of heart failure *(Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2016, Yancy et al 2017)*, although, some guidelines agree that some dihydropyridine calcium channel blockers may be used in certain co-morbid conditions if the patient has preserved LV function *(Ponikowski et al 2016).*
- In November 2017, the American College of Cardiology (ACC)/American Heart Association (AHA) released the 2017 Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults. For initial first-line therapy for stage 1 hypertension, they list thiazide diuretics, calcium channel blockers, and ACE inhibitors or ARBs. In African American adults with hypertension but without heart failure or CKD, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker. Two or more antihypertensive medications are recommended to achieve a BP target of < 130/80 mm Hg in most adults, especially in African American adults, with hypertension *(Whelton et al 2017)*.
- In August 2017, the American Academy of Pediatrics (AAP) published practice guidelines for screening and management of high blood pressure in children and adolescents. In hypertensive children and adolescents who have failed lifestyle modifications (particularly those who have LV hypertrophy on echocardiography, symptomatic hypertension, or stage 2 hypertension without a clearly modifiable factor [eg, obesity]), the guidelines recommend initiating pharmacologic treatment with an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic *(Flynn et al 2017).*

- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required *(Fihn et al 2012, Fihn et al 2014, O'Gara et al 2013, Montalescot et al 2013).* Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful *(Montalescot et al 2013, Amsterdam et al 2014)*. Other guidelines recommend long-acting calcium channel blockers and nitrates as a treatment option for coronary artery spasm. For vasospastic (Prinzmetal) angina, guidelines recommend calcium channel blockers alone or in combination with nitrates *(Amsterdam et al 2014).*
- For the treatment of aneurysmal SAH, oral nimodipine is recommended to reduce poor outcome related to SAH *(Connolly et al 2012, Diringer et al 2011).*
- For patients with ventricular tachycardias, non-dihydropyridine calcium channel blockers have a limited role and administration of these agents can lead to further cardiovascular decompensation (*Al-Khatib et al 2017)*. Verapamil is effective in treating idiopathic interfascicular reentrant left ventricular tachycardia.

SAFETY SUMMARY

Dihydropyridine

- All of the dihydropyridine calcium channel blocking agents are contraindicated in patients with hypersensitivity to any component of the medication. Nicardipine is contraindicated in patients with advanced aortic stenosis. The Adalat CC formulation of nifedipine is contraindicated in patients with cardiogenic shock and in patients who are concomitantly using strong CYP450 inducers such as rifampin. Nimodipine capsule is contraindicated for concomitant administration with strong CYP3A4 inhibitors such as some macrolide antibiotics, some anti-HIV protease inhibitors, some azole antimycotics and some antidepressants because of risk of significant hypotension.
- Intravenous administration of the contents of nimodipine capsules has resulted in serious adverse consequences including death, cardiac arrest, cardiovascular collapse, hypotension and bradycardia. As such, nimodipine capsules have a boxed warning against the use of nimodipine capsules for intravenous administration.
- Hypotension may occur occasionally during the initial titration or with dosage increases, and hence, blood pressure should be monitored during initial administration and titration. Dihydropyridines, specifically felodipine and nisoldipine, should be used cautiously in patients with congestive heart failure.
- Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure and as a result, patients with heart failure should be monitored carefully.
- Caution should be exercised when using dihydropyridine calcium channel blockers in patients with impaired hepatic function or reduced hepatic blood flow because these agents are extensively metabolized by the liver.
- In general, monitoring should be performed for blood pressure (with initiation and titration), heart rate and anginal pain. Patients should also be monitored for signs and symptoms of edema.

- Consensi (amlodipine/celecoxib) carries a boxed warning for the risk of serious cardiovascular and gastrointestinal (GI) events. Consensi is contraindicated in the setting of coronary artery bypass surgery. The celecoxib component is associated with serious GI adverse events, such as bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

Non-dihydropyridine

- Diltiazem is contraindicated in patients with i) acute myocardial infarction and pulmonary congestion documented by X-ray on admission, ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, and v) sick sinus syndrome except in the presence of a functioning ventricular pacemaker. Verapamil is contraindicated in patients with i) atrial fibrillation or flutter and an accessory bypass tract (Wolff-Parkinson-White, Lown-Ganong-Levine syndromes), ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, v) severe left ventricular dysfunction, and vi) sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- The precautions for diltiazem include the following: may have an additive effect on heart rate with concomitant use of beta blockers or digitalis; dermatologic reactions leading to erythema multiforme and/or exfoliative dermatitis have been reported; increased risk of toxicity with hepatic and/or renal impairment; hypotension; impaired ventricular function and worsening congestive heart failure have also been reported. The precautions for verapamil include the following: concomitant use of a beta blocker in patients with any degree of ventricular dysfunction and concomitant use of quinidine in patients with hypotrophic cardiomyopathy should be avoided; congestive heart failure may occur; elevated liver enzymes, particularly serum transaminase levels, have been reported; first-degree AV block, marked, or progression to second- or third-degree block may occur; hepatic function impairment may occur; sinus bradycardia, pulmonary edema, severe hypotension, second-degree AV block, sinus arrest, and death have been reported in patients with hypertrophic cardiomyopathy; hypotension and/or dizziness may occur; pulmonary edema may occur.
- In general, patients taking non-dihydropyridine calcium channel blocking agents should have their blood pressure monitored weekly during the initial period of titration. Heart rate and anginal pain should also be monitored. Patients should have their liver function monitored periodically. Electrocardiogram (ECG) should be monitored for PR interval prolongation in patients with impaired renal or hepatic function using verapamil. If the medication is being used for arrhythmia, then ECG and reduction in signs and symptoms should be monitored.
- The common adverse effects of diltiazem include bradyarrhythmia, cough, dizziness, fatigue, headache and peripheral edema. The common adverse effects of verapamil include constipation, dizziness, edema, headache, hypotension, influenza-like symptoms, pharyngitis, and sinusitis.

(Facts and Comparisons 2018, Micromedex 2.0 2018)

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration - Dihydropyridine

Drug	Available Formulations	Usual Recommended Frequency	Comments
Amlodipine	Oral tablets	Angina pectoris (chronic stable and vasospastic): Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily CAD: Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension:	Doses in excess of 5 mg daily have not been studied in pediatric patients. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Tablet: initial, 5 mg once daily; maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension in children 6 to 17 years of age: Tablet: initial, 2.5 mg once daily; maintenance, 2.5 to 5 mg once daily; maximum, 5 mg once daily	
Consensi (amlodipine/celecoxib)	Oral tablets	Hypertension and osteoarthritis: Initial, 5 mg/200 mg once daily (or 2.5 mg/200 mg in small, elderly, or frail patients or those with hepatic impairment); titrate to 5 mg/200 mg or 10 mg/200 mg once daily as needed.	The lowest effective dose of celecoxib for the shortest duration should be used Consensi may be substituted for its individual components
Felodipine	Oral extended-release tablets	Hypertension: Extended-release tablet: initial, 5 mg once daily; maintenance, 2.5 to 10 mg once daily	Dose adjustments should occur generally at intervals of not less than 2 weeks. Should be swallowed whole and not crushed or chewed; take without food or with a light meal
Isradipine	Oral capsules	Hypertension: Capsule: initial, 2.5 mg twice daily; maximum, 20 mg/day	Dose adjustments should occur in increments of 5 mg/day at 2 to 4 week intervals.
Nicardipine	Oral capsules	Angina pectoris (chronic stable): Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily Hypertension: Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily	Allow at least 3 days before increasing the dose to ensure achievement of steady state plasma drug concentrations (capsule formulation).
Nifedipine	Immediate-release capsules Extended-release tablets	Angina pectoris (chronic stable): Capsule: initial, 10 mg 3 times daily; maintenance, 10 to 20 mg 3 times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg once daily; maximum, 90 mg/day Angina pectoris (vasospastic): Capsule: initial, 10 mg 3 times daily; maintenance, 20 to 30 mg 3 to 4 times daily; maximum, 180 mg/day	Titration should proceed over a 7- to 14-day period. Extended-release tablets should be swallowed whole, not bitten or divided and should be taken on an empty stomach; co-administration with grapefruit juice should be avoided.

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Extended-release tablet: initial, 30 or 60 mg once daily; maximum, 90 mg/day Hypertension: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day	
Nimodipine	Oral capsules Oral solution	Subarachnoid hemorrhage: Capsule: 60 mg every 4 hours for 21 consecutive days Oral solution: 20 mL (60 mg) every 4 hours for 21 consecutive days	Dosing should be started within 96 hours of subarachnoid hemorrhage. Capsules should be swallowed whole with a little liquid and oral solution should only be administered enterally, preferably not less than 1 hour before or 2 hours after meals; grapefruit juice should be avoided; capsules should not be administered intravenously or by other parenteral routes.
Nisoldipine	Extended-release tablets	Hypertension: Extended-release tablet: initial, 20 mg once daily; maintenance, 20 to 40 mg/day; maximum, 60 mg/day Extended-release tablet (Sular and its generics): initial, 17 mg once daily; maintenance, 17 to 34 mg once daily; maximum, 34 mg once daily	Dose adjustments should occur at intervals of not less than 1 week. Extended-release tablets should be swallowed whole, not bitten, divided or crushed; should be taken on an empty stomach (1 hour before or 2 hours after a meal); grapefruit products should be avoided; administration with a high fat meal can lead to excessive peak drug concentration and should be avoided.

See the current prescribing information for full details

Table 5. Dosing and Administration – Non-dihydropyridine

Drug	Available Formulations	Usual Recommended Frequency	Comments
Diltiazem	Extended-release capsules Extended-release tablets	Angina pectoris (chronic stable): Extended-release capsule: initial, 120 or 180 mg once daily;	Tablet formulation should be taken before meals and at bedtime. Tiazac (extended-release) capsule formulation

Drug	Available Formulations	Usual Recommended Frequency	Comments
	Tablets	maintenance, 180 to 540 mg once daily; maximum, 540 mg once daily Extended-release tablet: initial, 180 mg once daily; maximum, 360 mg once daily Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses) <u>Angina pectoris (due to coronary artery spasm):</u> Extended-release capsule (Cardizem CD): initial, 120 or 180 mg once daily; maintenance, adjust dosage to each patient's needs up to 480 mg once daily Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses) <u>Hypertension</u>: Extended-release capsule: initial, 120 to 240 mg once daily; maintenance, 120 to 540 mg once daily; maximum, 540 mg once daily Extended-release tablet: initial, 180 to 240 mg once daily, although some patients may respond to lower doses; maximum, 540 mg once daily	may also be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents. Cardizem LA (extended-release) tablets should be swallowed whole and not chewed or crushed.
Verapamil	Extended-release capsules Extended-release tablets Sustained-release capsules Tablets	<u>Angina pectoris (chronic stable, unstable, and vasospastic):</u> Tablet: maintenance, 80 to 120 mg 3 times daily <u>Arrhythmias:</u> Tablet: maintenance, 240 to 320 mg/day, divided in 3 to 4 doses; maximum, 480 mg/day <u>Hypertension</u>: Sustained-release capsule: initial, 120 to 240 mg once daily; maintenance, 180 mg to 480 mg/day; maximum, 480 mg/day Extended-release capsule: initial, 100 mg to 200 mg once daily at bedtime; maintenance, 200 mg to	Calan 80 mg tablets are scored and can be divided into halves to provide a 40 mg dose. Calan SR should be administered with food and if needed the caplets can be divided in half without compromising the sustained-release properties of the drug. Verelan and Verelan PM capsules should not be crushed or chewed and they may be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete

Drug	Available Formulations	Usual Recommended Frequency	Comments
		400 mg once daily; maximum, 400 mg/day Extended-release tablet: initial, 120 to 180 mg in the morning; maintenance, 180 to 480 mg/day in 1 to 2 divided doses, maximum, 480 mg/day Tablet: initial, 80 mg 3 times daily; maintenance, 360 to 480 mg/day divided (3 to 4 times daily); maximum, 480 mg/day	swallowing of the capsule contents.

See the current prescribing information for full details

CONCLUSION

- All of the dihydropyridines, with the exception of nimodipine, are approved for the treatment of hypertension. Amlodipine, nicardipine, and nifedipine are also indicated for the treatment of angina. Additionally, amlodipine reduces the risk of hospitalization due to angina and reduces the risk of coronary revascularization procedures in patients with recently documented CAD. Consensi, a combination of amlodipine and celecoxib, was recently FDA-approved for the treatment of patients with hypertension and osteoarthritis. Nimodipine improves the neurological outcome of patients with an SAH by reducing the incidence and severity of ischemic deficits in patients with ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established.
- The dihydropyridines have been shown to favorably affect cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, ACE inhibitors, and ARBs in select diseases. However, the ALLHAT study demonstrated that patients of African or Caribbean descent (Black) had a lower rate of stroke when therapy was initiated with a calcium channel blocker compared to an ACE inhibitor.
- There is insufficient evidence to support that one dihydropyridine calcium channel blocker is safer or more efficacious than another, although most clinical trial experience has been with amlodipine and nifedipine.
- The non-dihydropyridine calcium channel blocking agents are approved for the treatment of angina, arrhythmias, and hypertension. Diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.
- Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure. Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo. Evidence suggests that there is no overall difference between diltiazem and verapamil compared to other antihypertensive agents (beta blockers, diuretics) in reducing cardiovascular events and mortality in patients with hypertension. There is insufficient evidence to support that one non-dihydropyridine calcium channel blocking agent is safer or more efficacious than another.
- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium-channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required. Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful. Long-acting calcium-channel blocking agents are also recommended in patients with variant angina and for patients with coronary artery spasm(s), known as vasospastic angina, with or without nitrates.
- Treatment options for atrial fibrillation include ventricular rate control or drug therapy to maintain sinus rhythm. The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control

strategies. Beta blockers or non-dihydropyridine calcium channel blockers are recommended for patients with persistent, paroxysmal, or permanent atrial fibrillation; however, in patients with decompensated heart failure or pre-excitation and atrial fibrillation, non-dihydropyridine calcium channel blockers should not be administered. Propafenone or flecainide ("pill-in-the-pocket") in combination with a beta blocker or non-dihydropyridine calcium channel blocker are options to terminate atrial fibrillation outside of a hospital for select patients. Non-dihydropyridine calcium channel blockers may also be prescribed as monotherapy or in combination with other treatment in patients with atrial fibrillation and co-morbid hypertrophic cardiomyopathy, certain acute coronary syndrome patients, or chronic obstructive pulmonary disease. In cases of ventricular and supraventricular arrhythmias, intravenous non-dihydropyridine calcium channel blockers are recommended. Oral non-dihydropyridine calcium channel blockers may be used for the chronic management of patients with symptomatic supraventricular tachycardia without ventricular excitation.

- Caution is advised with use in elderly patients with systolic heart failure; non-dihydropyridine calcium channel blockers have the potential to promote fluid retention and/or exacerbate heart failure.

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INTRODUCTION

Central Precocious Puberty (CPP)

- Puberty is a period of physical, hormonal, and psychological transition from childhood to adulthood, with accelerated linear growth and achievement of reproductive function *(Britto et al 2016)*. Pubertal timing is influenced by complex interactions of genetic, nutritional, environmental, and socioeconomic factors *(Macedo et al 2014).*
  - While there has been extensive discussion with regard to the definition of puberty, most pediatricians give an age limit of 8 years in girls and 9 to 9.5 years in boys for the lower limit of normal pubertal development *(Carel et al 2004)*.
- CPP is characterized by the early onset of pubertal manifestations in girls and boys *(Carel et al 2004)*.
  - CPP is caused by the disruption of the hypothalamic-pituitary-gonadal axis, which results in the early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion *(Carel and Léger 2008).*
  - These manifestations consist primarily of breast development in girls and testicular enlargement in boys *(Carel and Léger 2008)*.
- GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion and finally suppression of the release of gonadal sex hormones *(Fuqua 2013, Klein et al 2016).*
  - There are several GnRH agonists available in varying doses and formulations. Depot formulations are generally preferred due to improved compliance *(Guaraldi et al 2016).* GnRH agonists that are Food and Drug Administration (FDA)-approved for the treatment of CPP include:
    - Lupron Depot-Ped (leuprolide), available as monthly or every 3 month intramuscular (IM) injections.
    - Synarel (nafarelin) intranasal spray, a short-acting spray that requires multiple inhalations daily.
    - Supprelin LA (histrelin), available as a 1-year subcutaneous (SC) implant device.
    - Triptodur (triptorelin), administered as a single IM injection every 24 weeks. Of note, Trelstar (triptorelin pamoate) IM injection was the first FDA-approved triptorelin formulation; it was used off-label to treat CPP until Triptodur was made available in 2017 *(Klein et al 2016)*.
  - The optimal time to discontinue a GnRH agonist has not been established, but retrospective analyses suggest that discontinuation around the age of 11 years is associated with optimal height outcomes *(Carel and Léger 2008).*

Endometriosis

- Endometriosis is a chronic, estrogen-dependent disorder characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity *(Brown and Farquhar 2015, Giudice 2010, Schenken 2018).*
  - Endometriosis affects 6% to 10% of women of reproductive age; it is present in approximately 38% of women with infertility and in up to 87% of women with chronic pelvic pain (*Armstrong 2010).*
  - The clinical presentation of endometriosis is highly variable and ranges from debilitating non-menstrual pelvic pain (NMPP) to infertility to no symptoms. Patients can present with dysmenorrhea, abdominal or pelvic pain, dyspareunia, and infertility *(Schrager et al 2013).*
- Although several pharmacological options are available for the treatment of endometriosis, none provide a cure, long-term relief of symptoms, or resolution of infertility.
  - GnRH agonists, such as Zoladex 3.6 mg (goserelin), Lupaneta Pack (leuprolide acetate/norethindrone), Lupron Depot 3.75 mg or Lupron Depot 11.25 mg 3-month injection (leuprolide), and Synarel (nafarelin) are recommended as second-line pharmacologic therapy after non-steroidal anti-inflammatory drugs (NSAIDS) and oral contraceptives *(American College of Obstetricians and Gynecologists [ACOG] 2010, Armstrong 2010, American Society for Reproductive Medicine [ASRM] 2014).*
    - GnRH agonists are generally not recommended as a long-term therapy, due to the potential for dose and duration-dependent bone loss *(ACOG 2010).*
  - Orilissa (elagolix), the first and only available oral GnRH antagonist, was FDA-approved in July 2018 for the management of moderate to severe pain associated with endometriosis.
    - Elagolix exerts its effect by rapidly suppressing the pituitary ovarian hormones and produces a dose-dependent suppression of ovarian estrogen production that varies from partial to full suppression.
    - Similar to GnRH agonists, elagolix is indicated for short-term use, ie, 6 months for patients taking 200 mg orally twice daily (for coexisting dyspareunia) and 24 months for patients taking 150 mg orally daily.
    - Other GnRH antagonists, such as Cetrotide (cetrorelix), Firmagon (degarelix), and ganirelix are only available as an injectable formulation; however, these agents are not FDA-approved for the treatment of endometriosis.

Uterine fibroids

- Uterine fibroids, also known as uterine leiomyomas or myomas, are monoclonal tumors that arise from the uterine smooth-muscle tissue *(Sohn et al 2018).*
  - It is estimated that 60% of women of reproductive age are affected, and 80% of women develop the disease during their lifetime.
  - Heavy or prolonged menstrual bleeding, abnormal uterine bleeding, resultant anemia, pelvic pain, infertility, and/or recurrent pregnancy loss are generally associated with uterine fibroids.

- The majority of women with uterine fibroids either remain asymptomatic or develop symptoms gradually over time. When patients are symptomatic, the number, size, and/or location of fibroids are critical determinants of its clinical manifestations.

- Although curative treatment of uterine fibroids relies on surgical therapies, medical treatments are considered first-line to preserve fertility and avoid or delay surgery. Lupron Depot 3.75 mg is the only GnRH agonist that has been FDA-approved for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata *(Sohn et al 2018).*
  - Lupron Depot 3.75 mg is administered concomitantly with iron therapy. The clinician may wish to consider a 1-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. Lupron may be added if the response to iron alone is considered inadequate.

Infertility

- Infertility is typically defined as the inability to achieve pregnancy after 1 year of unprotected sexual intercourse *(Anwar and Anwar 2016).*
  - Infertility is common with a prevalence estimated at 9 to 18% *(Hanson et al 2017).*
  - Patients who are struggling to conceive report feelings of depression, anxiety, isolation, and loss of control *(Rooney and Domar 2018).*
  - An estimated 50% of infertility cases among heterosexual couples are attributable to female factors, 20% to male factors, and 30% to combined female and male factors or unknown factors (*Centers for Disease Control [CDC] 2018*, *Fauser 2018, Shreffler et al 2017*).
    - The most common causes of female infertility include ovulatory disorders (most commonly due to polycystic ovary syndrome [PCOS]), endometriosis, pelvic adhesions, tubal blockage, other tubal abnormalities, and hyperprolactinemia.
    - The most common causes of male infertility are low concentrations, poor motility, and abnormal morphology of sperm.
- Pharmacologic agents used in anovulatory women to induce or control ovulation include clomiphene (the most widely used fertility treatment), letrozole (off-label indication), gonadotropins (FSH products and human chorionic gonadotropin [hCG] products), and GnRH antagonists (cetrorelix and ganirelix). Other pharmacological agents used include metformin (in PCOS patients) and dopamine agonists (for hyperprolactinemic anovulation) *(Seli and Arici 2018).*
  - GnRH antagonists, such as cetrorelix and ganirelix, are used in conjunction with assisted reproductive technology (ART), which is defined as any fertility treatment in which either eggs or embryos are handled. The 2 most common ART procedures utilized in the U.S. are in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) *(CDC 2018).*
- Of note, all cancer indications for GnRH agonists are outside of the scope of this review.
- Medispan Class: Gonadotropin Releasing Hormone Agonists; Gonadotropin Releasing Hormone Antagonist

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cetrotide (cetrorelix) 0.25 mg injection	-
ganirelix 250 mcg injection	✔
Lupaneta Pack (leuprolide acetate 3.75 mg depot suspension; norethindrone acetate 5 mg tablets and leuprolide acetate 11.25 mg depot suspension; norethindrone acetate 5 mg tablets)	-
Lupron Depot-Ped (leuprolide acetate for depot suspension) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25 mg, 30 mg (3-month)	-
Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg (monthly), 11.25 mg (3-month)	-
Orilissa (elagolix) 150 mg, 200 mg tablets	-
Supprelin LA (histrelin) 50 mg implant	-
Synarel (nafarelin) nasal spray	-
Triptodur (triptorelin) 22.5 mg extended-release suspension	-
Zoladex (goserelin) 3.6 mg implant	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cetrotide (cetrorelix)	ganirelix	Lupaneta Pack (leuprolide/ norethindrone)	Lupron (leuprolide) Depot	Lupron Depot-Ped (leuprolide)	Orilissa (elagolix)	Supprelin LA (histrelin)	Synarel (nafarelin) intranasal spray	Triptodur (triptorelin)	Zoladex (goserelin) implant
Treatment of children with CPP					✔		✔	✔	✔	
Management of endometriosis, including pain relief and reduction of endometriotic lesions				✔				✔		✔
Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding										✔
Initial management of the painful symptoms of endometriosis			✔	✔ †						
Management of recurrence of endometriosis symptoms			✔	✔ †						
Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata				✔ ‡						
Management of moderate to severe pain associated with endometriosis						✔				
Inhibition of premature LH surges in women undergoing controlled ovarian stimulation*	✔	✔								

Abbreviations: CPP = central precocious puberty; LH = luteinizing hormone

*The word “stimulation” is used in the cetrorelix indication, while the word “hyperstimulation” is used in the ganirelix indication.

† In combination with norethindrone acetate 5 mg tablet taken once daily

‡ Concomitantly with iron therapy

(*Prescribing information: Cetrotide 2018, ganirelix 2018, Lupaneta Pack 2015, Lupron Depot-Ped 2017, Lupron Depot 2018, Orilissa 2018, Supprelin LA 2017, Synarel 2017, Triptodur 2018, Zoladex 2016*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

CPP

- The choice of GnRH agonist formulation depends on patient and clinician preference. These preparations have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis (*Harrington and Palmert 2017)*.
  - In a multicenter trial with histrelin implant for the treatment of CPP, peak LH and estradiol or testosterone were effectively suppressed, and no significant adverse events (AEs) were noted. Positive long-term safety and efficacy data were reported in 2 studies (a 2- and a 6-year study) that evaluated long-term hormonal suppression in CPP patients post histrelin implant insertion. More specifically, peak LH and FSH levels remained suppressed in both the 2- and the 6-year trial *(Harrington and Palmert 2017, Rahhal et al 2009, Silverman et al 2015*).
  - A randomized controlled trial (RCT) with 54 patients compared the 1-month (7.5 mg) and 3-month (11.25 mg and 22.5 mg) leuprolide formulations for the treatment of CPP. There were more patients with inadequate pubertal suppression in the 11.25 mg 3-month leuprolide depot group (as measured by mean stimulated LH levels > 4 IU/L) compared to the 7.5 mg monthly and 22.5 mg 3-month groups. Mean LH and FSH levels in the 22.5 mg 3-month dose group were not different from the monthly depot injections. No differences in estradiol levels, growth velocity, or bone age progression were observed between the dosing groups *(Fuld et al 2011).*

- In a phase 3, randomized, open-label (OL) study (N = 84), leuprolide 11.25 mg 3-month depot was compared to leuprolide 30 mg 3-month depot in children with CPP. There were 9 treatment failures (peak stimulated LH > 4 IU/L) in the 11.25 mg group and 2 in the 30 mg group. Basal sex steroid suppression, growth rates, pubertal progression, bone age advancement, and AEs were similar between both doses *(Lee et al 2012).*
- Clinical trials with nafarelin demonstrated a reduction in the peak response of LH to GnRH stimulation from a pubertal response to a pre-pubertal response within 1 month of treatment. Additionally, breast development was arrested or regressed in 82% of girls, while genital development was arrested or regressed in 100% of boys *(Synarel Product Information 2017)*.
- The efficacy of triptorelin 6-month injection was evaluated in an OL, single-arm clinical trial in females and males with CPP, ages 2 to 9 (N = 44). At 12 months, 97.7% of patients achieved pre-pubertal LH levels. Mean stimulated FSH and mean basal FSH levels were also lower at 12 months, compared to baseline. Additionally, the Tanner stage (a scale of physical development) was stable or reduced (manifested by a reduction in physical development) in 88.6% of patients *(Klein et al 2016)*.

Endometriosis

- A Cochrane Review meta-analysis of 41 trials (N = 4935) in patients with endometriosis compared the safety and effectiveness of GnRH agonists to no treatment, placebo, danazol, intrauterine progestins, or other GnRH agonists (*Brown et al 2010*).
  - GnRH agonists were more effective than no treatment or placebo.
  - There was no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis.
  - There was a benefit in overall resolution for GnRH agonists compared with danazol.
  - There was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel.
  - More AEs were reported in the GnRH agonist group.
  - No route of administration for GnRH agonists appeared to be superior to another.
- A RCT (N = 315) compared the efficacy of goserelin (3.6 mg every 28 days) to danazol 400 mg orally twice daily in females with endometriosis. Goserelin was found to be similar in efficacy and safety as compared to danazol. Both treatments significantly reduced mean subjective signs and symptoms scores during and after treatment *(Rock et al 1993).*
- A meta-analysis of 13 RCTs (N = 945) evaluated the effectiveness of GnRH agonists for endometriosis, with and without add-back therapy. Add-back therapy refers to the addition of hormone replacement therapy to GnRH agonists, in order to avoid AEs that are caused by GnRH agonist-induced hormone suppression. The evidence suggested that add-back therapy was more effective for symptomatic relief than GnRH agonists alone, both immediately after treatment and at 6 months. Add-back therapy increased estrogen levels, but did not reduce the efficacy of GnRH agonists for treating dysmenorrhea and dyspareunia *(Wu et al 2014).*
- The FDA approval of elagolix was based on the results of the Elaris Endometriosis trials, EM-I and EM-II, which were 2 phase 3, 6-month, double-blind (DB), placebo-controlled (PC), RCTs in women 18 to 49 years of age with moderate to severe endometriosis. Three treatment groups, elagolix 150 mg orally daily (n = 475), elagolix 200 mg orally twice daily (n = 477), and placebo (n = 734) were evaluated for efficacy and safety. (*Orilissa Dossier 2018, Taylor et al 2017*).
  - Patients were considered responders if they experienced a reduction of ≥ -0.81 from baseline score in dysmenorrhea pain and a reduction of ≥ -0.36 from baseline score in NMPP, and no increase in rescue analgesic use. At months 3 and 6, a significantly greater proportion of women in both elagolix dose groups met the clinical response criteria for the co-primary endpoints of dysmenorrhea and NMPP ($p < 0.001$).
  - The most common AEs were hot flushes, headache, and nausea. Bone mineral density (BMD) loss was significantly greater than placebo in the 150 mg daily and 200 mg twice daily groups at 6 months. Liver and kidney function parameters/analytes exhibited sporadic statistically significant changes throughout treatment but none of the differences between the elagolix doses and placebo were considered clinically significant. Additionally, there was 1 suicide reported in the EM-II trial, which was related to overdose with multiple non-trial medications.
  - Patients who completed EM-I or EM-II continued on to 1 of the 2 phase 3 extension trials, EM-III or EM-IV. The duration of treatment was 6 months (with continuation of the same elagolix dose from the 6-month EM-I/EM-II trials, for a total of 12 months of treatment), followed by a 12 month observation period *(Surrey et al 2018).*
    - The data from EM-III and EM-IV demonstrated that the response rates for dysmenorrhea and NMPP were maintained in women who continued treatment with elagolix. A decrease of 5 to 8% in lumbar spine BMD after 12 months of continuous treatment occurred in 2 to 3% of the 150 mg daily group and in 26 to 30% of the 200 mg twice daily group. The percentage of women with > 8% decrease in BMD in the lumbar spine, total hip, or femoral neck was 2 to 8% in the 150 mg daily group and 21% in the 200 mg twice daily group.

Uterine fibroids

- PEARL II was a DB, non-inferiority trial that included 307 patients randomly assigned to 5 or 10 mg of ulipristal vs leuprolide acetate depot, for 3 months of treatment. Uterine bleeding was controlled in 90% of patients receiving 5 mg of ulipristal acetate, in 98% of those receiving 10 mg of ulipristal acetate, and in 89% of those receiving leuprolide acetate, for differences (as compared with leuprolide acetate) of 1.2% (95% confidence interval [CI], -9.3 to 11.8) for 5 mg of ulipristal acetate and 8.8% (95% CI, 0.4 to 18.3) for 10 mg of ulipristal acetate. Median times to amenorrhea were 7 days for patients receiving 5 mg of ulipristal acetate, 5 days for those receiving 10 mg of ulipristal acetate, and 21 days for those receiving leuprolide acetate. Moderate-to-severe hot flashes were reported for 11% of patients receiving 5 mg of ulipristal acetate, for 10% of those receiving 10 mg of ulipristal acetate, and for 40% of those receiving leuprolide acetate ($p < 0.001$ for each dose of ulipristal acetate vs leuprolide acetate) *(Donnez et al 2012).*

Infertility

- A meta-analysis of 73 RCTs (N = 12,212) compared the efficacy and safety of GnRH antagonists (cetrorelix or ganirelix) to long-course GnRH agonist regimens in patients using these agents for controlled ovarian hyperstimulation in ART (*Al Inany et al 2016*).
  - There was no evidence of a difference in live birth rate between GnRH antagonist and long-course GnRH agonist regimens in 2303 patients (odds ratio [OR] = 1.02; 95% CI, 0.85 to 1.23; 12 RCTs; $I^2 = 27\%$).
  - GnRH antagonists were associated with a lower incidence of any grade of ovarian hyperstimulation syndrome (OHSS) compared to GnRH agonists in 7944 patients (OR = 0.61; 95% CI, 0.51 to 0.72; 36 RCTs; $I^2 = 31\%$).
  - There was no difference in miscarriage rate per woman between the GnRH antagonist group and GnRH agonist group as evaluated in 7082 patients (OR = 1.03; 95% CI, 0.82 to 1.29; 34 RCTs; $I^2 = 0\%$).

CLINICAL GUIDELINES

CPP

- American Academy of Pediatrics (AAP): Evaluation and referral of children with signs of early puberty *(Kaplowitz and Bloch 2016)*
  - Treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant.
  - If suppression of menses is the primary concern (rather than preservation of linear growth potential), then medroxyprogesterone depot IM injection every 3 months can be considered.
  - Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.

Endometriosis

- ACOG: Updates Guideline on Diagnosis and Treatment of Endometriosis (*ACOG 2010, Armstrong 2010)*
  - Progestins, danazol, extended-cycle combined oral contraceptives, NSAIDs, and GnRH agonists can be used for the initial treatment of pain in women with suspected endometriosis.
    - However, recurrence rates are high after the medication is discontinued. Empiric therapy with another suppressive medication is an option. For example, empiric therapy with a 3-month course of a GnRH agonist is appropriate if the initial treatment with an oral contraceptive or NSAID is unsuccessful.
  - In women with a history of endometriosis who wish to preserve their fertility, NSAIDs or combined oral contraceptives can be used to treat recurrent pain.
    - Oral or depot medroxyprogesterone acetate is also an effective treatment option.
    - If none of the above therapies is successful, then progestins, GnRH agonists, and androgens may be used.
    - The use of Mirena (levonorgestrel-releasing intrauterine system) reduces pelvic pain associated with endometriosis, but AEs are common.
  - If treatment with a GnRH agonist is successful, the use of an add-back regimen can reduce or eliminate bone mineral loss and provide symptomatic relief without reduction in pain relief.
    - Add-back regimens have been used in women undergoing long-term therapy; they may include progestins alone, low dose progestins, progestins plus bisphosphonates, or estrogens.
- ASRM: Treatment of pelvic pain associated with endometriosis: A committee opinion *(ASRM 2014)*
  - Endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.
  - Definitive diagnosis via laparoscopic surgery is recommended, with the option of treating visible endometriosis at that time.
  - Pharmacologic therapies such as NSAIDs, combined hormonal contraceptives, progestins, danazol, and GnRH agonists are recommended for the treatment of endometriosis.

- Surgical treatment with removal of the uterus and ovaries (total hysterectomy and bilateral salpingo-oophorectomy) is recommended in women with disabling symptoms who have completed childbearing and have failed to respond to multiple alternative regimens.

Uterine fibroids

- Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program: Management of Uterine Fibroids *(AHRQ 2017)*
  - GnRH agonists, mifepristone, ulipristal, and uterine artery embolism reduce fibroid size, and improve symptoms and quality of life. Myomectomy and hysterectomy also improve quality of life.
    - Moderate-strength evidence suggests that GnRH agonists (with and without add-back therapy) reduce the size of fibroids, the overall size of the uterus, and bleeding symptoms.
    - Low-strength evidence suggests that fibroid-related quality of life improves with GnRH agonists (with and without add-back therapy).
  - For women in their 30s, the chance of needing retreatment for fibroids within the next 2 years was 6 to 7% after medical treatment or myomectomy and 44% after urinary artery embolization (UAE). For older women, the chance was 9 to 19% after medical treatment or UAE and 0% after myomectomy.
- ACOG: Alternatives to hysterectomy in the management of leiomyomas *(ACOG 2008)*
  - GnRH agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and postoperative pain when given for 2 to 3 months preoperatively. Benefits of preoperative GnRH agonist administration should be weighed against their cost and side effects for individual patients.
  - Abdominal myomectomy is a safe and effective alternative to hysterectomy for the treatment of women with symptomatic leiomyomas.
  - Hormone therapy may cause some modest increase in uterine leiomyoma size but does not appear to have an impact on clinical symptoms. Therefore, this treatment option should not be withheld from women who desire or need such therapy.

Infertility

- The 2018 ASRM guidelines for PCOS and a 2016 World Health Organization (WHO)-funded PCOS guidelines make the following recommendations *(Balen et al 2016, Teede et al 2018):*
  - Although off-label, letrozole is recommended as first-line therapy for ovulation induction in women with PCOS and anovulatory infertility.
  - Clomiphene is also considered a first-line treatment option in women with PCOS and anovulatory infertility. Per the ASRM guidelines, clomiphene could be used in preference to metformin, when treating an obese patient (BMI ≥ 30 kg/m^2). Both guidelines recommend the use of clomiphene in combination with metformin for PCOS patients with clomiphene resistance.
  - Gonadotropins can be used as second-line pharmacological agents in women with PCOS and anovulatory infertility who have failed oral ovulation induction therapy (clomiphene and/or metformin). No significant differences in efficacy between preparations of gonadotropin agents have been noted.
  - A GnRH antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle over a GnRH agonist long protocol. The preferred protocol is known to reduce the duration of stimulation, total gonadotropin dose, and incidence of OHSS.

SAFETY SUMMARY

Contraindications

- Pregnancy
- Cetrotide carries the additional contraindication of severe renal impairment.
- Elagolix carries additional contraindications for known osteoporosis, severe hepatic impairment (Child-Pugh C), and concomitant use with strong OATP1B1 inhibitors (eg, cyclosporine and gemfibrozil).
- Lupaneta Pack carries additional contraindications, including undiagnosed uterine bleeding, breast-feeding, known/suspected/history of breast or other hormone-sensitive cancers, thrombotic/thromboembolic disorders, and liver tumors/liver disease.
- Lupron Depot carries additional contraindications, including undiagnosed abnormal uterine bleeding and breast-feeding.
- Nafarelin carries an additional contraindication for undiagnosed vaginal bleeding.

Warnings and Precautions

- An initial rise in gonadotropin and sex steroid levels may be seen during the first 2 to 4 weeks of therapy, due to the initial stimulatory effect of the drug (leuprolide, histrelin, triptorelin).

- Psychiatric events have been reported in patients taking GnRH agonists. Symptoms include crying, irritability, anger, and aggression (elagolix, histrelin, leuprolide, nafarelin, triptorelin). Suicidal ideation is an additional warning with elagolix.
- Convulsions have been observed in patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, or concomitant medications that may be associated with convulsions. Convulsions have also been reported in patients without the conditions mentioned above (leuprolide, histrelin, nafarelin, triptorelin).
- A reduction in BMD may be observed with most of the GnRH agonists/antagonists.
- Ovarian cysts have been reported during the first 2 months of therapy with Synarel and in post-marketing experience with Zoladex. Many, but not all, occurred in women with polycystic ovarian disease. These cystic enlargements may resolve after 4 to 6 weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

Key Adverse Effects

- The common AEs within this medication class (excluding histrelin) include hot flushes/sweats, headache, depression/emotional lability, acne, decreased libido, insomnia, and weight gain.
- Injection site pain was one of the most commonly reported AEs for leuprolide. Implant site reaction, including discomfort, bruising, soreness, pain, tingling, itching, implant area protrusion or swelling, was reported in 51% of patients in clinical trials with histrelin.
- Infections such as bronchitis, gastroenteritis, influenza, nasopharyngitis, otitis externa, pharyngitis, sinusitis, and upper respiratory tract infection were observed with triptorelin.
- In clinical trials, OHSS has been reported in 2.4% of patients treated with ganirelix and in 3.5% of patients treated with cetrorelix.

Drug Interactions

- Concomitant use of elagolix with a strong OATP1B1 inhibitor (eg. cyclosporine and gemfibrozil) is contraindicated.
- Concomitant use of elagolix with strong cytochrome P450 (CYP) 3A inhibitors should be limited to ≤ 1 month for the 200 mg twice daily dose and ≤ 6 months for the 150 mg daily dose. The co-administration of elagolix with inducers of CYP3A may decrease elagolix plasma concentrations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cetrotide (cetrorelix)	0.25 mg injection	SC	3 mg one time dose or 0.25 mg once daily	Dose should be adjusted based on individual response.
ganirelix	250 mcg injection	SC	Once daily	Dose should be adjusted based on individual response.
Lupaneta Pack (leuprolide/ norethindrone)	3.75 mg leuprolide syringe/5 mg norethindrone tablets 11.25 mg leuprolide syringe/5 mg norethindrone tablets	IM	Endometriosis: Leuprolide 3.75 mg monthly or 11.25 mg once every 3 months for up to 6 months and norethindrone once daily for up to 6 months. Retreatment should be considered for up to another 6 months if endometriosis symptoms recur	Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on BMD.
Lupron Depot (leuprolide acetate depot) 3.75 & 11.25 mg	Injection	IM	Endometriosis: 3.75 mg once monthly or 11.25 mg once every 3 months, alone or in combination with norethindrone acetate	Duration of therapy for endometriosis is 6 months; duration of therapy for uterine leiomyomata is up to 3 months.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Uterine leiomyomata: 3.75 mg once monthly or one 11.25 mg injection with concomitant iron therapy; 11.25 mg is indicated only for women for whom 3 months of hormonal suppression is deemed necessary	
Lupron Depot-Ped (leuprolide acetate depot) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25, 30 mg (3-month)	Powder for injection	IM	CPP: Once monthly (7.5 mg, 11.25 mg, or 15 mg), or leuprolide 11.25 mg or 30 mg once every 3 months	The dose of Lupron Depot-Ped should be individualized for each patient. The dose should be increased to the next available dose if adequate hormonal and clinical suppression is not achieved with the fixed dosing starting dose.
Orilissa (elagolix)	Tablets	Oral	Once daily for the 150 mg dose (duration = 24 months); twice daily for the 200 mg dose in patients with co-existing dyspareunia (duration = 6 months)	A lower dose and duration of therapy is required for patients with moderate hepatic impairment (Child-Pugh Class B); elagolix is contraindicated in patients with severe hepatic impairment (Child-Pugh C).
Supprelin LA (histrelin)	Implant	SC	CPP: Once every 12 months	Implant injected in the inner aspect of the upper arm.
Synarel (nafarelin)	Nasal spray	Intranasal	CPP: Twice daily (up to 3 times daily when a dose increase is required) Endometriosis: Twice daily	Sneezing during or immediately after treatment should be avoided, as this may impair drug absorption. For the endometriosis indication, treatment should be started between days 2 and 4 of the menstrual cycle.
Triptodur (triptorelin)	Injection	IM	CPP: Once every 24 weeks	Response (LH levels or serum concentration of sex steroid levels) should be monitored beginning 1 to 2 months post therapy initiation and during therapy as necessary to confirm maintenance of efficacy.
Zoladex (goserelin)	3.6 mg implant	SC	Endometriosis: Once every 28 days for a total of 6 months Endometrial thinning: Once every 28 days for a total of 1 to 2 months	No adjustment necessary in renal or hepatic impairment. For the endometriosis indication, data are limited to patients ≥ 18 years of age treated for 6 months. Retreatment is not recommended.

Abbreviations: BMD = bone mineral density; CPP = central precocious puberty; IM = intramuscular; LH = luteinizing hormone; SC = subcutaneous
See the current prescribing information for full details

CONCLUSION

- CPP is characterized by the early onset of pubertal manifestations in girls and boys.
  - GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (LH and FSH) secretion and finally suppression of the release of gonadal sex hormones.
  - There are several FDA-approved GnRH agonists available in the form of implants, depot injections, and nasal spray. Depot formulations are generally preferred due to improved compliance. These GnRH agonists have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis.
  - According to the AAP 2016 guidelines on the evaluation and referral of children with signs of early puberty, treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant. Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.
- Endometriosis is a common gynecological condition characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity.
  - A Cochrane Review meta-analysis of 41 trials (N = 4935) in patients with endometriosis found no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis. However, a benefit in overall resolution for GnRH agonists compared with danazol was observed. Additionally, there was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel. No route of administration for GnRH appeared to be superior to another.
  - The safety and efficacy of Orilissa (elagolix), a recently approved oral GnRH antagonist, were demonstrated in 2 placebo-controlled studies in 1686 premenopausal women with moderate to severe endometriosis pain. In both studies, a higher proportion of women treated with elagolix were responders vs placebo for dysmenorrhea and NMPP in a dose-dependent manner at month 3 ($p \leq 0.001$ for all comparisons except non-menstrual pelvic pain with elagolix 150 mg once daily in study 2, $p \leq 0.01$).
  - ACOG's 2010 endometriosis guidelines recommend progestins, danazol, extended-cycle combined oral contraceptives, NSAIDs, and GnRH agonists for the initial treatment of pain in women with suspected endometriosis. GnRH agonists can be used empirically in case of recurrence of endometriosis.
  - The 2014 ASRM guidelines recommend a definitive diagnosis via laparoscopic surgery, with the option of treating visible endometriosis at that time. Pharmacologic therapies such as NSAIDs, combined hormonal contraceptives, progestins, danazol, and GnRH agonists are recommended for the treatment of endometriosis.
- Although curative treatment of uterine fibroids relies on surgical therapies, medical treatments are considered first-line to preserve fertility and avoid or delay surgery. Lupron Depot 3.75 mg is the only GnRH agonist that has been FDA-approved for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata.
  - AHRQ's 2017 guidelines for the management of uterine fibroids recommend GnRH agonists to reduce fibroid size and improve symptoms (moderate-strength evidence). Fibroid-related quality of life may also improve with GnRH agonists (low-strength evidence).
- Infertility is a common condition that can have a substantially negative emotional, physical, and financial impact on a couple. GnRH antagonists, such as cetrorelix and ganirelix, may be reserved for second-line treatment to prevent premature LH surges, allowing for controlled ovarian stimulation during ART procedures.
  - The 2018 ASRM guidelines for PCOS and 2016 WHO-funded PCOS guidelines recommend letrozole (off-label) or clomiphene for first-line therapy in women with PCOS who have anovulatory infertility. Gonadotropins are recommended as an option in anovulatory women with PCOS who have failed clomiphene (± metformin).

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INTRODUCTION

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), and uveitis (UV), as well as several less common conditions.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (*Choy et al 2001*). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved 5 originator TNF inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi/Simponi Aria (golimumab), as well as 6 biosimilar TNF inhibitors: Amjevita (adalimumab-atto), Erelzi (etanercept-szzs), Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), Cyltezo (adalimumab-adbm), and Ixifi (infliximab-qbtx). Other agents targeting different cells and cytokines are also FDA-approved for RA treatment. These include Orencia (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell; Rituxan (rituximab), which targets CD20, a molecule that is found on the surface of B-cells; Actemra (tocilizumab) and Kevzara (sarilumab), which have activity directed against the IL-6 receptor; and Kineret (anakinra), which targets the IL-1 receptor. Oral agents on the market, Xeljanz and Xeljanz XR (tofacitinib) and Olumiant (baricitinib), target Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
- Other immunomodulators include Ilaris (canakinumab), which binds to the IL-1ß receptor and is approved to treat JIA; and Entyvio (vedolizumab), which binds to the α4β7 integrin and is approved to treat CD and UC. Otezla (apremilast), an oral, small-molecule phosphodiesterase 4 (PDE-4) inhibitor, and Stelara (ustekinumab), which targets the IL-12 and IL-23 cytokines, are each approved for the treatment of PsA and PsO; Stelara is additionally indicated for the treatment of CD. Cosentyx (secukinumab) and Taltz (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO and PsA; Cosentyx is additionally indicated to treat PsA and AS. Siliq (brodalumab), an IL-17 receptor antagonist, as well as Tremfya (guselkumab) and Ilumya (tildrakizumab-asmn), both IL-23 antagonists, are indicated for selected patients with PsO.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but are not discussed in detail; these include:
    - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); and 4) familial Mediterranean fever (FMF)
    - Kineret for the treatment of CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID)
    - Actemra for giant cell arteritis (GCA) and cytokine release syndrome (CRS).
- Rituxan is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA). These indications will not be discussed in this review.
- Tysabri (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (*Tysabri prescribing information 2018*). Arcalyst (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (*Arcalyst prescribing information 2016*).
- Although FDA-approved, the launch plans for the biosimilar drugs Amjevita (adalimumab-atto), Erelzi (etanercept-szzs), Cyltezo (adalimumab-adbm) and Ixifi (infliximab-qbtx) are pending and may be delayed; therefore, these agents are not currently included in this review. The manufacturer of Ixifi to date does not have plans to launch Ixifi in the United States.
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Biosimilar or Generic Availability	Type of Agent
Actemra (tocilizumab)	Genentech	01/08/2010	-	Human monoclonal antibody targeting the IL-6 receptor
Cimzia (certolizumab)	UCB	04/22/2008	-	TNFα inhibitor
Cosentyx (secukinumab)	Novartis	01/21/2015	-	Human monoclonal antibody to IL-17A
Enbrel (etanercept)	Amgen	11/02/1998	-*	sTNFR fusion protein, TNFα inhibitor
Entyvio (vedolizumab)	Takeda Pharmaceuticals America, Inc.	05/20/2014	-	Human monoclonal antibody binds to the α4β7 integrin
Humira (adalimumab)	AbbVie	12/31/2002	-*	TNFα inhibitor
Ilaris (canakinumab)	Novartis	06/17/2009	-	Human monoclonal antibody that binds to IL-1ß
Ilumya (tildrakizumab-asmn)	Sun Pharma Global	03/20/2018	-	Human monoclonal antibody to IL-23
Inflectra (infliximab-dyyb)	Celltrion/ Hospira/Pfizer	04/05/2016	N/A†	TNFα inhibitor
Kevzara (sarilumab)	Sanofi Genzyme Regeneron	05/22/2017	-	Human monoclonal antibody targeting IL-6 receptor
Kineret (anakinra)	Swedish Orphan Biovitrum	11/14/2001	-	IL-1 receptor antagonist
Olumiant (baricitinib)	Eli Lilly	05/31/2018	-	Small molecule Janus kinase (JAK) inhibitor
Orencia (abatacept)	Bristol Myers Squibb	12/23/2005	-	sCTLA-4-Ig recombinant fusion protein
Otezla (apremilast)	Celgene Corporation	03/21/2014	-	Small-molecule phosphodiesterase 4 inhibitor
Remicade (infliximab)	Janssen Biotech	8/24/1998	-†	TNFα inhibitor
Renflexis (infliximab-abda)	Merck	04/21/2017	N/A†	TNFα inhibitor
Rituxan (rituximab)	Genentech	11/26/1997	-	Anti-CD20 monoclonal antibody
Siliq (brodalumab)	Valeant	02/15/2017	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
Simponi/ Simponi Aria (golimumab)	Janssen Biotech	04/24/2009 and 07/18/2013	-	TNFα inhibitor
Stelara (ustekinumab)	Janssen Biotech	09/25/2009	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	Eli Lilly	03/22/2016	-	Human monoclonal antibody to IL-17A
Tremfya (guselkumab)	Janssen Biotech	07/13/2017	-	Human monoclonal antibody to IL-23 cytokine
Xeljanz / Xeljanz XR (tofacitinib)	Pfizer	11/06/2012 and 02/23/2016	-	Small molecule Janus kinase (JAK) inhibitor

*Erelzi (etanercept-szzs) has been FDA-approved as a biosimilar to Enbrel (etanercept). Amjevita (adalimumab-atto) and Cyltezo (adalimumab-adbm) have been FDA-approved as biosimilars to and Humira (adalimumab). The specific launch dates for these products are pending and may be delayed. Further information on Erelzi, Amjevita, and Cyltezo will be included in this review after these products have launched.
†Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), and Ixifi (infliximab-qbtx) have been FDA-approved as biosimilar agents to Remicade (infliximab), however, they are not FDA-approved as interchangeable biologics.
(Drugs@FDA, 2018; Prescribing information: Actemra, 2018; Cimzia, 2018; Cosentyx, 2018; Enbrel, 2018; Entyvio, 2018; Humira, 2018; Ilaris, 2017; Ilumya 2018; Inflectra, 2018; Kevzara, 2018; Kineret, 2018; Olumiant 2018; Orencia, 2017; Otezla, 2017; Remicade, 2018; Renflexis, 2017; Rituxan, 2018; Siliq, 2017; Simponi, 2018; Simponi Aria, 2018; Stelara, 2018; Taltz, 2018; Tremfya, 2017; Xeljanz/Xeljanz XR, 2018)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: CAPS, CRS, FMF, GCA, HIDS/MKD, and TRAPS)

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Actemra$^{\check{y}}$ (tocilizumab)	✔ *		✔ **	✔ **						
Cimzia (certolizumab)	✔	✔			✔ ‡	✔	✔			
Cosentyx (secukinumab)					✔ ‡	✔	✔			
Enbrel (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
Entyvio (vedolizumab)		✔						✔		
Humira (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔	✔ ▼
Ilaris" (canakinumab)			✔ **							

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Ilumya (tildrakizumab-asmn)					✔ ‡					
Inflectra (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Kevzara (sarilumab)	✔ *									
Kineret▼▼ (anakinra)	✔ ∞									
Olumiant (baricitinib)	✔									
Orencia (abatacept)	✔ ∞∞			✔ ⌂		✔				
Otezla (apremilast)					✔ ‡	✔				

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Remicade (infliximab)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Renflexis (infliximab-abda)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Rituxan‴ (rituximab)	✔ ⫩									
Siliq (brodalumab)					✔ ⫩					
Simponi (golimumab)	✔ ⫞					✔ ⫞⫞	✔	✔ ~		
Simponi Aria (golimumab)	✔ ⫞					✔	✔			
Stelara (ustekinumab)		✔ ⌐⌐⌐			✔ ‡	✔				

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Taltz (ixekizumab)					✔ ‡	✔				
Tremfya (guselkumab)					✔ ‡					
Xeljanz/ Xeljanz XR (tofacitinib)	✔ ǂǂ					✔		✔ (Xeljanz only)		

ʸActemra is also indicated for treatment of giant cell arteritis in adults and chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years.
*Patients with moderately to severely active RA who have had an inadequate response (or intolerance [Kevzara]) to ≥ 1 Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
**Patients 2 years and older.
†In combination with methotrexate (MTX) or used alone.
‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, with the exception of Enbrel, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, and Stelara, which is indicated for the treatment of patients 12 years and older with moderate to severe PsO.
‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.
‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of JIA for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼Treatment of non-infectious intermediate, posterior and panuveitis in adult patients.
▼▼Kineret is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID).
"Ilaris also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; and familial Mediterranean fever (FMF) in adult and pediatric patients.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 2 years and older with moderate to severely active PJIA. May be used as monotherapy or with MTX.
⌐For all patients 6 years of age and older, indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients who have had an inadequate response to conventional therapy. For adults, also indicated for reducing signs and symptoms and inducing clinical remission if patients have also lost a response to or are intolerant of infliximab.

⌐⌐Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD. And for patients 6 years of age and older for reducing signs and symptoms and inducing and maintaining clinical remission with moderately to severely active disease who have had an inadequate response to conventional therapy.
⌐⌐⌐Indicated for treatment of adult patients with moderately to severely active CD who have: 1) failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed a TNF blocker, or 2) failed or were intolerant to treatment with ≥ 1 TNF blockers
┴In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
┴┴For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Also for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy (Remicade only). The biosimilars Inflectra and Renflexis did not receive FDA approval for pediatric UC due to existing marketing exclusivity for Remicade for this indication (not for clinical reasons).
'''Rituxan also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA).
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to ≥ 1TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
┼ In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┼ ┼ Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
╪╪Indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
˜Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: inducing and maintaining clinical response; improving endoscopic appearance of the mucosa during induction; inducing clinical remission; and achieving and sustaining clinical remission in induction responders.

CLINICAL EFFICACY SUMMARY

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of Orencia (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (*Genovese et al 2011*).
- Orencia (abatacept), Remicade (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (n = 431). Enrolled patients had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after 6 months of treatment, some differences in favor of abatacept were evident after 1 year of treatment. After 1 year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (*Schiff et al 2008*).
- Treatment with Orencia (abatacept) was directly compared to treatment with Humira (adalimumab), when added to MTX, in a multicenter, investigator-blind, randomized controlled trial (n = 646) of RA patients with inadequate response to MTX. After 2 years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the 2 groups after 2 years of treatment. Rates of AEs were similar between treatment groups (*Schiff et al 2014*).
- The RAPID-1 and RAPID-2 studies compared Cimzia (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (*Keystone et al 2008, Smolen et al 2009a*). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every 2 weeks attained greater ACR 20, ACR 50 and ACR 70 responses compared to patients on placebo and MTX, respectively, after 24 weeks ($p \leq 0.01$). The response rates were sustained with active treatment over 52 weeks (*Keystone et al 2008*). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (*Keystone et al 2008, Smolen et al 2009a*). A trial evaluated Cimzia (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least 1 prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; $p < 0.001$). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (*Fleischmann et al 2009*).
- More Cimzia (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, $p \leq 0.05$) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least 6 months (*Smolen et al 2015a*).
- A randomized, double-blind, placebo-controlled trial (n = 316) conducted in Japan compared Cimzia (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤ 12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (*Atsumi et al 2016*). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; $p < 0.001$). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; $p < 0.001$) (*Atsumi et al 2017*).
- The FDA approval of Simponi (golimumab) for RA was based on 3 multicenter, double-blind, randomized, controlled trials in 1,542 patients ≥ 18 years of age with moderate to severe active disease. A greater percentage of patients from all 3 trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (*Emery et al 2009, Keystone et al 2009, Smolen et al 2009b*). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in

mean Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (*Keystone et al 2009, Smolen et al 2009b*). Response with golimumab + MTX was sustained for up to 5 years (*Keystone et al 2013a, Smolen et al 2015b*).

- Simponi Aria (golimumab) was studied in patients with RA. In 1 trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; $p < 0.001$) (*Kremer et al 2010*). In the GO-FURTHER trial (n = 592), golimumab 2 mg/kg IV or placebo was given at weeks 0, 4 and then every 8 weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [$p < 0.001$]) (*Weinblatt et al 2013*). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (*Bingham et al 2015*). In the GO-MORE trial, investigators treated patients with golimumab SQ for 6 months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ + IV group and the SQ golimumab group (*Combe et al 2014*).
- The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (*Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008*).
    - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (*Jones et al 2010*).
    - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (*Kremer et al 2011*). These benefits were maintained or improved at 2 years with no increased side effects (*Fleishmann et al 2013*).
    - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 ($p < 0.001$). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well ($p < 0.001$). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; $p < 0.0296$ for 4 mg/kg and $p < 0.0082$ for 8 mg/kg) (*Smolen et al 2008*).
    - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic

symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (*Genovese et al 2008).*

- RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (*Emery et al 2008*). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (*Gabay et al 2013*).

- More recently, results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (*Bijlsma et al 2016*). Patients (n = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p < 0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p = 0.06 for tocilizumab plus MTX vs MTX; p = 0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (n = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (*Burmester et al 2014a*). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (*Burmester et al 2016*). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (*Kivitz et al 2014*).
- A phase 3 trial (MONARCH) evaluating the efficacy of Kevzara (sarilumab) monotherapy vs Humira (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; p < 0.0001) (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (*Genovese et al 2015, Fleischmann et al 2017*). Additionally, a meta-analysis of 4 randomized controlled trials (RCTs) has shown that ACR 50 response rates were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (OR, 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (*Bae et al 2017).*
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the Xeljanz (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases in fatigue and pain (*Fleishmann et al 2012*). In another Phase 3 study, Xeljanz (tofacitinib), when

administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to Humira (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (*van Vollenhoven et al 2012*). The ORAL Scan trial showed the ACR 20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo ($p < 0.0001$ for both comparisons) (*van der Heijde et al 2013*). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; $p < 0.001$) (*Lee et al 2014*). No radiographic progression was defined as a change from baseline in the modified total Sharp score of < 0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.

- In the ORAL Step study, patients with RA who had an inadequate response to ≥ 1 TNF inhibitors were randomized to Xeljanz (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (*Burmester et al 2013a, Strand et al 2015a*). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; $p = 0.0024$) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; $p < 0.0001$) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; $p < 0.0001$) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; $p < 0.0001$) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.
- The approval of Olumiant (baricitinib) was based on 2 confirmatory, 24-week, phase 3 trials in patients with active RA. In RA-BEACON, enrolled patients (N = 527) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 TNF antagonist(s) (*Genovese et al 2016*). Patients received baricitinib once daily or placebo along with continuing a stable dose of a conventional DMARD. The primary endpoint, ACR 20 response at week 12, was achieved by 49% and 27% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). In RA-BUILD, enrolled patients (N = 684) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 conventional DMARD(s) (*Dougados et al 2017*). Patients received baricitinib once daily or placebo; concomitant conventional DMARDs were permitted but not required. The primary endpoint, ACR20 response at week 12, was achieved by 66% and 39% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$).
- Inflectra (infliximab-dyyb) was evaluated and compared to Remicade (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (*Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the Remicade and Inflectra groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the 2 products.
    - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
    - In the extension study (n = 302) through 102 weeks, all patients received Inflectra. Response rates were maintained, with no differences between the Inflectra maintenance group and the group who switched from Remicade to Inflectra.
- Renflexis (infliximab-abda) was evaluated and compared to Remicade (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized phase 3 trial (*Choe et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the Renflexis and Remicade groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the 2 products.
    - Secondary endpoints were also very similar between the 2 groups.
    - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking Remicade were re-randomized to continue Remicade or switch to Renflexis; patients initially taking Renflexis continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (*Renflexis FDA clinical review 2017*).
- Two studies, 1 double-blind and 1 open-label, evaluated Rituxan (rituximab) in patients who had failed treatment with a TNF blocker (*Cohen et al 2006, Haraoui et al 2011*). All patients continued to receive MTX. Both studies showed > 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (*Lopez-Olivo et al 2015*) examined Rituxan (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life.

- In the open-label ORBIT study (n = 295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either Rituxan (rituximab) (n = 144) or a TNF inhibitor (physician/patient choice of Enbrel [etanercept] or Humira [adalimumab]; n = 151) (*Porter et al 2016*). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
    - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified non-inferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was non-inferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).
- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (*Gottenberg et al 2016*). Patients (n = 300) were randomized to receive a second TNF inhibitor (n = 150) or a non-TNF-targeted biologic (n = 150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), and Remicade (infliximab), and the non-TNF biologics included Actemra (tocilizumab), Rituxan (rituximab), and Orencia (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of > 1.2 points resulting in a score of ≤ 3.2.
    - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (p = 0.003 or p = 0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (p = 0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.
- Another recent randomized trial (*Manders et al 2015*) evaluated the use of Orencia (abatacept) (n = 43), Rituxan (rituximab) (n = 46), or a different TNF inhibitor (n = 50) in patients (n =139) with active RA despite previous TNF inhibitor treatment. Actemra (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined Orencia (abatacept) for the treatment of RA. ACR 50 response was not significantly different at 3 months but was significantly higher in the abatacept group at 6 and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (*Maxwell et al 2009*).
- The safety and efficacy of Humira (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses, respectively, at 6 months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (*Navarro-Sarabia et al 2005*). In another study, patients received adalimumab 20 mg or 40 mg every other week for 1 year, and then could receive 40 mg every other week for an additional 9 years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (*Keystone et al 2013b*).
- A Phase 3, open-label study evaluated the long-term efficacy of Humira (adalimumab) for RA. Patients receiving adalimumab in 1 of 4 early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis;

however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (*Furst et al 2015*).

- A Cochrane review was performed to compare Kineret (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (*Mertens et al 2009*).
- In another Cochrane review, Enbrel (etanercept) was compared to MTX or placebo in adult patients with RA and found that at 6 months, 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15%, respectively, in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups, respectively. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (*Blumenauer et al 2003*). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (*O'Dell et al 2013*).
- A more recent Cochrane review (*Singh et al 2016a*) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included Xeljanz (tofacitinib) and 9 biologics (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Rituxan [rituximab], and Actemra [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
    - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
    - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS < 1.6 or DAS28 < 2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
    - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or Xeljanz (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (*Singh et al 2016b*). A total of 41 randomized trials (n = 14,049) provided data for this review. Key results are as follows:
    - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
    - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
    - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or Xeljanz (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (*Singh et al 2017[a]*). The review included 12 randomized trials (n = 3,364). Key results are as follows:
    - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
    - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
    - There were no published data for tofacitinib monotherapy vs placebo.

  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for Xeljanz (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Actemra [tocilizumab]) at 24 weeks (*Bergrath et al 2017*). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).
- Another recent Cochrane review (*Hazlewood et al 2016*) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or Xeljanz (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effect was small.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (*Singh et al 2017[b]*). Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), Remicade (infliximab), Orencia (abatacept), and Rituxan (rituximab). When combined with MTX, use of biologics showed a benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.
- A meta-analysis evaluated the efficacy of Remicade (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (*Wiens et al 2009*).
- Another meta-analysis of randomized controlled trials included Humira (adalimumab), Kineret (anakinra), Enbrel (etanercept), and Remicade (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; $p < 0.05$) (*Nixon et al 2007*).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (*Donahue et al 2012*). They concluded that there is limited head-to-head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of 2 biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of 6 trials (n = 1,927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (*Galvao et al 2016*). The biologics in the identified trials were TNF inhibitors, most commonly Enbrel (etanercept) or Humira (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA-approval of Humira (adalimumab) for the treatment of AS was based on 1 randomized, double-blind, placebo-controlled study (n = 315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; $p < 0.001$). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease

Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness which is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients ($p < 0.001$) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group ($p < 0.001$) (*van der Heijde et al 2006*).

- In 2 double-blind, randomized, placebo-controlled trials, the efficacy of Enbrel (etanercept) was evaluated in patients with AS (*Calin et al 2004, Gorman et al 2002*). Etanercept had a significantly greater response to treatment compared to placebo ($p < 0.001$) (*Gorman et al 2002*). More patients achieved an ASAS 20 response compared to placebo ($p < 0.001$) (*Calin et al 2004*). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (*Davis et al 2008*). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 ($p < 0.0001$). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group ($p < 0.0001$ for both) (*Braun et al 2011*).
- The FDA-approval of Simponi (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least 3 months (n = 356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (*Inman et al 2008*). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to 5 years in an open-label extension trial (*Deodhar et al 2015*). Safety profile through 5 years was consistent with other TNF inhibitors.
- The efficacy of Remicade (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There was significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks ($p < 0.0001$)(*Braun et al 2002*), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group ($p < 0.001$)(*van der Heijde et al 2005*).
- Inflectra (infliximab-dyyb) was evaluated alongside Remicade (infliximab; European Union formulation) for the treatment of AS in PLANETAS (n = 250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between Inflectra and Remicade. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the Remicade and Inflectra groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
    - In the extension study (n = 174) through 102 weeks, all patients received Inflectra. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of Cimzia (certolizumab) for the treatment of AS was established in 1 randomized, double-blind, placebo-controlled study (n = 325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared to placebo at 12 weeks (*Landewe et at 2014*). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (*Sieper et al 2015a*). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis which includes AS (*Sieper et al 2015b*).
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (*Baeten et al 2015*). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, $p < 0.001$ for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo

group ($p < 0.001$ for secukinumab 150 mg vs placebo; $p = 0.10$ for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150 mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20 response rates were 71.5% with both doses at week 104 (*Braun et al 2017, Marzo-Ortega et al 2017*). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (*Baraliakos et al 2017*).

- In 2 systematic reviews of TNF blockers for the treatment of AS, patients taking Simponi (golimumab), Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (*Machado et al 2013*). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (*Maxwell et al 2015*). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, Cosentyx (secukinumab), and Actemra (tocilizumab; not FDA-approved for AS) (*Chen et al 2016*). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.

Crohn's disease (CD)

- In a trial evaluating Remicade (infliximab) for induction of remission, significantly more patients achieved remission at 4 weeks with infliximab compared to placebo ($p < 0.005$)(*Targan et al 1997*). In a placebo-controlled trial, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction greater than or equal to 50% in the number of fistulas compared to patients treated with placebo ($p = 0.002$ and $p = 0.02$, respectively)(*Present et al 1999*). In an open-label trial evaluating the use of infliximab in pediatric CD patients, 88.4% responded to the initial induction regimen, and 58.6% were in clinical remission at week 10 (*Hyams et al 2007*).
- The safety and efficacy of Entyvio (vedolizumab) was demonstrated in 2 trials for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In 1 trial, a higher percentage of Entyvio-treated patients achieved clinical response and remission at week 52 compared to placebo. However, in the second trial, Entyvio did not achieve a statistically significant clinical response or clinical remission over placebo at week 6 (*Sandborn et al 2013, Sands et al 2014*).
- A meta-analysis evaluating Cimzia (certolizumab) use over 12 to 26 weeks for the treatment of CD demonstrated that the agent was associated with an increased rate of induction of clinical response (RR, 1.36; $p = 0.004$) and remission (RR, 1.95; $p < 0.0001$) over placebo. However, risk of infection was higher with certolizumab use (*Shao et al 2009*).
- Additionally, Humira (adalimumab), Cimzia (certolizumab) and Remicade (infliximab) demonstrated the ability to achieve clinical response (RR, 2.69; $p < 0.00001$; RR, 1.74; $p < 0.0001$ and RR, 1.66; $p = 0.0046$, respectively) and maintain clinical remission (RR, 1.68; $p = 0.000072$ with certolizumab and RR, 2.5; $p = 0.000019$ with infliximab; adalimumab, data not reported) over placebo in patients with CD. Adalimumab and infliximab also had a steroid-sparing effect (*Behm et al 2008*). Other systematic reviews have further demonstrated the efficacy of these agents in CD (*Singh et al 2014, Fu et al 2017*).
- In a systematic review of patients with CD who had failed a trial with Remicade (infliximab), the administration of Humira (adalimumab) was associated with remission rates of 19 to 68% at 1 year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in 0 to 19% of patients in up to 4 years of treatment (*Ma et al 2009*).
- A systematic review of 8 randomized clinical trials with TYSABRI (natalizumab) or Entyvio (vedolizumab) for the management of CD evaluated the rates of failure of remission induction (*Chandar et al 2015*). Fewer failures of remission induction were reported with natalizumab and vedolizumab compared to placebo (RR 0.87; 95% CI, 0.84 to 0.91; I^2=0%). The summary effect sizes were similar for both natalizumab (RR 0.86; 95% CI, 0.80 to 0.93) and vedolizumab (RR 0.87; 95% CI, 0.79 to 0.95). No significant difference was detected between the 2 active treatments ($p = 0.95$). No significant differences between natalizumab and vedolizumab were observed for rates of serious AEs, infections (including serious infections), and treatment discontinuation. Rates of infusion reactions in induction trials were more common with natalizumab over vedolizumab ($p = 0.007$). Progressive multifocal leukoencephalopathy (PML) has been reported with natalizumab but has not been reported with vedolizumab.
- The use of Stelara (ustekinumab) for the treatment of CD was evaluated in the UNITI-1, UNITI-2, and IM-UNITI studies (*Feagan et al 2016*). All were Phase 3, double-blind, placebo-controlled trials.
    - UNITI-1 (n = 741) was an 8-week induction trial that compared single IV doses of ustekinumab 130 mg IV, weight-based ustekinumab (~6 mg/kg), and placebo in patients with nonresponse or intolerance to ≥ 1 TNF inhibitors. The primary endpoint was clinical response at week 6, which was defined as a decrease from

baseline in the CDAI of ≥100 points or a CDAI score of < 150. A clinical response was achieved by 34.4%, 33.7%, and 21.5% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (p = 0.002 for 130 mg dose vs placebo; p = 0.003 for weight-based dose vs placebo). Benefits were also demonstrated on all major secondary endpoints, which included clinical response at week 8, clinical remission (CDAI < 150) at week 8, and CDAI decrease of ≥70 points at weeks 3 and 6.
    - UNITI-2 (n = 628) had a similar design to UNITI-1, but was conducted in patients with treatment failure or intolerance to immunosuppressants or glucocorticoids (with no requirement for prior TNF inhibitor use). In this trial, a clinical response was achieved by 51.7%, 55.5%, and 28.7% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (p < 0.001 for both doses vs placebo). Benefits were also demonstrated on all major secondary endpoints.
    - IM-UNITI was a 44-week maintenance trial that enrolled patients completing UNITI-1 and UNITI-2. Of 1,281 enrolled patients, there were 397 randomized patients (primary population); these were patients who had had a clinical response to ustekinumab induction therapy and were subsequently randomized to ustekinumab 90 mg SQ every 8 or 12 weeks or placebo. The primary endpoint, clinical remission at week 44, was achieved by 53.1%, 48.8%, and 35.9% of patients in the ustekinumab every 8 week, ustekinumab every 12 week, and placebo groups, respectively (p = 0.005 for every 8 week regimen vs placebo; p = 0.04 for every 12 week regimen vs placebo). Numerical and/or statistically significant differences for ustekinumab vs placebo were observed on key secondary endpoints including clinical response, maintenance of remission, and glucocorticoid-free remission.

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated Humira (adalimumab) for the treatment of HS (*Kimball et al 2016*). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of 2 treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
    - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (p = 0.003) and 58.9% vs 27.6% in PIONEER II (p < 0.001).
    - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
    - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (6 to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with Orencia (abatacept) (p = 0.0003). The time to flare was significantly different favoring abatacept (p = 0.0002) (*Ruperto et al 2008*).
- Humira (adalimumab) was studied in a group of patients (4 to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (p = 0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (p = 0.02). ACR Pedi scores were

significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (*Lovell et al 2008*).

- A double-blind, multicenter, randomized controlled trial compared Humira (adalimumab) and placebo in 46 children ages 6 to 18 years with enthesitis-related arthritis (*Burgos-Vargas et al 2015*). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, p = 0.039). A total of 7 patients (3 placebo; 4 adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; p = 0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.
- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, Enbrel (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; p = 0.003) (*Lovell et al 2000*). Ninety-four percent of patients who remained in an open-label 4 year extension trial met ACR Pedi 30; C-reactive protein (CRP) levels, articular severity scores, and patient pain assessment scores all decreased. There were 5 cases of serious AEs related to etanercept therapy after 4 years (*Lovell et al 2006*).
- The approval of Actemra (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (n = 112). Children age 2 to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; p < 0.0001)(*De Benedetti et al 2012*). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (*Brunner et al 2015*). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; p < 0.0024).
- In 2 trials in patients with SJIA, Ilaris (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (*Ruperto et al 2012*).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; 1 each for Kineret (anakinra), Ilaris (canakinumab), and Actemra (tocilizumab), and 2 for rilonacept (not FDA-approved for JIA and not included in this review) (*Tarp et al 2016*). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, Humira (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX (p < 0.001) and placebo (p < 0.001) groups, respectively (*Saurat et al 2008*).
- More than 2,200 patients were enrolled in 2 published, pivotal, phase III trials that served as the primary basis for the FDA approval of Stelara (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks 0, 4, and every 12 weeks thereafter (*Leonardi et al 2008, Papp et al 2008, Langley et al 2015*). In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (p < 0.0001 for both). PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (p < 0.0001) (*Leonardi et al 2008*). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo (p < 0.0001). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. More partial responders at week 28 who received 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (*Papp et al 2008*). A total of 70% (849 of 1212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (*Langley et al 2015*).

- In a study comparing Enbrel (etanercept) and Stelara (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; p = 0.01 vs ustekinumab 45 mg; p < 0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (*Griffiths et al 2010).*
- Approval of Otezla (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; p < 0.0001) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; p < 0.0001) at 16 weeks (*Papp et al 2015, Paul et al 2015a*).
    - Additional analyses of the ESTEEM trials have been published. In 1 analysis (*Thaçi et al 2016*), the impact of apremilast on health-related quality of life, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (*Rich et al 2016*), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- Cosentyx (secukinumab) was evaluated in 2 large, phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
    - In ERASURE (n = 738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
    - In FIXTURE (n = 1306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, Enbrel (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
- Two smaller, phase 3, double-blind, placebo-controlled trials evaluated Cosentyx (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
    - In FEATURE (n = 177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (*Blauvelt et al 2015*).
    - In JUNCTURE (n = 182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (*Paul et al 2015b*).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of Cosentyx (secukinumab) (*Blauvelt et al 2015, Langley et al 2014, Paul et al 2015b*).
- In the CLEAR study, Cosentyx (secukinumab) 300 mg SQ every 4 weeks and Stelara (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; p < 0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; p < 0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.
- A meta-analysis of 7 Phase 3 clinical trials demonstrated the efficacy of Cosentyx (secukinumab) vs placebo and vs Enbrel (etanercept) in patients with PsO (*Ryoo et al 2016*). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the 1-year trials.

- The use of Taltz (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
    - UNCOVER-1 (n = 1296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (*Gordon et al 2016, Taltz product dossier 2016*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively ($p < 0.001$ for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively ($p < 0.001$ for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
    - UNCOVER-2 (n = 1224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (*Griffiths et al 2015*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - UNCOVER-3 (n = 1346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (*Griffiths et al 2015*). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (*Gordon et al 2016*). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The IXORA-S study (n = 676) was a head-to-head study that compared Taltz (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to Stelara (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (*Reich et al 2017[b]).* The primary endpoint, PASI 90 response at week 12, was achieved by 72.8% and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively ($p < 0.001$); superior efficacy of ixekizumab was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted $p < 0.05$).
- The use of Siliq (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
    - AMAGINE-1 (n = 661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12 (*Papp et al 2016*). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥ 2 and those initially receiving placebo received brodalumab 210 mg every 2 weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥ 3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of

patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively ($p < 0.001$ for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).

- AMAGINE-2 (n = 1831) and AMAGINE-3 (n = 1881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, Stelara (ustekinumab), and placebo (*Lebwohl et al 2015*). Brodalumab was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
  - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively ($p < 0.001$ for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively ($p < 0.001$ for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; $p = 0.08$ for brodalumab 140 mg vs ustekinumab).
  - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively ($p < 0.001$ for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively ($p < 0.001$ for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; $p = 0.007$ for brodalumab 140 mg vs ustekinumab).
  - In both studies, the 2 brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA success rates, maintenance with brodalumab 210 mg or 140 mg every 2 weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- The use of Tremfya (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, and NAVIGATE trials. All were phase 3, double-blind, randomized trials.
  - Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or Humira (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
    - In VOYAGE 1 (n = 837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 ($p < 0.001$), and a higher percentage of patients achieved PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; $p<0.001$) (*Blauvelt et al 2017*). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16

(85.1% vs 65.9%), week 24 (84.2% vs. 61.7%), and week 48 (80.5% vs 55.4%; p < 0.001). PASI 90 score was also achieved in a higher percentage of patients with guselkumab vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; p < 0.001).
        - In VOYAGE 2 (n = 992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) (p < 0.001 for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) (p < 0.001). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.
    - In NAVIGATE (n = 871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (*Langley et al 2017*). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; p < 0.001). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; p = 0.001); at week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group (p ≤ 0.001).
- The approval of Ilumya (tildrakizumab-asmn) was based on 2 randomized, double-blind, multicenter, phase 3 trials: reSURFACE1 (772 patients) and reSURFACE2 (1,090 patients). Enrolled adult patients with moderate-to-severe chronic plaque psoriasis received tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo in both studies; reSURFACE 2 also included an Enbrel (etanercept) arm. Only the tildrakizumab-asmn 100 mg dose was approved by the FDA. The coprimary endpoints included the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 reduction from baseline) at week 12 (*Reich et al 2017*).
    - In reSURFACE 1, PASI 75 response was achieved by 64% and 6% of the tildrakizumab-asmn 100 mg and placebo arms at week 12, respectively; a PGA response was achieved by 58% vs 7% of the tildrakizumab-asmn 100 mg and placebo groups, respectively (p < 0.0001 for both comparisons).
    - In reSURFACE 2, PASI 75 response was achieved by 61% and 6% of the tildrakizumab-asmn 100 mg and placebo arms, respectively; a PGA response was achieved by 55% vs 4% of the tildrakizumab-asmn 100 mg and placebo groups, respectively (p < 0.0001 for both comparisons). A higher proportion of patients in the tildrakizumaz 100 mg group achieved PASI 75 vs etanercept (61% vs 48%, respectively; p = 0.001), but the rates of PGA responses did not differ significantly between groups (55% vs 48%, respectively; p = 0.0663).
- For most immunomodulators that are FDA-approved for the treatment of PsO, the indication is limited to adults. In 2016, Enbrel (etanercept) received FDA approval for treatment of PsO in pediatric patients age ≥ 4 years. Limited information from published trials is also available on the use of Stelara (ustekinumab) in adolescent patients (age 12 to 17 years).
    - A 48-week, double-blind, placebo-controlled trial (n = 211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (*Paller et al 2008*). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 (p < 0.001). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including 3 infections) occurred in 3 patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (n = 182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (*Paller et al 2016*).
    - A 52-week, double-blind, placebo-controlled trial (n = 110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (*Landells et al 2015*). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) (p < 0.001 for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively (p < 0.001 for

both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.

- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (*Feldman 2015*). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with Enbrel (etanercept) plus MTX may be beneficial for therapy-resistant patients (*Busard et al 2014; Gottlieb et al 2012*).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, Humira (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response ($p < 0.00001$) while Enbrel (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo ($p < 0.00001$ for both strengths vs placebo). The Remicade (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group ($p < 0.0001$). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (*Schmitt et al 2008*).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥24 weeks) for moderate-to-severe PsO (*Nast et al 2015a*). A total of 25 randomized trials (n = 11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for Remicade (infliximab), 11.97 (95% CI, 8.83 to 16.23) for Cosentyx (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for Stelara (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for Humira (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for Enbrel (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for Otezla (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.
- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, Humira (adalimumab), Cosentyx (secukinumab), and Stelara (ustekinumab) were characterized by high efficacy and tolerability, Remicade (infliximab) and Taltz (ixekizumab) were characterized by high efficacy and poorer tolerability, and Enbrel (etanercept), MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (*Jabbar-Lopez et al 2017*).
- A Cochrane review evaluated biologics in patients with moderate to severe PsO in 109 studies (*Sbidian E et al 2017*) between 12 and 16 weeks after randomization. Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), Stelara (ustekinumab), Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), Remicade (infliximab), and Tremfya (guselkumab). The network meta-analysis showed that all of the biologics were significantly more effective in achieving PASI 90 compared to placebo. Cosentyx (secukinumab), Taltz (ixekizumab), and Siliq (brodalumab) were significantly more effective than Remicade (infliximab), Humira (adalimumab), and Enbrel (etanercept), but not Cimzia (certolizumab). Stelara (ustekinumab) was superior to Enbrel (etanercept). There was no significant difference amongst the agents in the risk of serious adverse effects.

Psoriatic arthritis (PsA)

- In 2 trials, PsA patients receiving Humira (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 ($p = 0.012$) in a trial (n = 100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial ($p < 0.001$) (*Genovese et al 2007, Mease et al 2005*). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; $p < 0.001$) (*Mease et al 2005*).
- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of Enbrel (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo ($p < 0.0001$). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 ($p = 0.0154$) and 13% ($p < 0.0001$) of placebo-treated patients (*Mease et al 2000*). In a second trial, the mean annualized rate of change in the mTSS with Enbrel (etanercept) was -0.03 unit, compared to 1 unit with placebo ($p < 0.0001$). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients ($p = 0.001$). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; $p < 0.0001$). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; $p < 0.001$) (*Mease et al 2004*).

- The FDA approval of Simponi (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (n = 405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (*Kavanaugh et al 2009*).
    - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year 5 were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every 4 weeks (*Kavanaugh et al 2014b*).
    - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (*Kavanaugh et al 2016*).
- In another trial, more Remicade (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients ($p < 0.001$) (*Antoni et al 2005*).
- The efficacy of Cimzia (certolizumab) in the treatment of PsA was established in 1 multicenter, double-blind, placebo controlled trial (n = 409). Patients were randomized to receive placebo, Cimzia 200 mg every 2 weeks, or Cimzia 400 mg every 4 weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (*Mease et al 2014*).
- The FDA-approval of Stelara (ustekinumab) for PsA was based on the results of 2 randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (n = 615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; $p < 0.0001$ for both comparisons); responses were maintained at week 52 (*McInnes et al 2013*). Similar results were observed in the PSUMMIT 2 trial (n = 312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response ($p < 0.001$) (*Ritchlin et al 2014*).
    - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (*McInnes et al 2013*). At week 100 (*Kavanaugh et al 2015a*), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and health-related quality of life (HRQoL) were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on 2 multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 *(Mease et al 2015, McInnes et al 2015*). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
    - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; $p < 0.0001$ vs placebo).
    - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
    - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (*Kavanaugh et al 2017*).
    - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively ($p < 0.0001$ for secukinumab 300 mg and 150 mg; $p < 0.05$ for 75 mg vs placebo).

  - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- The efficacy of Otezla (apremilast) was demonstrated in 3 placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the Otezla groups had ≥ 20% improvement in symptoms, as defined by ACR response criteria (*Cutolo et al 2013, Edwards et al 2016, Kavanaugh et al 2014a*). Clinical improvements observed at 16 weeks were sustained at 52 weeks (*Edwards et al 2016, Kavanaugh et al 2015b*).
- Orencia (abatacept) gained FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2011, Mease et al 2017*). In a phase 2 dose-finding trial (n = 170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (*Mease et al 2011*). Compared to placebo (19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; p = 0.006) and 30/10 mg/kg (42%; p = 0.022) but not 3 mg/kg (33%). A phase 3 trial (n = 424) randomized patients to abatacept 125 mg weekly or placebo (*Mease et al 2017*). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; p < 0.001).
- A small, single-center randomized trial (N = 100) compared Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (*Atteno et al 2010*). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Simponi (golimumab) over 24 weeks for the treatment of PsA (*Fénix et al 2013*). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of 9 randomized controlled trials and 6 observational studies evaluated Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (*Lemos et al 2014*). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- A meta-analysis of 8 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), and Stelara (ustekinumab) in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with PsA (*Bilal et al 2018*). Patients who used these agents were more likely to achieve ACR 20, ACR 50, and ACR70 after 24 weeks of treatment. Another network meta-analysis of 6 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), and Stelara (ustekinumab) over 24 weeks in patients with active PsA (*Wu et al 2018*). The investigators found that all agents improved ACR20 and ACR50 at week 24 compared to placebo. A different network meta-analysis of 8 studies evaluated Orencia (abatacept), Otezla (apremilast), Stelara (ustekinumab), and Cosentyx (secukinumab) in the achievement of ACR 20 and ACR 50 in adults with moderate to severe PsA (*Kawalec et al 2018*). The investigators found a significant difference in ACR20 response rate between Cosentyx (secukinumab) 150 mg and Otezla (apremilast) 20 mg (RR, 2.55; 95% CI, 1.24 to 5.23) and Cosentyx (secukinumab) 300 mg and Otezla (apremilast) 20 mg (RR, 3.57; 95% CI, 1.48 to 8.64) or Otezla (apremilast) 30 mg (RR, 2.84; 95% CI, 1.18 to 6.86).
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
  - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (*Ungprasert et al 2016a*). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: Enbrel [etanercept], Remicade [infliximab], Humira [adalimumab], and Simponi [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving Cimzia (certolizumab), Otezla (apremilast), or Stelara (ustekinumab). Patients receiving Cosentyx (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
  - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (Orencia [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF

inhibitors (*Ungprasert et al 2016b*). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
    - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.

Ulcerative colitis (UC)

- Two trials (ACT 1 and ACT 2) evaluated Remicade (infliximab) compared to placebo for the treatment of UC. In both trials, clinical response at week 8 was significantly higher in infliximab 5 and 10 mg/kg treated patients compared to placebo treated patients (all $p < 0.001$). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies (*Rutgeerts et al 2005*). A randomized open-label trial evaluated infliximab at different dosing intervals for the treatment of pediatric UC. At week 8, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%) (*Hyams et al 2012*).
- In the ULTRA 2 study, significantly more patients taking Humira (adalimumab) 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week for 52 weeks achieved clinical remission and clinical response vs patients taking placebo (*Sandborn et al 2012*). These long term results confirm the findings of ULTRA 1. This 8-week induction trial demonstrated that adalimumab in same dosage as ULTRA 2 was effective for inducing clinical remission (*Reinisch et al 2011*). In ULTRA 1, significant differences between the adalimumab and placebo groups were only achieved for 2 of the secondary end points at week 8, i.e., rectal bleeding and PGA subscores. Conversely, in ULTRA 2, significantly greater proportions of adalimumab-treated patients achieved almost all secondary end points at week 8. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of 3 randomized trials comparing adalimumab to placebo demonstrated that adalimumab increased the proportion of patients with clinical responses, clinical remission, mucosal healing, and inflammatory bowel disease questionnaire responses in the induction and maintenance phases. It also increased the proportion of patients with steroid-free remission in the maintenance phase (*Zhang et al 2016*).
- Simponi (golimumab) was studied in 1,064 patients with moderate to severe UC. Patients receiving golimumab 200 mg then 100 mg or golimumab 400 mg then 200 mg at weeks 0 and 2 were compared to patients receiving placebo. At week 6, significantly greater proportions of patients in the golimumab 200/100 mg and golimumab 400/200 mg groups (51.8%, and 55%, respectively) were in clinical response than patients assigned to placebo (29.7%; $p < 0.0001$ for both comparisons) (*Sandborn et al 2014b*). In a study enrolling patients who responded in a prior study with golimumab, the proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47 vs 31.2%; $p < 0.001$ and $p = 0.01$, respectively) (*Sandborn et al 2014a*).
- The safety and efficacy of Entyvio (vedolizumab) was evaluated in a trial for UC in patients who responded inadequately to previous therapy. A higher percentage of Entyvio-treated patients achieved or maintained clinical response and remission over placebo at weeks 6 and 52, as measured by stool frequency, rectal bleeding, endoscopic findings, and PGA (*Feagan et al 2013*). A systematic review and meta-analysis (n = 606; 4 trials) demonstrated that vedolizumab was superior to placebo for clinical response (RR, 0.82; 95% CI, 0.75 to 0.91), induction of remission (RR, 0.86; 95% CI, 0.80 to 0.91), and endoscopic remission (RR, 0.82; 95% CI, 0.75 to 0.91) (*Bickston et al 2014, Mosli et al 2015*).
- A network meta-analysis of 12 trials of biologic-naïve patients with moderate-severe UC ranked infliximab and vedolizumab highest for induction of clinical remission and mucosal healing among tofacitinib, vedolizumab, golimumab, adalimumab, and infliximab (*Singh et al 2018*). Among patients with prior exposure to anti-TNF agents (4 trials), the results ranked tofacitinib the highest for induction of clinical remission and mucosal healing.

Uveitis (UV)

- The safety and efficacy of Humira (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in 2 randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
    - VISUAL I (n = 217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥2 weeks (*Jaffe et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; $p < 0.001$).
    - VISUAL II (n = 226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (*Nguyen et al 2016a*). Patients were randomized to adalimumab

(80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; p = 0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.

Multiple indications

- The efficacy of infliximab-dyyb (European Union formulation) in patients (n = 481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (*Jørgensen et al 2017*). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

CAPS, CRS, FMF, GCA, HIDS/MKD, and TRAPs

- The efficacy of Kineret (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n = 11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (*Kineret prescribing information 2016*). A cohort study of 26 patients followed for 3 to 5 years demonstrated sustained improvement in disease activity and inflammatory markers (*Sibley et al 2012*).
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, and FMF.
    - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (*Ilaris prescribing information 2016*). Published data supports the use of canakinumab for these various CAPS phenotypes (*Koné-Paut et al 2011, Kuemmerle-Deschner et al 2011, Lachmann et al 2009*).
    - Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period. Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (*Ilaris prescribing information 2016*).
- The efficacy and safety of Actemra (tocilizumab) has been evaluated for treatment of GCA and CRS.
    - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (*Stone et al 2017*). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or received placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo ($p < 0.01$).
    - The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (*Actemra prescribing information 2017*). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.

Treatment Guidelines

- RA:
    - In patients with moderate or high disease activity despite DMARD monotherapy, the ACR recommends the use of combination DMARDs, a TNF inhibitor, or a non-TNF inhibitor biologic (tocilizumab, abatacept, or rituximab); tofacitinib is another option in patients with established RA, mainly in patients failing or intolerant to biologic DMARDs. If disease activity remains moderate or high despite use of a TNF inhibitor, a non-TNF biologic is recommended over another TNF inhibitor or tofacitinib. Anakinra was excluded from the ACR guideline because of its low use and lack of new data (*Singh et al 2016c*).

- EULAR guidelines are similar to ACR guidelines. These guidelines state that if the treatment target is not reached with a conventional DMARD strategy in a patient with poor prognostic factors, addition of a biologic DMARD or a targeted synthetic DMARD (eg, tofacitinib) should be considered, with current practice being a biologic DMARD. Biologic and targeted synthetic DMARDs should be combined with a conventional DMARD, but in patients who cannot use a conventional DMARD concomitantly, a targeted synthetic DMARD or an IL-6 inhibitor (eg, tocilizumab) may have some advantages compared with other biologic DMARDs. The guideline notes that if a TNF inhibitor has failed, patients may receive another TNF inhibitor or an agent with another mode of action. An effective biologic should not be switched to another biologic for non-medical reasons (*Smolen et al 2017*).
- The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (*ACR 2016*). Similarly, the Task Force on the Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).
- EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).

- JIA:
  - The American College of Rheumatology (ACR) published recommendations for the treatment of JIA in 2011, followed by an update in 2013 focusing on the management of SJIA (and tuberculosis screening) (*Beukelman et al 2011, Ringold et al 2013*).
    - According to the 2011 guideline, recommendations for JIA treatment vary based on factors such as disease characteristics and activity, current medication, and prognostic features. For patients with a history of arthritis in ≥ 5 joints (which includes extended oligoarthritis, polyarthritis, and some related subtypes), a TNF inhibitor is generally recommended in patients with continued disease activity after receiving an adequate trial of a conventional DMARD. In patients with a history of ≥ 5 affected joints failing a TNF inhibitor, treatment approaches may include switching to a different TNF inhibitor or abatacept (*Beukelman et al 2011*).
    - According to the 2013 update, the inflammatory process in SJIA is likely different from that of other JIA categories, with IL-1 and IL-6 playing a central role. In patients with SJIA and active systemic features, recommendations vary based on the active joint count and the physician global assessment. Anakinra is 1 of the recommended first-line therapies; canakinumab, tocilizumab, and TNF-inhibitors are among the second-line therapies. In patients with SJIA and no active systemic features, treatments vary based on the active joint count. Abatacept, anakinra, tocilizumab, and TNF inhibitors are among the second-line treatments for these patients (*Ringold et al 2013*).

- UC:
  - For the treatment of UC, sulfasalazine is recommended by the American College of Gastroenterology (ACG) as first-line treatment of active disease. Balsalazide, mesalamine, olsalazine and sulfasalazine are recommended for maintenance of remission and reduction of relapses. If these therapies fail, infliximab should be considered (*Kornbluth et al 2010*). Note that other immunomodulators were not indicated for UC when these guidelines were written; an update is currently in process.

- CD:
  - The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or are refractory to thiopurines or methotrexate. These agents can be considered for treating perianal fistulas, and infliximab can also treat enterocutaneous and rectovaginal fistulas in CD. Adalimumab, certolizumab, and infliximab are effective for the maintenance of anti-TNF induced remission; due to the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors. The guideline

acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*).

  - The American Gastroenterological Association (AGA) recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). The AGA supports the use of TNF inhibitors and/or thiopurines as pharmacologic prophylaxis in patients with surgically-induced CD remission (*Nguyen et al 2017*).
  - An AGA Institute clinical decision tool for CD notes the importance of controlling both symptoms and the underlying inflammation, and makes recommendations for treatments (budesonide, azathioprine, 6-mercaptopurine, prednisone, MTX, a TNF inhibitor, or certain combinations) based on the patient's risk level (*Sandborn 2014*).
  - The European Crohn's and Colitis Organisation (ECCO) recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis. Furthermore, the ECCO guideline states that all currently available TNF inhibitors seem to have similar efficacy in luminal CD and similar AE profiles; therefore the choice depends on availability, route of administration, patient preference, and cost. Vedolizumab is noted to be an appropriate alternative to TNF inhibitors for some patients (*Gomollón et al 2017*).

- Pregnancy in inflammatory bowel disease:
  - Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy. Because of the low risk of transfer across the placenta, certolizumab may be preferred in women who initiate TNF inhibitor therapy during pregnancy (*Nguyen et al 2016b*).
- PsO and PsA:
  - Consensus guidelines from the National Psoriasis Foundation Medical Board state that treatment of PsO includes topical agents; oral therapies such as acitretin, cyclosporine, and MTX; and biologic therapies (*Hsu et al 2012*).
  - Guidelines from the American Academy of Dermatology state that for the management of PsO, topical agents including corticosteroids are used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease (*Menter et al 2008, Menter et al 2009a, Menter et al 2009b, Menter et al 2010, Menter et al 2011*). Biologic agents are routinely used when ≥ 1 traditional systemic agents are not tolerated, fail to produce an adequate response, or are unable to be used due to patient comorbidities. First-line agents for PsO (> 5% BSA) with concurrent PsA include adalimumab, etanercept, golimumab, infliximab, MTX, or a combination of a TNF blocker and MTX.
  - Guidelines for PsO from the European Dermatology Forum, European Association for Dermatology and Venereology, and International Psoriasis Council (European S3 guidelines) state that adalimumab, etanercept, infliximab, and ustekinumab are recommended as second-line medications for induction and long-term treatment if phototherapy and conventional systemic agents were inadequate, contraindicated, or not tolerated (*Nast et al 2015b*). In patients with PsA and active joint involvement despite use of NSAIDs and a potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, it is recommended to start synthetic DMARDs early to prevent progression of disease and erosive joint destruction. For inadequately responding patients with PsA after at least 1 synthetic DMARD, biologic DMARDS are recommended in combination with synthetic DMARDs or as monotherapy.
  - The American Academy of Dermatology recommends that moderate to severe PsA that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with MTX, TNF-blockers, or both (*Gottleib et al 2008, Menter et al 2009b, Menter et al 2011*).
  - EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. For patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics are not appropriate (*Gossec et al 2016, Ramiro et al 2016*).
  - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, or a PDE-4 inhibitor (*Coates et al 2016).*
- AS:

- Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (Ankylosing spondylitis [AS] is synonymous with radiographic axial spondyloarthritis; these guidelines also include non-radiographic axial spondyloarthritis). The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. Biologic DMARDs should be considered in patients with persistently high disease activity despite conventional treatments, and current practice is to start with a TNF inhibitor. If a TNF inhibitor fails, switching to another TNF inhibitor or to an IL-17 inhibitor should be considered (*van der Heijde et al 2017*).
- The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs. No particular TNF inhibitor is preferred over another, except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom infliximab or adalimumab would be preferred over etanercept (*Ward et al 2016).*

- Ocular inflammatory disorders:
  - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (*Levy-Clarke et al 2014*). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
- Additional indications:
  - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
  - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (*Ozen et al 2016*).
  - No recent guidelines were identified for CAPS, CRS, GCA, HIDS/MKD, or TRAPS.

SAFETY SUMMARY

- Contraindications:
  - Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Entyvio (vedolizumab), Ilaris (canakinumab), Ilumya (tildrakizumab-asmn), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Otezla (apremilast), Remicade (infliximab), Renflexis (infliximab-abda), Stelara (ustekinumab), and Taltz (ixekizumab) use in patients with hypersensitivity to any component of the product.
  - Siliq in patients with Crohn's disease because Siliq may cause worsening of disease.
  - Enbrel (etanercept) in patients with sepsis.
  - Kineret (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
  - Remicade (infliximab), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:
  - Actemra (tocilizumab), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Simponi / Simponi Aria (golimumab), and Xeljanz / Xeljanz XR (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
  - In addition, Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
  - Rituxan (rituximab) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).

  - Siliq has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
  - Olumiant (baricitinib) has a boxed warning for thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis.
- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of HBV or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Pancytopenia
  - Worsening and new onset congestive heart failure
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Malignancy and lymphoproliferative disorders
  - Avoiding live vaccinations
  - Noninfectious pneumonia with Stelara (ustekinumab)
  - Increased lipid parameters and liver function tests with Actemra (tocilizumab), Xeljanz / Xeljanz XR (tofacitinib) and Kevzara (sarilumab)
  - Increased incidence of CD and UC with Cosentyx (secukinumab) and Taltz (ixekizumab); risk of new-onset CD or exacerbation of CD with Siliq (brodalumab)
  - Diarrhea, nausea, and vomiting with Otezla (apremilast)
  - Depression with Otezla (apremilast)
  - Gastrointestinal perforations with Xeljanz / Xeljanz XR (tofacitinib), Olumiant (baricitinib), Actemra (tocilizumab), Kevzara (sarilumab), and Rituxan (rituximab)
  - PML with Entyvio (vedolizumab)
  - Thrombosis with Olumiant (baricitinib)
  - Consult prescribing information for other drug-specific warnings/precautions
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension and headache.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a 5-year study in RA and a 10-year study in patients with early RA (*Keystone et al 2014a, Burmester et al 2014b*). In the 5-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 patient-years and 2.8 events per 100 patient-years, respectively. The rate of serious events was highest in the first 6 months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over 5 years in patients with RA (*Keystone et al 2014b*). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 patient-years), and upper respiratory infections (rate of 7.3 per 100 patient-years). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 patient-years for malignancies.
    - Abatacept has been evaluated in 2 long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the 7 year follow-up and a 52-week double-blind study (*Westhovens et al 2014*). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 patient-years), malignancies (3.2 events per 100 patient-years), and autoimmune events (1.2 events per 100 patient-years). In a 5-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year 1 and year 5, respectively.
    - Data from 5 RCTs of Actemra (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4,009 patients with moderate to severe RA

received at least 1 dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 patient-years (PY). The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (*Genovese et al 2013*).

- A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the Enbrel (etanercept) plus DMARD group and the DMARD alone group at 6 months, 12 months, and 2 years. At 3 years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at 6 months, flu-like syndrome at 6 months and 2 years, infection at 6 months and 2 years, malignancy at 12 months and 2 years, pneumonia at 12 months, and serious infection at 12 months and 2 years between the etanercept plus DMARD group and the DMARD group (*Lethaby et al 2013*).
- A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (*Strand et al 2015b*). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.
- A meta-analysis analyzed 50 randomized controlled trials and long-term extension studies evaluating biologic DMARDs and tofacitinib to compare the risks of malignancies in patients with RA (*Maneiro et al 2017*). The overall risk of malignancies was 1.01 (95% CI, 0.72 to 1.42) for all TNF antagonists, 1.12 (95% CI, 0.33 to 3.81) for abatacept, 0.54 (95% CI, 0.20 to 1.50) for rituximab, 0.70 (95% CI, 0.20 to 2.41) for tocilizumab, and 2.39 (95% CI, 0.50 to 11.5) for tofacitinib. The authors concluded that treatment with biologic DMARDs or tofacitinib does not increase the risk of malignancies.

o PsO

- A total of 3,117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3) and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
- In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.
- In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
- A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8

years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; $p < 0.001$) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; $p = 0.002$) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.

- PsA
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.
- AS
  - A meta-analysis of 25 randomized controlled studies with 2,403 patients with AS or non-radiographic axial spondyloarthritis treated with agents such as adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, and secukinumab showed no significant increase in the risk of serious infections with biologic agents compared to controls (OR, 1.42; 95% CI, 0.58 to 3.47) (*Wang et al 2018*).
  - Another meta-analysis of 14 randomized controlled trials with 2,032 patients with AS that were treated with adalimumab, certolizumab, etanercept, golimumab, or infliximab revealed no significant difference between TNF inhibitors and placebo for overall serious adverse events (OR, 1.34; 95% CI, 0.87 to 2.05), risk of serious infections (OR, 1.59; 95% CI, 0.63 to 4.01), risk of malignancy (OR, 0.98; 95% CI, 0.25 to 3.85), and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95 to 2.54) (*Hou et al 2018*).
- Multiple indications
  - One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (*Burmester et al 2013b*).
  - Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
  - A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
  - Several recent meta-analyses evaluated the safety of TNF inhibitors.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up 1 to 36 months) and 7 open-label extension studies (follow-up 6 to 48 months) (*Minozzi et al 2016*). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.

- An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up 2 to 36 months) and 6 open-label extension trials (follow-up 6 to 48 months) (*Bonovas et al 2016*). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Do not give 2 immunomodulators together.
  - For Xeljanz / Xeljanz XR (tofacitinib), adjust dose with potent inhibitors of cytochrome P450 (CYP) 3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.
- Risk Evaluation and Mitigation Strategy (REMS)
  - Siliq (brodalumab) is available only through the Siliq REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
    - Prescribers must be certified with the program.
    - Patients must sign a patient-prescriber agreement form.
    - Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive the product.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Actemra (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe: 162 mg/0.9 mL	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: <100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; >100 kg, 162 mg administered SQ every week. **PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks. <30 kg, 162 mg SQ every 3 weeks; ≥30 kg, 162 mg SQ every 2 weeks. **SJIA:** <30 kg, 12 mg/kg IV every 2 weeks; ≥30 kg, 8 mg/kg IV every 2 weeks. **GCA:** 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** <30 kg, 12 mg/kg IV; ≥30 kg, 8 mg/kg IV; maximum, 800 mg per infusion.	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, and SJIA, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count and low ANC.	Give as a single 60-minute intravenous infusion. <30 kg, use a 50 mL infusion bag. ≥30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe. Rotate injection sites.
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsA:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks. **PsO:** 400 mg SQ every other week or 400 mg SQ initially and at weeks 2 and 4,	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as 2 200 mg SQ injections in separate sites in the thigh or abdomen.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		followed by 200 mg every other week **AS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks.		
Cosentyx (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 150 mg/1 mL Vial: 150 mg lyophilized powder	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks **PsA, AS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks	**PsO:** For some patients, a dose of 150 mg may be acceptable. **PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed. If active PsA continues, consider 300 mg dose.	Each 300 mg dose is given as 2 subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.
Enbrel (etanercept)	Prefilled syringe: 25 mg and 50 mg Prefilled SureClick autoinjector: 50 mg Multiple-use vial: 25 mg lyophilized powder Solution Cartridge: 50 mg	**RA, AS, PsA:** 50 mg SQ weekly **PsO (adults):** 50 mg SQ twice weekly for 3 months, then 50 mg weekly **PJIA and PsO (pediatrics):** ≥63 kg, 50 mg SQ weekly; <63 kg, 0.8 mg/kg SQ weekly	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued **JIA:** NSAIDs glucocorticoids, or analgesics may be continued	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
Entyvio (vedolizumab)	Lyophilized cake for injection in 300 mg single-dose vial	**CD and UC:** 300 mg administered by intravenous infusion at time 0, 2, and 6 weeks, and then every 8weeks thereafter. Discontinue therapy if there is no evidence of therapeutic benefit by week 14.	All immunizations should be to date according to current guidelines prior to initial dose.	Entyvio should be reconstituted at room temperature and prepared by a trained medical professional. It should be used as soon as possible after reconstitution and dilution.
Humira (adalimumab)	Prefilled syringe: 10 mg/0.1 mL 10 mg/0.2 mL 20 mg/0.2 mL 20 mg/0.4 mL	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week if not on MTX.	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Single-use pen: 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL Single-use vial: 40 mg/0.8 mL	**PJIA:** 10 kg to <15 kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week **CD, HS and UC:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week. **PsO and UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **CD in pediatric patients ≥ 6 years and older:** 17 kg to < 40 kg: 80 mg on day 1 (given as two 40 mg injections) and 40 mg 2 weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4. ≥40 kg: 160 mg on day (given in 1 day or split over 2 consecutive days) and 80 mg 2 weeks later (on day 15); maintenance dose is 40 mg every other week starting at week 4.	analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued. **CD and UC:** aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or MTX may be continued if necessary. Needle cover of the syringe contains dry rubber (latex).	May bring to room temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Ilaris (canakinumab)	Vial: 150 mg (lyophilized powder and injection solution formulations)	**SJIA:** ≥7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks **TRAPS, HIDS/MKD, and FMF**: ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 4 weeks	For CAPS: children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg For TRAPS, HIDS/MKD, and FMF: If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤40 kg) or 300 mg (weight >40 kg)	Do not inject into scar tissue.
Ilumya (tildrakizumab-asmn)	Prefilled syringe: 100 mg/mL	**PsO:** 100 mg SQ at weeks 0 and 4, and then every 12 weeks		Should be administered only by a healthcare provider. Bring to room temperature (30 minutes) prior to injecting.
Inflectra (infliximab-dyyb)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL Prefilled pen:	**RA:** 200 mg SQ every 2 weeks.	**RA:** give with or without MTX or other conventional DMARDs	Patients may be taught to self-inject. Bring to room temperature (30 minutes [pre-filled syringe] or 60 minutes

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	150 mg/1.14 mL 200 mg/1.14 mL		Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	[pre-filled pen]) prior to injecting. Rotate injection sites.
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID):** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily.	Patients may be taught to self-inject. A new syringe must be used for each dose.
Olumiant (baricitinib)	Tablet: 2 mg	**RA:** 2 mg once daily	Avoid use in combination with other JAK inhibitiors, biologic DMARDs, or potent immunosuppressants such as azathioprine and cyclosporine	May be taken with or without food.
Orencia (abatacept)	Vial: 250 mg Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** IV: <60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; >100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** IV: 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg. SQ: 2 to 17 years, 10 to <25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥		IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		50 kg, 125 mg once weekly. **PsA:** IV: follow adult RA IV schedule. SQ: 125 mg once weekly without IV dose.		
Otezla (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms. Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	May be taken with or without food. Do not crush, split, or chew the tablets.
Remicade (infliximab)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		maintenance regimen of 5 mg/kg every 6 weeks.		
Renflexis	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Rituxan (rituximab)	Vial: 100 mg 500 mg	**RA:** 1,000 mg IV every 2 weeks times 2 doses. Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Siliq (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
Simponi/ Simponi Aria (golimumab)	SmartJect® autoinjector: 50 mg and 100 mg Prefilled syringe: 50 mg and 100 mg Aria, Vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks. **Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks.	**RA:** give with MTX **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. **Aria**: IV infusion should be over 30

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			Aria (RA): give with MTX (**PsA, AS)**: give with or without MTX or other non-biologic DMARDs. Corticosteroids, NSAIDs, and/or analgesics may be continued. Efficacy and safety of switching between IV and SQ formulations have not been established.	minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
Stelara (ustekinumab)	Prefilled syringe: 45 mg and 90 mg Vial: 130 mg	**PsO, PsA**: ≤100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. >100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (adolescents):** <60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg >100 kg, 90 mg **CD**: Initial single IV dose: ≤55 kg, 260 mg; >55 kg to ≤85 kg, 390 mg; >85 kg, 520 mg; followed by 90 mg SQ every 8 weeks (irrespective of body weight)	Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject using the prefilled syringes. Stelara for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride and infused over at least 1 hour. Rotate injection sites.
Tremfya (guselkumab)	Prefilled syringe: 100 mg	**PsO:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks		Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting.
Taltz (ixekizumab)	Prefilled syringe: 80 mg Autoinjector: 80 mg	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks **PsA:** 160 mg by SQ injection at week 0,		Patients may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		followed by 80 mg every 4 weeks NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		
Xeljanz / Xeljanz XR (tofacitinib)	Tablet: 5 mg, 10 mg Extended release Tablet: 11 mg	**RA:** 5 mg PO twice daily or 11 mg PO once daily **PsA:** 5 mg PO twice daily, used in combination with non-biologic DMARDs; 11 mg once daily used in combination with nonbiologic DMARDs **UC (Xeljanz):** 10 mg PO twice daily for at least 8 weeks, then 5 or 10 mg twice daily. Discontinue 10 mg twice daily dose after 16 weeks if no response	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use of Xeljanz in combination DMARDs or with potent immunosuppres-sants such as azathioprine and cyclosporine is not recommended. Dose interruption is recommended for management of lymphopenia (< 500 cells/mm^3), neutropenia (ANC < 500 cells/mm^3) and anemia. Dose adjustment needed for hepatic and renal impairment and patients taking CYP450 inhibitors.	May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew.

ANC=absolute neutrophil count; AS=ankylosing spondylitis; CRS=cytokine release syndrome; DMARD=disease-modifying anti-rheumatic drug; GCA=giant cell arteritis; HS=hidradenitis suppurative; IV=intravenous infusion; JAK=Janus kinase; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID=neonatal-onset multisystem inflammatory disease; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; UC=ulcerative colitis.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Actemra (tocilizumab)	Frequency of serious infection greater in ≥65 years. Use caution.	Not studied in children <2 years. Safety and efficacy only established in SJIA, PJIA, and CRS.	No dose adjustment in mild or moderate impairment. Not studied in severe impair-ment.	Not studied in patients with impairment.	Unclassified† Limited data in pregnant women not sufficient to determine risks. Unknown whether excreted in breast milk; risks and benefits should be considered.
Cimzia (certolizumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution.	Safety and effectiveness have not been established.	No data	No data	Unclassified† Limited data from ongoing pregnancy registry not sufficient to inform risks. Minimal exrection in breast milk; risks and benefits should be considered.
Cosentyx (secukinumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use with caution.
Entyvio (vedolizumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy category B* Unknown whether excreted in breast milk; use with caution.
Enbrel (etanercept)	Use caution.	Not studied in children <2 years with PJIA or <4 years with PsO.	No data	No data	Unclassified† Available studies do not reliably support association with major birth defects. Present in low levels in breast milk; consider risks and benefits.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Humira (adalimumab)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Only studied in PJIA (ages 2 years and older) and CD (6 years and older).	No data	No data	Unclassified† Present in low levels in breast milk; consider risks and benefits.
Ilaris (canakinumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS).	No data	No data	Unclassified† Limited data from postmarketing reports not sufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Ilumya (tildrakizumab-asmn)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Inflectra (infliximab-dyyb)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
Kevzara (sarilumab)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Safety and efficacy not established.	Dosage adjustment not required in mild to moderate renal impairment. Kevzara has not been studied in severe renal impairment.	No data.	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Kineret (anakinra)	Use caution.	For NOMID, has been used in all ages. Not possible to give a dose <20 mg.	CrCl<30 mL/min: give dose every other day	No data	Unclassified† Data on use in pregnant women insufficient to inform risks.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					Unknown whether excreted in breast milk; use caution.
Olumiant (baricitinib)	No overall differences were observed in the safety and efficacy profiles of elderly patients.	Safety and efficacy have not been established.	Use not recommended in patients with estimated glomerular filtration rate < 60 mL/min/1.73 m^2	No dose adjustment for mild or moderate impairment; not recommended in patients with severe hepatic impairment	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use caution.
Orencia (abatacept)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Not recom-mended in <2 years. IV dosing has not been studied in patients < 6 years old. ClickJect autoinjector subcutaneous injection has not been studied in patients < 18 years.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk.
Otezla (apremilast)	No overall differences were observed in the safety profile of elderly patients.	Safety and efficacy have not been established.	The dose of Otezla should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl<30 mL/min).	No dosage adjustment necessary.	Pregnancy category C* Unknown whether excreted in breast milk; use caution.
Remicade (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD or UC.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Renflexis (infliximab-abda)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Not recommended in < 6 years in children with CD.	No data	No data	Unclassified† Available data do not report clear association with adverse outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Rituxan (rituximab)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Safety and effectiveness have not been established.	No data	No data	Unclassified† May potentially cause B-cell lymphocytopenia due to in-utero exposure. Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
Siliq (brodalumab)	No differences in safety or efficacy were observed between older and younger patients, but the number of patients ≥65 years was insufficient to determine any differences in response.	Safety and effectiveness in <18 years have not been established.	No data	No data	Unclassified† There are no human data in pregnant women to inform risks. Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
Simponi/ Simponi Aria (golimumab)	SQ: No differences in AEs observed between older and younger patients. Use caution. IV Aria: Use caution.	Effectiveness in <18 years has not been established (Simponi). Safety and effectiveness in < 18 years have not been established (Aria).	No data	No data	Pregnancy category B* (Aria) Unclassified† No adequate and well-controlled trials in pregnant women. (Simponi). Unknown whether excreted in breast milk. Discontinue nursing or discontinue the drug (Aria). Consider risks and benefits (Simponi).

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Stelara (ustekinumab)	No differences observed between older and younger patients. Use caution.	Safety and effectiveness have not been established.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; systemic exposure to breasted infant expected to be low; consider risks and benefits.
Taltz (ixekizumab)	No differences observed between older and younger patients; however, the number of patients ≥65 years was not sufficient to determine differences.	Safety and effectiveness have not been established.	No data	No data	Unclassified† There are no available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Tremfya (guselkumab)	No differences observed between older and younger patients; however, the number of patients ≥ 65 years was not sufficient to determine differences.	Safety and efficacy have not been established.	No data	No data	Unclassified† No available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Xeljanz / Xeljanz XR (tofacitinib)	Frequency of serious infection is greater in ≥65 years. Use caution.	Safety and effectiveness have not been established.	Reduce dose to 5 mg daily in moderate to severe impairment.	Reduce dose to 5 mg daily in moderate hepatic impairment. Not recom-mended in severe hepatic impairment.	Unclassified† No adequate and well-controlled studies in pregnancy are available. Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

CrCl=creatinine clearance; CRS=cytokine release syndrome; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; SJIA=systemic juvenile idiopathic arthritis

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Immunomodulators for a variety of conditions associated with inflammation are available. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
    - In patients with RA, abatacept and infliximab showed comparable efficacy at 6 months, but abatacept demonstrated greater efficacy after 1 year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (*Schiff et al 2008*).
    - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over 2 years in a single-blind study (*Schiff et al 2014*).
    - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
    - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (*Gabay et al 2013*). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
    - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have non-inferior efficacy to initial TNF inhibitor treatment (*Porter et al 2016*).
    - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (*Gottenberg et al 2016*). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population *(Manders et al 2015*).
    - Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR study, a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The proportion of patients achieving PASI 90 at week 16 was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; $p < 0.0001$).
    - In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; $p < 0.001$) (*Reich et al 2017 [b]).*
    - A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (*Griffiths et al 2010*).
    - In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (*Langley et al 2014*).
    - In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
    - In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (*Lebwohl et al 2015*).
    - In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab *(Blauvelt et al 2017, Reich et al 2017[a]*).
    - No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (*Park et al 2013, Park et al 2016, Park et al 2017, Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (*Choe et al 2017, Shin et al 2015*).
    - In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (*Jørgensen et al 2017*).
    - More comparative studies are needed.

- For RA, patients not responding to initial DMARD treatment may be treated with combination DMARDs, TNF inhibitors, non-TNF inhibitor biologics, and/or tofacitinib (*Singh et al 2016c; Smolen et al 2017*). EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- For the management of PsO, biologic agents are routinely used when ≥ 1 traditional systemic agents are not tolerated, fail to product an adequate response, or are unable to be used due to patient comorbidities (*Gottleib et al 2008, Menter et al 2008, Menter et al 2009a, Menter et al 2009b, Menter et al 2010, Menter et al 2011, Nast et al 2015b*). EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX (*Gossec et al 2016, Ramiro et al 2016*). For patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics are not appropriate. Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, and PDE-4 inhibitors (*Coates et al 2016*).
- In patients with JIA and involvement of ≥ 5 joints, the ACR recommends the use of a TNF inhibitor after an adequate trial of a conventional DMARD (*Beukelman et al 2011*). The ACR updated guideline for SJIA notes that IL-1 and IL-6 play a central role in the inflammatory process for this condition, and recommend agents such as anakinra, canakinumab, tocilizumab, abatacept, and TNF inhibitors among either first- or second-line treatments (*Ringold et al 2013*).
- According to the ACG, for the treatment of UC, infliximab should be considered after failure of first-line non-biologic agents (*Kornbluth et al 2010*). Other immunomodulators were not indicated for UC when these guidelines were written.
- The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or are refractory to thiopurines or methotrexate. These agents can be considered for treating perianal fistulas, and infliximab can also treat enterocutaneous and rectovaginal fistulas in CD. Adalimumab, certolizumab, and infliximab are effective for the maintenance of anti-TNF induced remission as monotherapy or in combination with azathioprine/6-mercaptopurine or methotrexate. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). ECCO recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis; vedolizumab is an alternative for some patients (*Gomollón et al 2017*).
- Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy (*Nguyen et al 2016b*).
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
- Joint guidelines from ASAS and EULAR state that biologic DMARDs should be considered in patients with AS and persistently high disease activity despite conventional treatments (*van der Heijde et al 2017*). The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients (*Ward et al 2016*).
- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (*Levy-Clarke et al 2016*).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, and tofacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors and tofacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior.
- Warnings, precautions, and AE profiles vary in this class.

- All of the biologic agents with the exception of apremilast and tofacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast and tofacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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