# South Dakota
## Department of Social Services

Medicaid P&T Committee Meeting

March 13, 2020

DSS

Strong Families - South Dakota's Foundation and Our Future

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

**SOUTH DAKOTA**
**MEDICAID P&T COMMITTEE MEETING**
**REVISED AGENDA**

**March 13, 2020**
**1:00 – 3:00 PM**
**Teleconference**
**Dial-in: 866-410-8397**
**Conference Code: 268 622 5055**

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 UC218
4300 Cheyenne Boulevard

**Call to order**

**Approval of previous meeting minutes**

**PA update**

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

**Old business**
- **CGRP utilization**
- **Orilissa utilization**
- **PA criteria reviews**
  - **Review utilization for Lyrica PA**
  - **Review utilization for Lidoderm PA**
  - **Review utilization for Ketoconazole Topical PA**
  - **Review utilization for Triptan PA**
  - **Review utilization for GLP-1 Receptor Agonist PA**
- **Opioid update**

**New business**
- **Compound utilization review**
- **Maintenance medication 90-day fill review**
- **Atypical Antipsychotic utilization in children**
- **Ubrelvy**
- **Gvoke & Baqsimi (Glucagon Agents)**

**Public comment accepted after individual topic discussion**
**Next meeting date 6/5/2020 & adjournment**

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

Friday, December 13, 2019
1:00 – 3:00 pm CT

**Members and DSS Staff**

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

**Administrative Business**

Darger called the meeting to order at 1:02 PM. The minutes of the June meeting were presented. Ladwig made a motion to approve. Van Gilder seconded the motion. Motion was approved unanimously.

**Prior Authorization Update (PA) and Statistics**

The committee reviewed the PA activity report from July 1, 2019 to September 30, 2019. A total of 1,884 PAs were reviewed of which 296 requests (15.71%) were received via telephone and 1,063 requests (56.42%) were received via fax, and 525 (27.87%) were reviewed via electronically.

**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, 2019 to September 30, 2019. The top five therapeutic classes based on paid amount were atypical antipsychotics, disease-modifying anti-rheumatic agents, anticonvulsants, amphetamines, and respiratory/CNS stimulants. The top 15 therapeutic classes make up 24.77% 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 7.43% of total claims. Darger and Ladwig discussed USP Chapter 800 Standards for Safe Handling of Hazardous Drugs. They requested utilization of compound claims to review at the next meeting.

**Old Business**

The committee reviewed the calcitonin gene related peptide (CGRP) utilization comparing 2Q19 vs 3Q19. Utilization continues to increase each quarter, including utilization shift from Aimovig to Emgality. Petrik commented seeing similar utilization shifts on the commercial plan side. The committee also reviewed utilization for Orilissa for 3Q19. Committee requested to review utilization for both classes again at the next meeting.

The committee reviewed 3Q19 opioid outcomes compared to previous quarters from the opioid initiatives. Utilization and MME levels indicate decreased trend.

**New Business**

**PA Criteria Review**

The committee reviewed all PA criteria currently in effect. Jockheck reminded the committee to also consider removing PAs that are not necessary due to availability of generics, outdated, or now considered out of scope. The following decisions were made, including requesting follow up information for a more in-depth review at the next meeting:

- Lyrica – Committee reviewed utilization for Lyrica and pregabalin for PA removal consideration. Darger requested to review gabapentin utilization at the next meeting before making a decision. It was suggested to also include duloxetine utilization and how other Medicaid states were handling Lyrica, especially surrounding areas.
- Hepatitis C – Snyder provided an update regarding the committee's recommendation from the June meeting. DSS continues to evaluate the recommendation.
- Lidoderm – Darger requested utilization for Lidoderm.
- Ketoconazole Topical – Committee inquired if there were PAs for Extina or Xolegel.
- Head Lice – Committee reviewed utilization and discussed the merits of this PA. Darger commented the PA was developed because of heavy utilization of lindane since providers did not know OTC permethrin was covered. In addition, the potential for Soolantra cream (indications for rosacea) used for head lice treatment was discussed.
- Topical Acne – Committee reviewed utilization for topical acne and rosacea treatment. Baack made a motion to create a rosacea PA. Van Gilder seconded the motion. Motion was approved unanimously.
- Growth Hormones – Baack made a motion to modify PA criteria from "for small gestational age (SGA)" to "for small gestational age plus post-natal growth failure at one year". Ladwig seconded the motion. Motion was approved unanimously.
- Anticoagulants – Van Gilder questioned the need for a PA. Darger commented drugs are used appropriately and suggested monitoring utilization when PA removed. Van Gilder made a motion to remove PA on Eliquis, Pradaxa, Savaysa, and Xarelto. Baack seconded the motion. Motion was approved unanimously.
- Triptans – Ladwig requested to review utilization prior to consideration for PA removal.
- Nasal Steroids – Ladwig requested to review utilization prior to consideration for PA removal.
- Methadone – After discussing previous reasons for the PA on methadone and since it is part of the long-acting-opioid (LAO) PA and MED Limit PA, Ladwig made a motion to remove PA. Baack seconded the motion. Motion was approved unanimously.
- Ophthalmic Antihistamines – Committee reviewed utilization for ophthalmic antihistamines. Ladwig made a motion to remove PA on olopatadine ophthalmic drops. Van Gilder seconded the motion. Motion was approved unanimously.

Engelbrecht made a motion to approve all the PA criteria as amended today. Baack seconded the motion. Motion was approved unanimously.

Ladwig requested reviewing GLP-1 orals at the next meeting.

**Review of Sunosi**

Sunosi clinical information was presented for review. Committee recommended adding Sunosi to Xyrem PA. Ladwig made a motion to add PA to Sunosi. Engelbrecht seconded the motion. Motion was approved unanimously.

**Review of Apadaz**
Apadaz clinical information was presented for review. Apadaz is included in the MED Limit PA. Committee recommended adding Apadaz to LAO PA. Engelbrecht made a motion to add PA to Apadaz. Ladwig seconded the motion. Motion was approved unanimously.

Darger read Governor Noem's proclamation designating December 13 as James Engelbrecht Day who devoted his life service to medical practice for the last 45 years. Engelbrecht is retiring after the December 13th meeting. Engelbrecht has been on the committee for the last 16 years. He stated this was the best committee he has served on where experts from pharmacy and medical come together to serve the community of South Dakota.

The next meeting is scheduled for March 13, 2019. Tentative meeting dates for next year are June 5, 2020. Engelbrecht announced as a point of personal preference made a motion to adjourn the meeting and the committee seconded the motion. The motion passed unanimously and the meeting adjourned at 2:32 PM.

# PA Report
## 10/1/2019 – 12/31/2019

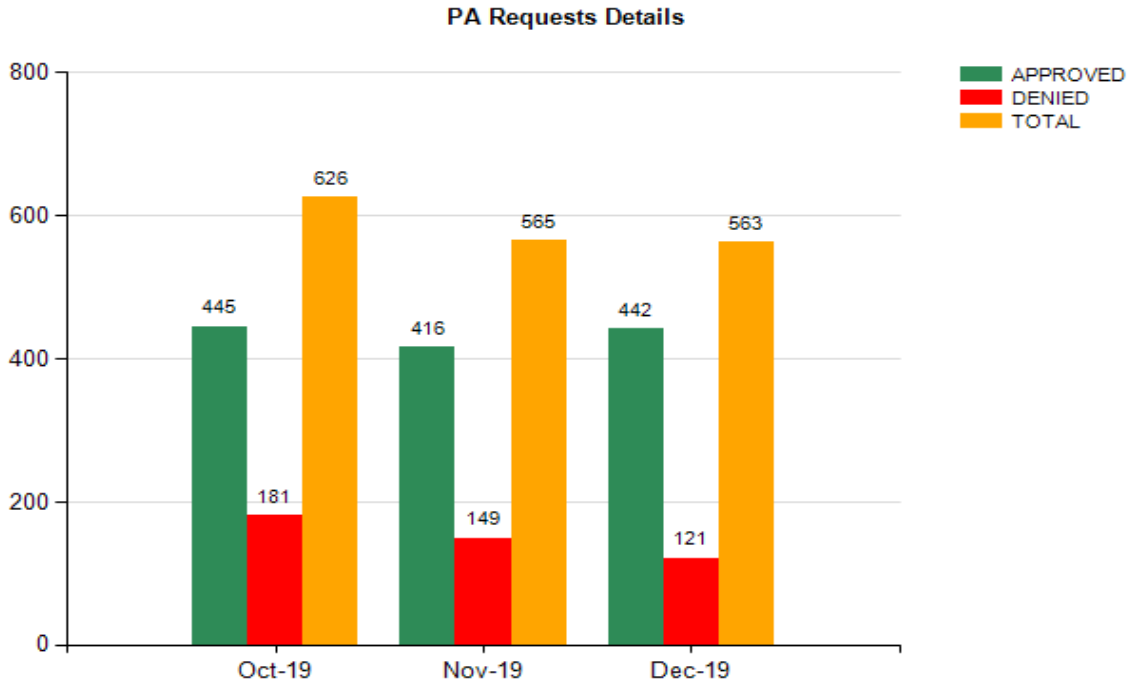
### Compliance Summary

| Priority | Total PAs | PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs) | PAs Not Compliant | % PAs Compliant | % PAs Not Compliant |
|---|---|---|---|---|---|
| STANDARD | 1,708 | 1,708 | 0 | 100% | 0% |
| URGENT | 46 | 46 | 0 | 100% | 0% |
| **GRAND TOTAL** | **1,754** | **1,754** | **0** | | |

| | # of | Phone Requests | | Fax Requests | | Real-Time PA | |
|---|---|---|---|---|---|---|---|
| Drug Class | Requests | # | % | # | % | # | % |
| **TOTAL** | **1,754** | **235** | **13.40%** | **1,027** | **58.55%** | **492** | **28.05%** |

### PA Initial Requests Summary

| Month | Approved | Denied | Total |
|---|---|---|---|
| Oct-19 | 445 | 181 | 626 |
| Nov-19 | 416 | 149 | 565 |
| Dec-19 | 442 | 121 | 563 |
| **4Q19** | **1,303** | **451** | **1,754** |
| **Percent of Total** | **74.29%** | **25.71%** | |



## Top 5 Therapeutic Classes for PA

| Drug Class | Approved | Denied | Total | Approval Rate | % of Total Requests | Most Requested Products |
|---|---|---|---|---|---|---|
| 59 - ANTIPSYCHOTICS/ANTIMANIC | 230 | 28 | 258 | 89.15% | 14.71% | ARIPIPRAZOLE |
| 58 - ANTIDEPRESSANTS* | 170 | 39 | 209 | 81.34% | 11.92% | DUOXETINE |
| 65 - ANALGESICS - OPIOID* | 146 | 59 | 205 | 71.22% | 11.69% | TRAMADOL, HYDROCODONE/APAP |
| 49 - ULCER DRUGS/ ANTISPASMODICS/ANTICHOLINERG | 155 | 24 | 179 | 86.59% | 10.21% | ESOMEPRAZOLE MAGNESIUM |
| 90 - DERMATOLOGICALS* | 83 | 90 | 173 | 47.98% | 9.86% | MALATHION, LIDOCAINE |
| Others - | 519 | 211 | 730 | 71.10% | 41.62% | |
| **4Q19** | **1,303** | **451** | **1,754** | **74.29%** | | |

## PA Drug Class Summary

| Drug Class | Approved | Denied | Total | Approval Rate |
|---|---|---|---|---|
| 59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS* | 230 | 28 | 258 | 89.15% |
| 58 - ANTIDEPRESSANTS* | 170 | 39 | 209 | 81.34% |
| 65 - ANALGESICS - OPIOID* | 146 | 59 | 205 | 71.22% |
| 49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG | 155 | 24 | 179 | 86.59% |
| 90 - DERMATOLOGICALS* | 83 | 90 | 173 | 47.98% |
| 72 - ANTICONVULSANTS* | 60 | 47 | 107 | 56.07% |
| 83 - ANTICOAGULANTS* | 81 | 4 | 85 | 95.29% |
| 27 - ANTIDIABETICS* | 72 | 2 | 74 | 97.30% |
| 52 - GASTROINTESTINAL AGENTS - MISC.* | 44 | 14 | 58 | 75.86% |
| 67 - MIGRAINE PRODUCTS* | 17 | 34 | 51 | 33.33% |
| 66 - ANALGESICS - ANTI-INFLAMMATORY* | 38 | 6 | 44 | 86.36% |
| 54 - URINARY ANTISPASMODICS | 28 | 13 | 41 | 68.29% |
| 61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX | 30 | 10 | 40 | 75.00% |
| 41 - ANTIHISTAMINES* | 28 | 6 | 34 | 82.35% |
| 86 - OPHTHALMIC AGENTS* | 4 | 20 | 24 | 16.67% |
| 16 - ANTI-INFECTIVE AGENTS - MISC.* | 15 | 4 | 19 | 78.95% |
| 12 - ANTIVIRALS* | 7 | 12 | 19 | 36.84% |
| 62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT | 13 | 4 | 17 | 76.47% |
| 30 - ENDOCRINE AND METABOLIC AGENTS - MISC.* | 13 | 2 | 15 | 86.67% |
| 50 - ANTIEMETICS* | 11 | 4 | 15 | 73.33% |
| 75 - MUSCULOSKELETAL THERAPY AGENTS* | 9 | 4 | 13 | 69.23% |
| 44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS* | 7 | 4 | 11 | 63.64% |
| 36 - ANTIHYPERTENSIVES* | 6 | 2 | 8 | 75.00% |
| 60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT | 2 | 6 | 8 | 25.00% |
| 45 - RESPIRATORY AGENTS - MISC.* | 5 | 1 | 6 | 83.33% |
| 40 - CARDIOVASCULAR AGENTS - MISC.* | 3 | 3 | 6 | 50.00% |
| 21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES | 5 | 0 | 5 | 100.00% |
| 33 - BETA BLOCKERS* | 5 | 0 | 5 | 100.00% |
| 39 - ANTIHYPERLIPIDEMICS* | 4 | 1 | 5 | 80.00% |
| 79 - MINERALS & ELECTROLYTES* | 3 | 0 | 3 | 100.00% |
| 34 - CALCIUM CHANNEL BLOCKERS* | 2 | 1 | 3 | 66.67% |
| 03 - MACROLIDES | 1 | 2 | 3 | 33.33% |
| 82 - HEMATOPOIETIC AGENTS* | 2 | 0 | 2 | 100.00% |
| 02 - CEPHALOSPORINS* | 0 | 2 | 2 | 0.00% |
| 42 - NASAL AGENTS - SYSTEMIC AND TOPICAL* | 0 | 2 | 2 | 0.00% |
| 25 - CONTRACEPTIVES* | 1 | 0 | 1 | 100.00% |
| 68 - GOUT AGENTS* | 1 | 0 | 1 | 100.00% |
| 94 - DIAGNOSTIC PRODUCTS* | 1 | 0 | 1 | 100.00% |
| 99 - MISCELLANEOUS THERAPEUTIC CLASSES* | 1 | 0 | 1 | 100.00% |
| 85 - HEMATOLOGICAL AGENTS - MISC.* | 0 | 1 | 1 | 0.00% |
| **4Q19** | **1,303** | **451** | **1,754** | |
| **Percent of Total** | **74.29%** | **25.71%** | | |

## PA Appeals Summary

| Month | Approved | Approved % | Denied | Denied % | Total |
|---|---|---|---|---|---|
| Oct-19 | 19 | 67.86% | 9 | 32.14% | 28 |
| Nov-19 | 14 | 87.50% | 2 | 12.50% | 16 |
| Dec-19 | 14 | 82.35% | 3 | 17.65% | 17 |
| **4Q19** | **47** | **77.05%** | **14** | **22.95%** | **61** |

## Appeals Detail

| Drug Class | Approved | Denied | Total | Approval Rate |
|---|---|---|---|---|
| AMITIZA | 7 | 0 | 7 | 100.00% |
| DUPIXENT | 3 | 2 | 5 | 60.00% |
| PREGABALIN | 3 | 1 | 4 | 75.00% |
| MYRBETRIQ | 3 | 0 | 3 | 100.00% |
| EPCLUSA | 0 | 3 | 3 | 0.00% |
| AIMOVIG | 2 | 0 | 2 | 100.00% |
| AJOVY | 2 | 0 | 2 | 100.00% |
| EMGALITY | 2 | 0 | 2 | 100.00% |
| FLUOXETINE HCL | 2 | 0 | 2 | 100.00% |
| OXYCODONE HCL | 2 | 0 | 2 | 100.00% |
| UPTRAVI | 2 | 0 | 2 | 100.00% |
| CLINDAMYCIN/BENZOYL PEROXIDE | 1 | 1 | 2 | 50.00% |
| VICTOZA | 1 | 1 | 2 | 50.00% |
| DESVENLAFAXINE ER | 1 | 0 | 1 | 100.00% |
| DULOXETINE HYDROCHLORIDE | 1 | 0 | 1 | 100.00% |
| ENOXAPARIN SODIUM | 1 | 0 | 1 | 100.00% |
| HAEGARDA | 1 | 0 | 1 | 100.00% |
| HARVONI | 1 | 0 | 1 | 100.00% |
| INGREZZA | 1 | 0 | 1 | 100.00% |
| KINERET | 1 | 0 | 1 | 100.00% |
| KUVAN | 1 | 0 | 1 | 100.00% |
| LINZESS | 1 | 0 | 1 | 100.00% |
| MALATHION | 1 | 0 | 1 | 100.00% |
| METHADONE HCL | 1 | 0 | 1 | 100.00% |
| MORPHINE SULFATE ER | 1 | 0 | 1 | 100.00% |
| NUCALA | 1 | 0 | 1 | 100.00% |
| OLOPATADINE HCL | 1 | 0 | 1 | 100.00% |
| RISPERIDONE | 1 | 0 | 1 | 100.00% |
| TOLTERODINE TARTRATE ER | 1 | 0 | 1 | 100.00% |
| ZOLPIDEM TARTRATE ER | 1 | 0 | 1 | 100.00% |
| AUSTEDO | 0 | 1 | 1 | 0.00% |
| CLONIDINE HCL | 0 | 1 | 1 | 0.00% |
| DAPSONE | 0 | 1 | 1 | 0.00% |
| EPIDIOLEX | 0 | 1 | 1 | 0.00% |
| HORIZANT | 0 | 1 | 1 | 0.00% |
| MAVYRET | 0 | 1 | 1 | 0.00% |
| **4Q19** | **47** | **14** | **61** | |

# Top 15 Therapeutic Classes & Top 50 Drugs

| TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 10/1/2019 – 12/31/2019 | | | | |
|---|---|---|---|---|
| **AHFS Description** | **Total Rxs** | **Pharmacy Due Amount** | **Paid/Rx** | **%Total Claims** |
| SELECTIVE-SEROTONIN REUPTAKE INHIBITORS | 11,826 | $150,917.53 | $12.76 | 5.90% |
| MISCELLANEOUS ANTICONVULS | 10,696 | $942,432.96 | $88.11 | 5.34% |
| SELECTIVE BETA-2-ADRENERGIC AGONISTS | 8,132 | $511,580.00 | $62.91 | 4.06% |
| ATYPICAL ANTIPSYCHOTICS | 7,954 | $1,987,980.11 | $249.93 | 3.97% |
| AMINOPENICILLIN ANTIBIOTICS | 7,893 | $114,952.81 | $14.56 | 3.94% |
| SECOND GENERATION ANTIHIS | 7,609 | $88,764.55 | $11.67 | 3.80% |
| RESPIRATORY AND CNS STIMULANTS | 6,864 | $876,134.79 | $127.64 | 3.42% |
| AMPHETAMINES | 6,290 | $1,083,255.58 | $172.22 | 3.14% |
| ADRENALS | 6,289 | $596,028.78 | $94.77 | 3.14% |
| PROTON-PUMP INHIBITORS | 5,889 | $206,446.50 | $35.06 | 2.94% |
| OPIATE AGONISTS | 5,789 | $208,738.33 | $36.06 | 2.89% |
| THYROID AGENTS | 3,671 | $69,703.29 | $18.99 | 1.83% |
| MISC. CENTRAL NERVOUS SYS | 3,385 | $147,179.71 | $43.48 | 1.69% |
| HMG-COA REDUCTASE INHIBIT | 3,314 | $42,021.48 | $12.68 | 1.65% |
| LEUKOTRIENE MODIFIERS | 3,309 | $49,125.77 | $14.85 | 1.65% |
| **Total Top 15 Therapeutic Classes** | **98,910** | **$7,075,262.19** | **$71.53** | **49.35%** |

| TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 10/1/2019 – 12/31/2019 | | | | |
|---|---|---|---|---|
| **AHFS Description** | **Total Rxs** | **Pharmacy Due Amount** | **Paid/Rx** | **%Total Claims** |
| ATYPICAL ANTIPSYCHOTICS | 7,954 | $1,987,980.11 | $249.93 | 3.97% |
| DISEASE-MODIFYING ANTIRHEUMATIC AGENTS | 228 | $1,099,622.67 | $4,822.91 | 0.11% |
| AMPHETAMINES | 6,290 | $1,083,255.58 | $172.22 | 3.14% |
| MISCELLANEOUS ANTICONVULS | 10,696 | $942,432.96 | $88.11 | 5.34% |
| RESPIRATORY AND CNS STIMULANTS | 6,864 | $876,134.79 | $127.64 | 3.42% |
| ANTINEOPLASTIC AGENTS | 315 | $686,700.00 | $2,180.00 | 0.16% |
| SKIN AND MUCOUS MEMBRANE | 392 | $673,680.21 | $1,718.57 | 0.20% |
| RAPID-ACTING INSULINS | 1,263 | $631,817.68 | $500.25 | 0.63% |
| ADRENALS | 6,289 | $596,028.78 | $94.77 | 3.14% |
| LONG-ACTING INSULINS | 1,412 | $582,714.76 | $412.69 | 0.70% |
| SELECTIVE BETA-2-ADRENERGIC AGONISTS | 8,132 | $511,580.00 | $62.91 | 4.06% |
| HEMOSTATICS | 43 | $491,588.96 | $11,432.30 | 0.02% |
| CYSTIC FIBROSIS (CFTR) CORRECTORS | 25 | $486,790.98 | $19,471.64 | 0.01% |
| IMMUNOMODULATORY AGENTS | 35 | $348,811.63 | $9,966.05 | 0.02% |
| INCRETIN MIMETICS | 432 | $318,322.18 | $736.86 | 0.22% |
| **Total Top 15 Therapeutic Classes** | **50,370** | **$11,317,461.29** | **$224.69** | **25.13%** |

| | |
|---|---|
| **Total Rx Claims from 10/1/2019 – 12/31/2019** | **200,413** |

| TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 10/1/2019 – 12/31/2019 | | | | | |
|---|---|---|---|---|---|
| **AHFS Description** | **Drug Label Name** | **Total Rxs** | **Pharmacy Due Amount** | **Paid/Rx** | **%Total Claims** |
| AMINOPENICILLIN ANTIBIOTICS | AMOXICILLIN | 6,201 | $78,730.73 | $12.70 | 3.09% |
| RESPIRATORY AND CNS STIMULANTS | METHYLPHENIDATE HYDROCHLO | 5,001 | $627,187.87 | $125.41 | 2.50% |
| SECOND GENERATION ANTIHIS | CETIRIZINE HYDROCHLORIDE | 4,229 | $45,026.00 | $10.65 | 2.11% |
| PROTON-PUMP INHIBITORS | OMEPRAZOLE | 3,501 | $39,974.09 | $11.42 | 1.75% |
| AMPHETAMINES | VYVANSE | 3,420 | $928,308.14 | $271.44 | 1.71% |
| LEUKOTRIENE MODIFIERS | MONTELUKAST SODIUM | 3,299 | $46,152.37 | $13.99 | 1.65% |
| MISCELLANEOUS ANTICONVULS | GABAPENTIN | 3,273 | $56,873.01 | $17.38 | 1.63% |
| SELECTIVE BETA-2-ADRENERGIC AGONISTS | ALBUTEROL SULFATE HFA | 3,170 | $146,550.94 | $46.23 | 1.58% |
| SEROTONIN MODULATORS | TRAZODONE HYDROCHLORIDE | 3,023 | $31,308.54 | $10.36 | 1.51% |
| THYROID AGENTS | LEVOTHYROXINE SODIUM | 2,980 | $51,616.44 | $17.32 | 1.49% |
| OTHER MACROLIDE ANTIBIOTICS | AZITHROMYCIN | 2,904 | $52,121.58 | $17.95 | 1.45% |
| SELECTIVE-SEROTONIN REUPTAKE INHIBITORS | FLUOXETINE HCL | 2,801 | $26,273.67 | $9.38 | 1.40% |
| AMPHETAMINES | AMPHETAMINE/DEXTROAMPHETA | 2,709 | $134,958.12 | $49.82 | 1.35% |
| SELECTIVE BETA-2-ADRENERGIC AGONISTS | ALBUTEROL SULFATE | 2,547 | $51,553.96 | $20.24 | 1.27% |
| ANGIOTENSIN-CONVERTING EN | LISINOPRIL | 2,218 | $20,060.05 | $9.04 | 1.11% |
| SELECTIVE-SEROTONIN REUPTAKE INHIBITORS | ESCITALOPRAM OXALATE | 2,129 | $27,250.72 | $12.80 | 1.06% |
| OPIATE AGONISTS | HYDROCODONE/APAP | 2,028 | $28,477.59 | $14.04 | 1.01% |
| SELECTIVE-SEROTONIN REUPTAKE INHIBITORS | SERTRALINE HCL | 2,018 | $23,350.09 | $11.57 | 1.01% |
| ATYPICAL ANTIPSYCHOTICS | ARIPIPRAZOLE | 1,899 | $44,450.49 | $23.41 | 0.95% |
| SECOND GENERATION ANTIHIS | LORATADINE | 1,863 | $21,355.10 | $11.46 | 0.93% |
| HMG-COA REDUCTASE INHIBIT | ATORVASTATIN CALCIUM | 1,858 | $22,003.44 | $11.84 | 0.93% |
| ANTIDEPRESSANTS, MISCELLANEOUS | BUPROPION HYDROCHLORIDE E | 1,753 | $32,747.63 | $18.68 | 0.87% |
| CENTRAL ALPHA-AGONISTS | CLONIDINE HCL | 1,708 | $18,141.97 | $10.62 | 0.85% |
| SELECTIVE-SEROTONIN REUPTAKE INHIBITORS | FLUOXETINE HYDROCHLORIDE | 1,702 | $30,059.45 | $17.66 | 0.85% |
| AMINOPENICILLIN ANTIBIOTICS | AMOXICILLIN/CLAVULANATE P | 1,687 | $35,746.81 | $21.19 | 0.84% |
| ADRENALS | PREDNISONE | 1,671 | $17,594.93 | $10.53 | 0.83% |
| SELECTIVE-SEROTONIN REUPTAKE INHIBITORS | SERTRALINE HYDROCHLORIDE | 1,665 | $19,647.75 | $11.80 | 0.83% |
| 3RD GENERATION CEPHALOSPORIN | CEFDINIR | 1,637 | $34,380.11 | $21.00 | 0.82% |
| CORTICOSTEROIDS | FLUTICASONE PROPIONATE | 1,636 | $25,364.49 | $15.50 | 0.82% |
| MISC. CENTRAL NERVOUS SYS | GUANFACINE ER | 1,608 | $33,484.85 | $20.82 | 0.80% |
| ATYPICAL ANTIPSYCHOTICS | RISPERIDONE | 1,578 | $19,572.76 | $12.40 | 0.79% |
| BIGUANIDES | METFORMIN HYDROCHLORIDE | 1,528 | $12,789.93 | $8.37 | 0.76% |
| COMPOUNDS | COMPOUNDS | 1,508 | $74,483.74 | $49.39 | 0.75% |
| 1ST GENERATION CEPHALOSPORIN ANTIBIO | CEPHALEXIN | 1,483 | $25,485.22 | $17.18 | 0.74% |
| BENZODIAZEPINES (ANTICONV | CLONAZEPAM | 1,430 | $15,505.41 | $10.84 | 0.71% |
| ATYPICAL ANTIPSYCHOTICS | QUETIAPINE FUMARATE | 1,391 | $18,709.99 | $13.45 | 0.69% |
| MISCELLANEOUS ANTICONVULS | LAMOTRIGINE | 1,346 | $18,863.26 | $14.01 | 0.67% |
| MISCELLANEOUS ANTICONVULS | LEVETIRACETAM | 1,278 | $25,472.57 | $19.93 | 0.64% |
| 5-HT3 RECEPTOR ANTAGONIST | ONDANSETRON ODT | 1,271 | $19,293.83 | $15.18 | 0.63% |
| OPIATE AGONISTS | TRAMADOL HCL | 1,259 | $13,687.71 | $10.87 | 0.63% |
| ADRENALS | PREDNISOLONE SODIUM PHOSP | 1,212 | $19,800.91 | $16.34 | 0.60% |
| CENTRALLY ACTING SKELETAL MUSCLE RELAX | CYCLOBENZAPRINE HYDROCHLO | 1,207 | $11,481.77 | $9.51 | 0.60% |
| CORTICOSTEROIDS (SKIN, MUCOUS MEMB) | TRIAMCINOLONE ACETONIDE | 1,207 | $17,912.67 | $14.84 | 0.60% |
| OTHER NONSTEROIDAL ANTI-INFLAM AGENTS | IBUPROFEN | 1,164 | $14,607.20 | $12.55 | 0.58% |
| MISCELLANEOUS ANTICONVULS | TOPIRAMATE | 1,160 | $16,066.30 | $13.85 | 0.58% |
| SULFONAMIDES (SYSTEMIC) | SULFAMETHOXAZOLE/TRIMETHO | 1,154 | $19,383.30 | $16.80 | 0.58% |
| DIHYDROPYRIDINES | AMLODIPINE BESYLATE | 1,131 | $10,569.57 | $9.35 | 0.56% |
| ANTIDEPRESSANTS, MISCELLANEOUS | MIRTAZAPINE | 1,117 | $16,202.95 | $14.51 | 0.56% |
| VITAMIN D | VITAMIN D | 1,092 | $10,894.45 | $9.98 | 0.54% |
| ANTIBACTERIALS (SKIN & MU | MUPIROCIN | 1,014 | $27,332.56 | $26.96 | 0.51% |
| **TOTAL TOP 50 DRUGS** | | **103,668** | **$3,158,867.03** | **$30.47** | **51.72%** |

| TOP 50 DRUGS BASED ON AMOUNT PAID FROM 10/1/2019 – 12/31/2019 | | | | | |
|---|---|---|---|---|---|
| **AHFS Description** | **Drug Label Name** | **Total Rxs** | **Pharmacy Due Amount** | **Paid/Rx** | **%Total Claims** |
| AMPHETAMINES | VYVANSE | 3,420 | $928,308.14 | $271.44 | 1.71% |
| RESPIRATORY AND CNS STIMULANTS | METHYLPHENIDATE HYDROCHLO | 5,001 | $627,187.87 | $125.41 | 2.50% |
| ATYPICAL ANTIPSYCHOTICS | LATUDA | 387 | $424,940.61 | $1,098.04 | 0.19% |
| ATYPICAL ANTIPSYCHOTICS | INVEGA SUSTENNA | 189 | $406,438.94 | $2,150.47 | 0.09% |
| DISEASE-MODIFYING ANTIRHEUMATIC AGNTS | HUMIRA PEN | 58 | $373,680.13 | $6,442.76 | 0.03% |
| RAPID-ACTING INSULINS | NOVOLOG FLEXPEN | 550 | $303,737.09 | $552.25 | 0.27% |
| ATYPICAL ANTIPSYCHOTICS | ARISTADA | 117 | $289,170.88 | $2,471.55 | 0.06% |
| CYSTIC FIBROSIS (CFTR) CORRECTORS | ORKAMBI | 13 | $272,086.49 | $20,929.73 | 0.01% |
| ADRENALS | FLOVENT HFA | 975 | $221,856.38 | $227.55 | 0.49% |
| SKIN AND MUCOUS MEMBRANE | STELARA | 12 | $213,940.42 | $17,828.37 | 0.01% |
| MOVEMENT DISORDER THERAPY | INGREZZA | 34 | $213,351.38 | $6,275.04 | 0.02% |
| ATYPICAL ANTIPSYCHOTICS | VRAYLAR | 187 | $209,797.03 | $1,121.91 | 0.09% |
| LONG-ACTING INSULINS | LANTUS SOLOSTAR | 581 | $201,804.11 | $347.34 | 0.29% |
| CYSTIC FIBROSIS (CFTR) POTENTIATORS | KALYDECO | 8 | $191,243.14 | $23,905.39 | 0.00% |
| CYSTIC FIBROSIS (CFTR) CORRECTORS | TRIKAFTA | 8 | $191,239.84 | $23,904.98 | 0.00% |
| SOMATOTROPIN AGONISTS | NORDITROPIN FLEXPRO | 54 | $184,705.61 | $3,420.47 | 0.03% |
| ANTINEOPLASTIC AGENTS | AFINITOR DISPERZ | 6 | $179,359.08 | $29,893.18 | 0.00% |
| MISCELLANEOUS ANTICONVULS | VIMPAT | 234 | $173,492.79 | $741.42 | 0.12% |
| SKIN AND MUCOUS MEMBRANE | COSENTYX SENSOREADY PEN | 29 | $172,616.56 | $5,952.30 | 0.01% |
| MUCOLYTIC AGENTS | PULMOZYME | 44 | $171,163.51 | $3,890.08 | 0.02% |
| IMMUNOMODULATORY AGENTS | ACTIMMUNE | 3 | $164,688.30 | $54,896.10 | 0.00% |
| ATYPICAL ANTIPSYCHOTICS | REXULTI | 156 | $156,037.09 | $1,000.24 | 0.08% |
| HEMOSTATICS | RECOMBINATE | 3 | $154,598.16 | $51,532.72 | 0.00% |
| DISEASE-MODIFYING ANTIRHEUMATIC AGNTS | ENBREL SURECLICK | 29 | $146,647.44 | $5,056.81 | 0.01% |
| SELECTIVE BETA-2-ADRENERGIC AGONISTS | ALBUTEROL SULFATE HFA | 3,170 | $146,550.94 | $46.23 | 1.58% |
| AMPHETAMINES | AMPHETAMINE/DEXTROAMPHETA | 2,709 | $134,958.12 | $49.82 | 1.35% |
| DISEASE-MODIFYING ANTIRHEUMATIC AGNTS | HUMIRA | 23 | $134,462.16 | $5,846.18 | 0.01% |
| LONG-ACTING INSULINS | LEVEMIR FLEXTOUCH | 291 | $130,127.68 | $447.17 | 0.15% |
| ATYPICAL ANTIPSYCHOTICS | INVEGA TRINZA | 17 | $126,126.87 | $7,419.23 | 0.01% |
| MISCELLANEOUS GI DRUGS | CHOLBAM | 6 | $124,188.00 | $20,698.00 | 0.00% |
| MISCELLANEOUS ANTICONVULSANTS | BANZEL | 66 | $124,064.91 | $1,879.77 | 0.03% |
| HCV POLYMERASE INHIBITOR ANTIVIRALS | EPCLUSA | 5 | $121,530.90 | $24,306.18 | 0.00% |
| LONG-ACTING INSULINS | TRESIBA FLEXTOUCH | 247 | $115,178.34 | $466.31 | 0.12% |
| DISEASE-MODIFYING ANTIRHEUMATIC AGNTS | XELJANZ XR | 26 | $113,257.46 | $4,356.06 | 0.01% |
| SKIN AND MUCOUS MEMBRANE | DUPIXENT | 38 | $111,263.70 | $2,927.99 | 0.02% |
| MISCELLANEOUS ANTICONVULS | EPIDIOLEX | 45 | $107,421.88 | $2,387.15 | 0.02% |
| RAPID-ACTING INSULINS | NOVOLOG | 214 | $107,237.23 | $501.11 | 0.11% |
| ANTINEOPLASTIC AGENTS | IBRANCE | 9 | $106,800.06 | $11,866.67 | 0.00% |
| INCRETIN MIMETICS | TRULICITY | 146 | $106,397.71 | $728.75 | 0.07% |
| DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS | JANUVIA | 264 | $105,887.62 | $401.09 | 0.13% |
| SELECTIVE BETA-2-ADRENERGIC AGONISTS | ADVAIR HFA | 302 | $103,276.08 | $341.97 | 0.15% |
| ATYPICAL ANTIPSYCHOTICS | ABILIFY MAINTENA | 50 | $102,023.26 | $2,040.47 | 0.02% |
| RAPID-ACTING INSULINS | NOVOLOG PENFILL | 260 | $101,436.53 | $390.14 | 0.13% |
| SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHB | JARDIANCE | 220 | $99,509.36 | $452.32 | 0.11% |
| RESPIRATORY AND CNS STIMULANTS | DEXMETHYLPHENIDATE HCL ER | 989 | $98,505.09 | $99.60 | 0.49% |
| INCRETIN MIMETICS | VICTOZA | 125 | $97,970.73 | $783.77 | 0.06% |
| ADRENALS | SYMBICORT | 294 | $94,860.70 | $322.66 | 0.15% |
| EENT DRUGS, MISC | OXERVATE | 4 | $94,400.00 | $23,600.00 | 0.00% |
| HIV INTEGRASE INHIBITORS | GENVOYA | 31 | $92,781.72 | $2,992.96 | 0.02% |
| RIFAMYCIN ANTIBIOTICS | XIFAXAN | 48 | $90,910.75 | $1,893.97 | 0.02% |
| **TOTAL TOP 50 DRUGS** | | **21,697** | **$9,463,218.79** | **$436.15** | **10.83%** |

# Utilization

**Time frame**: 7/1/2019 – 12/31/2019
Red font denotes drug is on Prior Authorization

**CGRP Inhibitors**

| | 3Q 2019 | | | | 4Q 2019 | | | |
|---|---|---|---|---|---|---|---|---|
| **Drug Name** | **Total Rx** | **Paid Amount** | **Paid/Rx** | **Utilizing Members** | **Total Rx** | **Paid Amount** | **Paid/Rx** | **Utilizing Members** |
| AIMOVIG | 49 | $27,560.62 | $562.46 | 21 | 47 | $26,441.09 | $562.58 | 18 |
| AJOVY | 7 | $3,934.35 | $562.05 | 3 | 15 | $8,422.72 | $561.51 | 6 |
| EMGALITY | 26 | $16,251.92 | $625.07 | 10 | 34 | $21,882.09 | $634.59 | 14 |
| | | | | **Female 32 Male 2 Total 34** | | **Female avg age 40 Male 18, 58 years** | | **Female 35 Male 2 Total 37** |

**Orilissa**

| | 3Q 2019 | | | | 4Q 2019 | | | |
|---|---|---|---|---|---|---|---|---|
| **Drug Name** | **Total Rx** | **Paid Amount** | **Paid/Rx** | **Utilizing Members** | **Total Rx** | **Paid Amount** | **Paid/Rx** | **Utilizing Members** |
| ORILISSA | 4 | $3,312.86 | $828.22 | 3 | 1 | $828.06 | $828.06 | 1 |

*Some states are watching utilization; other states added to PA

**Lyrica**

| | 3Q 2019 | | | | 4Q 2019 | | | |
|---|---|---|---|---|---|---|---|---|
| **Drug Name** | **Total Rx** | **Paid Amount** | **Paid/Rx** | **Utilizing Members** | **Total Rx** | **Paid Amount** | **Paid/Rx** | **Utilizing Members** |
| LYRICA | 189 | $94,348.28 | $499.20 | 130 | 17 | $8,053.06 | $473.71 | 7 |
| pregabalin | 237 | $6,638.71 | $28.01 | 142 | 445 | $9,344.68 | $21.00 | 166 |
| gabapentin | 3,157 | $54,391.97 | $17.23 | 1,248 | 3,274 | $56,775.72 | $17.34 | 1,249 |

PA Criteria:

- Diagnosis of neuropathic pain associated with postherpetic neuralgia, fibromyalgia, or diabetic peripheral neuropathy, trigeminal neuralgia and trial of tricyclic antidepressant or gabapentin
- Diagnosis of partial onset seizure and Lyrica used as adjunctive therapy
- Diagnosis of neuropathic pain associated with spinal cord injury or radiculopathy
- No concomitant gabapentin therapy

Gabapentin concurrent utilization with opioids and/or BZD

- gabapentin utilization January to December 2019 – 1,970 utilizers
    - gabapentin with opioids – 1,190 utilizers
    - gabapentin with BZD – 570 utilizers
    - gabapentin with opioids and BZD – none

**Lidoderm: 3Q-4Q 2019**

| Drug Name | Total Rx | Paid Amount | Paid/ Rx | Utilizing Mbrs | Age Range | SA* PA Request | SA* PA Denied | PA Approve | PA Deny |
|---|---|---|---|---|---|---|---|---|---|
| LIDODERM | 0 | | | | | 1,253 | 0 | 10 | 165 |
| lidocaine cream 3% | 3 | $74.71 | $24.90 | 2 | 44, 47 | | | | |
| lidocaine gel 2% | 29 | $2,279.36 | $78.60 | 16 | 1 - 55 | | | | |
| lidocaine ointment 5% | 45 | $1,033.96 | $22.98 | 23 | 0 - 63 | | | | |
| lidocaine pad 5% | 12 | $1,084.86 | $90.41 | 5 | 38 - 62 | | | | |
| lidocaine solution 4% | 2 | $46.72 | $23.36 | 1 | 62 | | | | |
| ZTLIDO PAD 1.8% | 1 | $265.28 | $265.28 | 1 | 60 | | | | |

PA Criteria: Diagnosis of postherpetic neuralgia (SilentAuth)

*SA: Silent Auth PAs

**Topical Ketoconazole: 3Q-4Q 2019**

| Drug Name | Total Rx | Paid Amount | Paid/Rx | Utilizing Members | Age Range |
|---|---|---|---|---|---|
| EXTINA foam | 0 | | | | |
| XOLEGEL gel | 0 | | | | |
| XOLEGEL kit | 0 | | | | |
| XOLEGEL DUO/kit | 0 | | | | |
| ketoconazole aer 2% | 3 | $1,297.47 | $432.49 | 1 | 19 |
| ketoconazole cream 2% | 379 | $12,351.91 | $32.5 | 324 | 0 - 64 |
| ketoconazole shampoo | 333 | $6,771.76 | $17.87 | 186 | 0 - 67 |

PA Criteria: Trial of ketoconazole cream or shampoo

**Triptan: 3Q-4Q 2019**

| Drug Name | Total Rx | Paid Amount | Paid/Rx | Utilizing Members | Age Range |
|---|---|---|---|---|---|
| eletriptan tab | 71 | $4,084.69 | $57.53 | 21 | 18 - 64 |
| frovatriptan tab | 4 | $1,134.73 | $283.68 | 1 | 37 |
| naratriptan tab | 18 | $539.39 | $29.91 | 9 | 18 - 63 |
| rizatriptan tab | 154 | $2,775.12 | $18.02 | 69 | 11 - 53 |
| sumatriptan tab | 812 | $12,495.12 | $115.39 | 377 | 7 - 64 |
| Imitrex tab | 2 | $1,145.64 | $572.82 | 2 | 58 |
| zomatriptan tab | 27 | $1,245.21 | $46.12 | 11 | 16 - 59 |
| TREXIMET | 0 | | | | |
| sumatriptan injection | 36 | $8,876.81 | $246.57 | 11 | 9 - 51 |
| sumatriptan nasal spray | 30 | $6,722.42 | $224.08 | 17 | 6 - 51 |
| Zomig spray | 2 | $965.57 | $482.79 | 2 | 29, 48 |
| MAXALT MLT | 0 | | | | |
| rizatriptan ODT | 31 | $569.29 | $18.36 | 17 | 7 - 62 |
| ZOMIG ZMT | 0 | | | | |
| **TOTAL** | **1,187** | **$40,553.99** | | **Female 417 (81%)<br>Male 99 (19%)<br>Total 516** | |

PA Criteria for Tablet: Trial of generic triptan

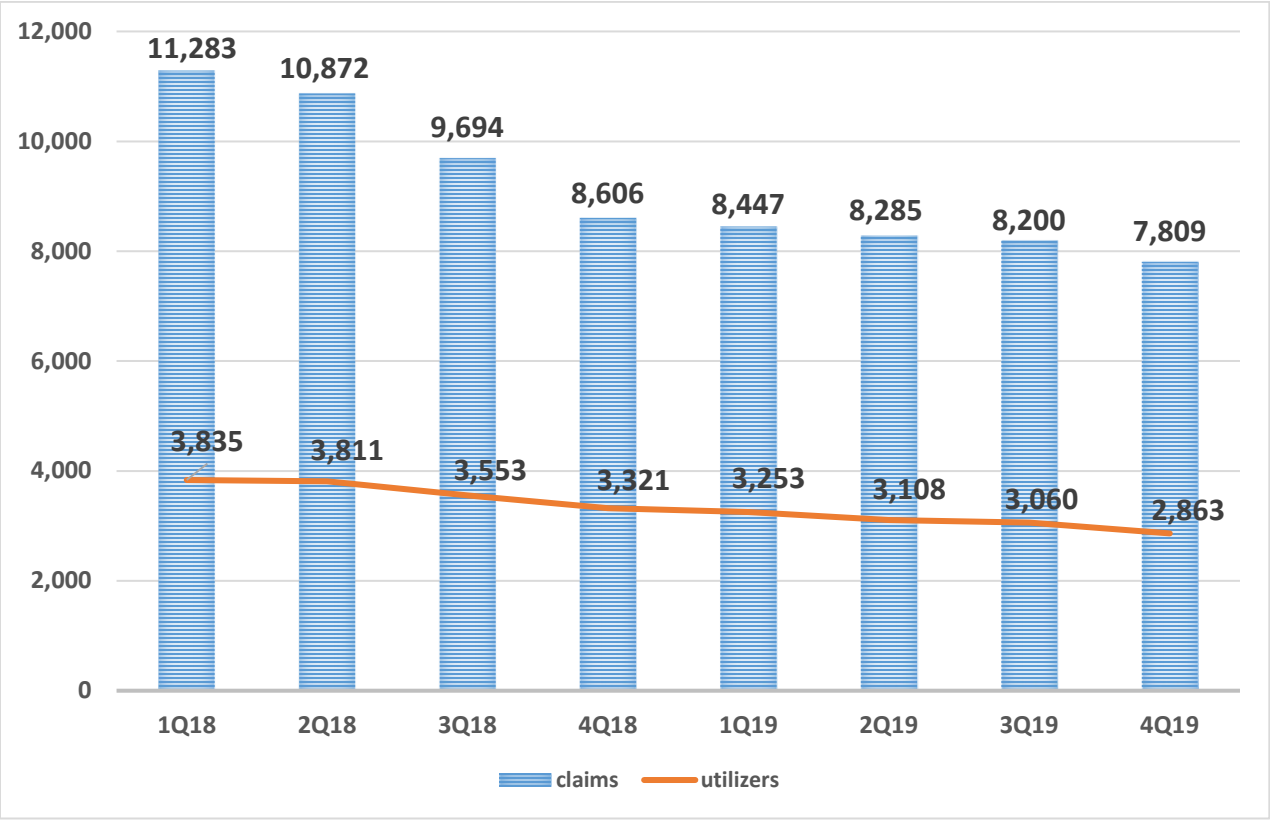
PA Criteria for ODT: Patient is less than 13 years old OR diagnosis of dysphagia

**GLP-1 Receptor Agonists: 3Q-4Q 2019**

| Drug Name | Total Rx | Paid Amount | Paid/Rx | Utilizing Members | Age Range |
|---|---|---|---|---|---|
| ADLYXIN (lixisenatide) | 0 | | | | |
| BYDUREON PEN (exenatide ER) | 63 | $42,856.68 | $680.26 | 19 | 34 - 64 |
| BYDUREON BCise | 66 | $43,136.43 | $653.58 | 16 | 19 - 63 |
| BYETTA (exenatide) | 8 | $5,685.05 | $710.63 | 2 | 38 - 39 |
| OZEMPIC (semaglutide) | 172 | $124,879.85 | $726.05 | 47 | 18 - 64 |
| TRULICIY (dulaglutide) | 289 | $210,008.99 | $726.67 | 68 | 22 - 68 |
| VICTOZA (liraglutide) | 247 | $189,571.21 | $767.49 | 62 | 13 - 64 |
| RYBELSUS (semaglutide) **tablet** | 1 | $779.63 | $779.63 | 1 | 55 |
| TANZEUM (albiglutide) disc 2018 | 0 | | | | |
| **TOTAL** | **846** | **$616,907.84** | **$729.21** | **Female 148<br>Male 57<br>Total 205** | |

PA Criteria: Diagnosis of Type 2 diabetes mellitus

# Opioid Update



# Opioid Utilization Snapshot

## SDM 4Q2019

Sep 19 to Dec 19

Opioid Claims **7,809**

**3.7%** prescription claims filled for an opioid

***0.1% higher than Med D benchmark***

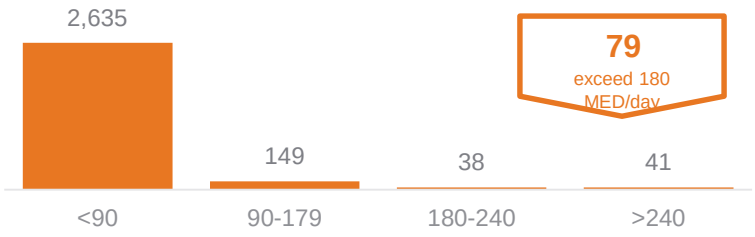
Utilizers **2,863**

**36.8%** are high utilizers [1]

***7% lower than high utilizers Med D benchmark***

### Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]




Shoppers: Poly Pharmacy

**43** opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

**168** Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

## 3Q2019

Jun 19 to Sep 19

Opioid Claims **8,200**

**4.0%** prescription claims filled for an opioid

***0.3% lower than Med D benchmark***

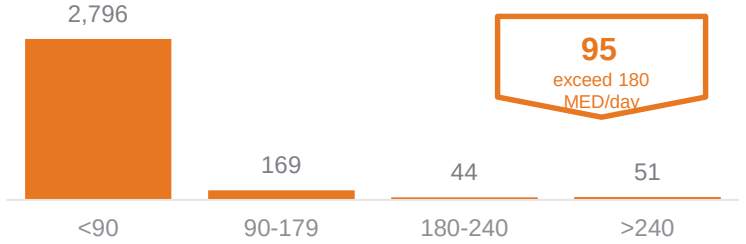
Utilizers **3,060**

**36.0%** are high utilizers [1]

***9.1% lower than high utilizers Med D benchmark***

### Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]




Shoppers: Poly Pharmacy

**48** opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

**193** Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

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[1]Defined as 3+ opioid scripts within 120 days period; [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

# SDM

Sep 19 to Dec 19

## Opioid Utilization Snapshot

### Opioid Claims

**7,809**

**3.7%** prescription claims filled for an opioid

***0.1% higher than Med D benchmark***

### Utilizers

**2,863**

**36.8%** are high utilizers[1]

***7.0% lower than high utilizers Med D benchmark***

Short acting opioids **61.5%** of opioid Rxs

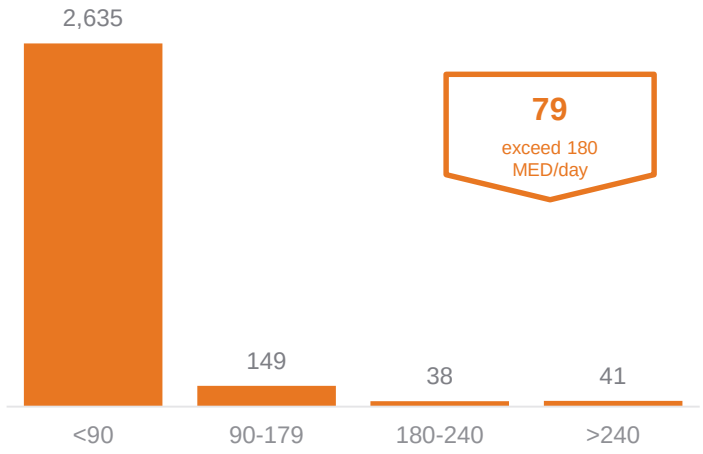
MAT[2] **617** of opioid Rxs

Rescue Therapy[3] 13 Rx(s)

CDC Guidelines advise prescribers to manage pain with lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day

### Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]




[1]Defined as 3+ opioid scripts within 120 days period; [2]**MAT** - Medication Assisted Therapy (e.g., buprenorphine, etc..); [3] **Overdose Rescue Therapy** – opioid overdose reversal with Narcan (naloxone), etc. [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

# SDM

Sep 19 to Dec 19

## Opioid Utilization Opportunity Assessment

Shoppers: Poly Pharmacy

**43**

opioid utilizing members with 3+ pharmacies

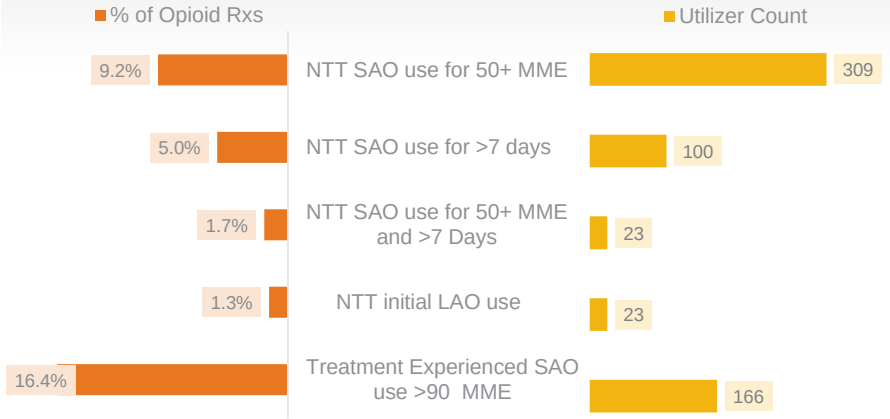
Shoppers: Poly Prescriber

**168**

opioid utilizing members with 3+ prescribers

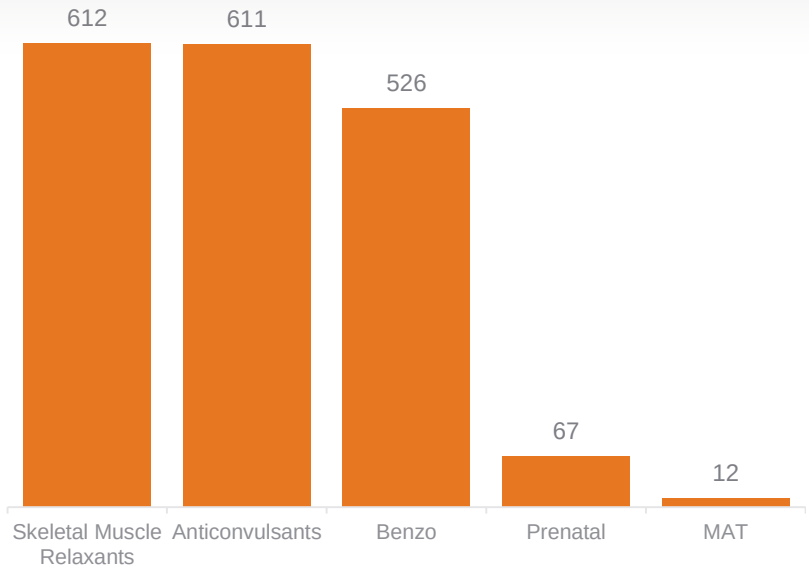
**13.6%**
**of all Opioid Rxs**

Non-Compliance to CDC Guidelines[7] for Opioid Prescriptions (NTT[8] and Chronic)




A retrospective review of claims indicates that **401 utilizing members** during this timeframe would have hit our opioid fill UMs if program was implemented.

Utilizers with Opioid Medication Combinations[9]

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[7]JAMA. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464; [8]NTT – New To Therapy SAO – Short Acting Opioid; LAO – Long Acting Opioid;
[9]Anticonvulsants - gabapentin, pregabalin, anticonvulsant benzodiazepines (clobazam, clonazepam, diazepam)

# Field Definitions

## Dashboard is based on the 120 days of most recent history claims.

### Opioid Utilization Snapshot

**Opioid claims** – total number of opioid claims identified within most recent 120 days claims history
% of Opioid claims - % of opioid claims out of total claims with the period
**Benchmark %** (claims)- indicates percent difference of your prescription claims filled for an opioid in comparison to segment benchmark
**% of Short Acting Opioids** – percent of SAO scripts out of total opioid scripts
**MAT Rxs** – a number of Medication Assisted Therapy (e.g., buprenorphine, etc.) scripts out of total opioid scripts
**Rescue Therapy** – a number of Rxs for opioid overdose reversal with Narcan (naloxone), etc
**Utilizer count** – total number of utilizers with opioid Rxs within the period
**% of high utilizers** - % of utilizers with 3+ opioid scripts within 120 days period
**Benchmark %** (utilizers)- indicates percent difference of your opioid utilizers in comparison to segment benchmark
**Utilizers by Cumulative MED (graph)** - Morphine Equivalent Dose is relative potency of an opioid to standard of morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; **[Total call out]** is a sum of utilizers with 180+ MED.
**MME** – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

### Opioid Utilization Opportunity Assessment

**Shoppers: Poly Pharmacy** – a number of opioid utilizing members with 3 or more pharmacies
**Shoppers: Poly Prescriber** – a number of opioid utilizing members with 3 or more prescribers
**Non-Compliance to CDC Guidelines for Opioid Prescriptions (NTT and Chronic) (graph)** – depicts a number of members and % opioid Rxs for New To Therapy (NTT) and chronic opioid use for each of the defined categories; **% Total** – indicates total percent of opioid scripts for the categories.
**Retrospective members (call out)** - a retrospective review of claims indicating the number members that would have hit Orx opioid fill UMs if program was implemented during the reporting time period.
**Opioid Medication Combinations of High-Risk (graph)** – depicts a number of opioid utilizers for each opioid/drug type combination.

# Utilization

**Compound Summary**

Time frame: January 2019 to December 2019

| Total # of Ingredients Submitted | Total $ of Ingredients Submitted | Total # of Paid Ingredients | Total $ Submitted of Paid Ingredients | Total $ of Ingredients paid | Dispensing Fees | Total Count of Paid Rxs | Total Paid Amount | Total Member Count |
|---|---|---|---|---|---|---|---|---|
| 16,417 | $1,126,646.44 | 8,287 | $930,512.97 | $222,473.34 | $62,012.11 | 5,937 | $272,315.98 | 1,676 |

| Member Age Range | Utilizing Members | Total # of Rx | Total Paid Amount | Plan Cost/Mbr | Plan Cost/Rx | Avg # Rx/Mbr |
|---|---|---|---|---|---|---|
| 0 to 1 years old | 693 | 1,585 | $32,514.69 | $46.92 | $20.51 | 2.29 |
| 2 to 5 years old | 358 | 1,155 | $27,183.79 | $75.93 | $23.54 | 3.23 |
| 6 to 12 years old | 273 | 1,466 | $107,156.47 | $392.51 | $73.09 | 5.37 |
| 13 to 17 years old | 131 | 642 | $13,915.26 | $106.22 | $21.67 | 4.90 |
| 18 to 64 years old | 272 | 1,055 | $90,282.65 | $331.92 | $85.58 | 3.88 |
| 65 to 88 years old | 4 | 34 | $1,263.12 | $315.78 | $37.15 | 8.50 |

| Drug | Utilizing Members | Total # of Rx | Total Paid Amount | Plan Cost/Rx | Age Range |
|---|---|---|---|---|---|
| OMEPRAZOLE CAP 40MG, 20MG 10MG | 260 | 874 | $24,846.32 | $95.56 | 0 - 64 |
| NYSTOP POW, NYSTATIN TAB-SUS-POW-OINT-CRE, NYAMYC POW | 447 | 659 | $13,174.33 | $19.99 | 0 - 63 |
| LANSOPRAZOLE CAP 30MG 15MG | 184 | 645 | $20,709.23 | $32.10 | 0 - 53 |
| BANOPHEN LIQ, BACLOFEN 20MG, 10MG, | 136 | 589 | $8,781.71 | $14.90 | 0 - 63 |
| CLONIDINE TAB 0.3MG, 0.2MG, 0.1MG, POW | 39 | 375 | $3,993.73 | $10.64 | 0 - 55 |
| LIDOCAINE SOL, POW, OINT, GEL | 319 | 369 | $6,898.20 | $18.69 | 0 - 88 |
| TOPIMRATE TAB 100MG, 200MG | 15 | 169 | $2,004.98 | $29.06 | 1 - 18 |
| TETRACAINE POW HCL | 58 | 125 | $1,215.19 | $9.72 | 1 - 28 |
| CLONAZEPAM TAB 2MG, 1MG | 14 | 107 | $1,198.58 | $11.20 | 0 - 35 |
| ZONISAMIDE CAP 100MG | 15 | 97 | $1,489.66 | $15.36 | 1 - 19 |
| KETOCONAZOLE CREAM 2% | 66 | 93 | $3,666.28 | $39.42 | 0 - 77 |

**Maintenance Medication 90-day Dispensing Fee Estimated Savings**

| Rx Count | Total # of Rxs after 3 – 30 day fills | Total # Rxs converted to 90 day fills | Dispensing fee amount estimated for 90 day fill | Estimated dispensing fee savings 100% conversion |
|---|---|---|---|---|
| 284,121 | 152,283 | 50,761 | $504,285 | ~$1 million |

- Based on 2019 utilization
- Generics only
- Maintenance medications only

**Atypical Antipsychotic Utilization in Children** (17 years old and younger)

| Drug Name | Unique Members | Percent |
|---|---|---|
| Number of members taking 1 antipsychotic | 816 | 1.12% |
| Number of members taking more than 1 antipsychotic but **not** concurrently over 90 days | 9 | 0.012% |
| Number of members taking more than 1 antipsychotic concurrently for at least 90 consecutive days | 229 | 0.31% |
| Total number of members on antipsychotics | 1,054 | 1.44% |
| Total number of members 17 years old and younger | 72,952 | |

-Based on 2019 utilization
-excludes IHS network claims
-includes IHS members under total number of 17 years old and `younger

## INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2017, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016)*.
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 4 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm and galcanezumab-gnlm are 2 humanized monoclonal antibodies that target and potently bind the CGRP ligand, in most cases both the α and β isoforms. Ubrogepant is the only oral CGRP inhibitor (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of

olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.

- Two investigational CGRP inhibitors with near-term anticipated approvals include rimegepant, an oral tablet and oral disintegrating tablet CGRP inhibitor, and eptinezumab, an IV formulation that could be funded under the medical benefit. Additional CGRP inhibitors early in their development include vazegepant, the first intranasally administered CGRP inhibitor, and atogepant, another oral CGRP inhibitor (*Biohaven press release 2019*, *Staines 2019*).
- In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe is not currently in early phase studies for the indication of cluster headache (*Clinicaltrials.gov 2019*).

- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

**Table 1. Medications Included Within Class Review**

| Drug | Generic Availability |
|---|---|
| Aimovig (erenumab−aooe) | − |
| Ajovy (fremanezumab-vfrm) | − |
| Emgality (galcanezumab-gnlm) | − |
| Ubrelvy (ubrogepant) | − |

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

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

| Indication | **Aimovig** (erenumab−aooe) | **Ajovy** (fremanezumab-vfrm) | **Emgality** (galcanezumab-gnlm) | **Ubrelvy** (ubrogepant) |
|---|---|---|---|---|
| Acute treatment of migraine with or without aura in adults | - | - | - | ✔ * |
| Preventive treatment of migraine in adults | ✔ | ✔ | ✔ | - |
| Treatment of episodic cluster headache in adults | - | - | ✔ | - |

* Limitation of use: Not indicated for the preventive treatment of migraine.

(*Prescribing information: Aimovig 2019, Ajovy 2018, Emgality 2019, Ubrelvy 2019*)

- 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

- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura and in 1 open-label extension (OLE) trial in unpublished formats.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 OLE trial with data from interim analyses in published and unpublished formats.
- Fremanezumab-vfrm has been studied as preventive therapy in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes, with data in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and

safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).

- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, and the definitions of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

**Prevention of episodic migraine**

*Erenumab-aooe*

- The STRIVE trial was a 6-month, double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).
- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

*Fremanezumab-vfrm*

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*).

- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD as approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

*Galcanezumab-gnlm*

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
  - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).

**Prevention of chronic migraine**

*Erenumab-aooe*

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

*Fremanezumab-vfrm*

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*).
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

*Galcanezumab-gnlm*

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

**Treatment of episodic cluster headache**

*Galcanezumab-gnlm*

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2019, Emgality prescribing information 2019, Goadsby et al 2019*).

**Treatment of acute migraine (with or without aura)**

*Ubrogepant*

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2019*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the most bothersome symptom (MBS) freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
    - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
    - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
  - In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

**Open-label extensions (OLE) and long-term safety studies**

- One published OLE with data to 1 year and 1 unpublished abstract with data to ≥ 3 years evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) in patients with episodic migraine. Of 472 patients in the parent study, 308 patients completed 1 year of open-label (OL) treatment. For the ≥ 3 year assessment, of the 383 patients enrolled in the OLE, 250 continued into the 140 mg once monthly dosing. At the time of interim analysis, 236 patients remained in the OLE (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018*).
  - There may be greater improvements with sustained therapy based on a 1-year OLE interim analysis of episodic migraine patients treated with erenumab-aooe 70 mg once monthly. Patients had a mean value of 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days

(mean change of 2.5 days). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change of 5.1 days). After 64 weeks, 65% (n = 184) of episodic migraine patients achieved a ≥ 50% reduction in MMDs and 26% (n = 73) had achieved a migraine-free status. The most frequently reported adverse events (≥ 4.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, influenza, and back pain.

- One unpublished OLE evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) with data to 1 year in patients with chronic migraine. A total of 609 patients with chronic migraine enrolled in the OLE. A total of 199 increased their dose from 70 mg to 140 mg by week 28 (*Amgen [data on file] 2018, Tepper et al 2018*).
  - Patients with chronic migraine had a mean value of 18.8 MMDs at parent study baseline. After a total of 1 year of treatment, the number of MMDs was reduced to 8.5 in the erenumab-aooe 70 mg group and 10.5 in the erenumab-aooe 140 mg group. After 1 year of erenumab-aooe 70 mg and 140 mg monthly dosing, a total of 53% and 67% of chronic migraine patients achieved a ≥ 50% reduction in MMDs and 6% and 13% had achieved a migraine-free status, respectively. The most frequently reported adverse events (≥ 2.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, and arthralgia.
- Another unpublished safety study, the CGAJ study, evaluated galcanezumab-gnlm 120 mg (plus 240 mg loading dose) and 240 mg monthly dosing to 1 year in patients with episodic or chronic migraine. At baseline, 80.7% of patients in the galcanezumab-gnlm 120 mg arm and 77.0% in the galcanezumab-gnlm 240 mg arm had episodic migraine. A total of 270 patients who had a history of ≥ 4 MMHDs and ≥ 1 headache-free day/month for the past 3 months continued galcanezumab-gnlm treatment (*Eli Lilly and Company [data on file] 2018, Emgality [dossier] 2018, Stauffer et al 2017*).
  - At baseline, patients had a mean value of 9.7 to 11.4 (standard deviation [SD], 6.0 to 6.6) MMHDs. After a total of 1 year of treatment, the number of MMHDs was reduced to 5.6 days in the galcanezumab-gnlm 120 mg group and 6.5 days in the galcanezumab-gnlm 240 mg group. After ≥ 12 consecutive months of treatment, 24.2% of patients treated with galcanezumab-gnlm 120 mg and 34.8% of patients treated with galcanezumab-gnlm 240 mg maintained response. The most frequently reported adverse events (incidence ≥ 15.0%) were injection site pain, nasopharyngitis, and upper respiratory tract infections. One patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. There were no overall concerns regarding safety or tolerability.
- The long-term safety of ubrogepant was evaluated in 813 patients with intermittent dosing administered for up to 1 year in an OLE. Of the 813 patients, 421 patients were exposed to ubrogepant 50 mg or 100 mg for ≥ 6 months, and 364 patients were exposed for ≥ 1 year. All patients were treated for ≥ 2 migraine attacks/month, on average. In the OLE, 2.5% of patients withdrew from ubrogepant treatment because of an adverse reaction. The most common adverse reaction resulting in discontinuation in the OLE was nausea (*Clinicaltrials.gov [NCT02873221] 2019, Ubrelvy prescribing information 2019*).
- Caution should be exercised in applying results from extension trials. The OL design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; results are useful for reporting trends in treatment. Additionally, there is no comparator to account for placebo effects.

## CLINICAL GUIDELINES

**Acute treatment of migraine**

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)

        - Magnesium IV
        - Isometheptene compounds
        - Combination medications (codeine/APAP, tramadol/APAP)
        - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
    - Ubrogepant was reviewed by the AHS prior to FDA-approval for recommendation. The AHS recommend it may have a role in patients with cardiovascular (CV) conditions or in cases of triptan contraindications. Further recommendations include patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
        - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
    - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

**Prevention of migraine**

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
    - Level A (established efficacy and > 2 Class I trials):
        - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
        - Beta blockers: metoprolol, propranolol, and timolol
        - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
    - Level B (probably effective and 1 Class I or 2 Class II trials):
        - Antidepressants: amitriptyline and venlafaxine
        - Beta blockers: atenolol and nadolol
        - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
    - Level C (possibly effective and 1 Class II trial):
        - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
        - Angiotensin II receptor blockers (ARBs): candesartan
        - Alpha agonists: clonidine and guanfacine
        - Antiepileptic drugs: carbamazepine
        - Beta blockers: nebivolol and pindolol
        - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
    - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
    - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
    - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).

- Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).
- Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
- Consider propranolol (Level B).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

**Cluster headache**

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)
  - Level C (possibly effective and 1 Class II trial):
    - Lithium
    - Verapamil
    - Warfarin
    - Melatonin

## SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. In cases of serious or severe reactions, treatment should be discontinued.
- Erenumab-aooe has an additional warning and precaution associated with constipation with serious complications noted post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
- For the prevention of migraine, erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. The most common adverse reactions observed in CGRP inhibitor prevention studies included injection site reactions (all agents) and constipation (erenumab-aooe only).
- For the treatment of episodic cluster headache, galcanezumab−gnlm was evaluated for 2 months in trials and the safety profile was similar to those adverse events observed in migraine prevention trials. Two patients discontinued DB treatment due to adverse events.
- For the treatment of acute migraines, the safety of ubrogepant was evaluated for up to 1 year in an OLE in patients who had ≥ 2 attacks/month. The most common adverse events were nausea (2 to 4%) and somnolence (2 to 3%). The most common adverse reaction resulting in discontinuation in the OLE was nausea.

- CGRP is a vasodilator and is found at higher concentrations during a migraine attack. In the 1-year interim analysis of an OLE study with erenumab-aooe, 2 patients had severe adverse events (an arteriosclerosis event and a myocardial ischemia event), of which 1 was fatal and 1 was confounded by sumatriptan administration. No additional concerns were raised within the OLE at ≥ 3 years, including any CV events. In a long-term safety study of patients treated with galcanezumab-gnlm for 1 year, 1 patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. A total of 9 patients reported serious adverse events with ubrogepant 50 mg (sinus tachycardia, intestinal obstruction, gait disturbance, cholelithiasis, acute cholecystitis, allergy, pneumonia, pelvic inflammatory disease, post procedure infection, hypertensive crisis, and a substance-induced mood disorder) and 12 with the 100 mg (colitis, hiatus hernia, acute pancreatitis, non-cardiac chest pain, cholelithiasis, acute cholecystitis, gastroenteritis, pneumonia, sepsis, subdural hematoma, ketoacidosis, hemiparesis, abortion, ectopic pregnancy, suicidal ideation, and acute respiratory failure); however, not all events may be related to treatment. The long-term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized *(Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018, Clinicaltrials.gov [NCT02873221] 2019, Eli Lilly and Company [data on file] 2018, Stauffer et al 2017, Tepper et al 2018)*.
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| Aimovig (erenumab−aooe) | Auto-injector (70 mg/mL or 140 mg/mL) | SC | Once monthly (70 or 140 mg) | May be self−administered by patients in the abdomen, thigh, or back of upper arm.<br><br>Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe.<br><br>Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days. |
| Ajovy (fremanezumab−vfrm) | Prefilled syringe (225 mg/1.5 mL) | SC | Once monthly (225 mg) or once every 3 months (675 mg) | May be self−administered by patients in the abdomen, thigh, or back of upper arm.<br><br>The prefilled syringe cap is not made with natural rubber latex.<br><br>Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, fremanezumab-vfrm has a limited stability of 24 hours. |
| Emgality (galcanezumab−gnlm) | Auto-injector (120 mg/mL)<br>Prefilled syringe (100 mg/mL or 120 mg/mL) | SC | *Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly | May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. |

| Drug | Available Formulations | Route | Usual Recommended Frequency | Comments |
|---|---|---|---|---|
| | | | *Episodic cluster headache*: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period | The cap is not made with natural rubber latex.<br><br>Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days. |
| Ubrelvy (ubrogepant) | Oral tablets (50 and 100 mg) | PO | *Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the initial dose. Max dose: 200 mg in 24 hours. | The safety of treating > 8 migraines in a 30 day period has not been established.<br><br>Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment.<br><br>Avoid use in patients with end stage renal disease (CrCL < 15 mL/min).<br><br>Take with or without food |

See the current prescribing information for full details
**Abbreviations**: CrCL = creatinine clearance; PO = oral; SC = subcutaneous
**Note**: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

## CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Ubrogepant is indicated for acute treatment of migraine with or without aura. Erenumab-aooe, fremanezumab−vfrm, and galcanezumab−gnlm are indicated for the prevention of migraine. Galcanezumab−gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
  - For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics.

Recent AHS guidelines state that ubrogepant may have a role in patients with CV conditions or in cases of triptan contraindications. It is also noted that other CGRP inhibitors may shortly be FDA-approved for use.

- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 1.0 to 2.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 3.1 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, ubrogepant has a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children. Based on current data, the safety profiles of the CGRP inhibitors are generally mild with the most common adverse effects observed being injection site reactions in SC formulations and nausea in oral formulations.
- Overall, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm represent another therapy option in the prevention of episodic or chronic migraine. Fremanezumab-vfrm is the only agent in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches and ubrogepant is the only CGRP inhibitor indicated for acute treatment of migraines and also the only oral formulation. The frequency of administration (and route or dose) vary by indication. Further long-term study is warranted.

## APPENDICES

- **Appendix A. AAN levels of evidence classification** *(AAN 2017, Gronseth et al 2011)*

| *Rating of recommendation* | |
|---|---|
| A | Established as effective, ineffective, or harmful for the given condition in the specified population |
| B | Probably effective, ineffective, or harmful for the given condition in the specified population |
| C | Possibly effective, ineffective, or harmful for the given condition in the specified population |
| U | Data inadequate or conflicting; given current knowledge, treatment is unproven. |
| *Rating of therapeutic article* | |
| Class I | RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal |

| | |
|---|---|
| | potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs. |
| Class II | Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e). |
| Class III | Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment. |
| Class IV | Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable. |

- **Appendix B. AAN/AHS levels of evidence classification** *(Oskoui et al 2019[b])*

| *Level of obligation; magnitude of benefit* | |
|---|---|
| A | Must; large benefit relative to harm |
| B | Should; moderate benefit relative to harm |
| C | May; small benefit relative to harm |
| U | No recommendation supported; too close to call |

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| MEDICATION* | MARKETER | AVAILABILITY |
|---|---|---|
| **Baqsimi** (glucagon) | Lilly USA, LLC. | **Brand:** 3 mg nasal powder (intranasal device containing 1 dose) [1-pack or 2-pack] |
| **GlucaGen HypoKit** (glucagon) | Boehringer Ingelheim Pharmaceuticals, Inc. | **Brand:** 1 mg injection (single-dose vial of powder; disposable syringe containing sterile water for reconstitution) |
| **Glucagon Emergency Kit** (glucagon) | Fresenius Kabi | **Brand:** 1 mg injection (single-dose vial of powder; prefilled syringe containing diluent for reconstitution) |
| **Glucagon Emergency Kit** (glucagon) | Lilly USA, LLC. | **Brand:** 1 mg injection (single-dose vial of powder; prefilled syringe containing sterile water for reconstitution) |
| **Gvoke** (glucagon) | Xeris Pharmaceuticals, Inc. | **Brand:** 0.5 mg/0.1 mL, 1 mg/0.2 mL prefilled auto-injectors; 0.5 mg/0.1 mL, 1 mg/0.2 mL prefilled syringes [1-pack or 2-pack] |
| **Therapeutic Class:** Antidote, Hypoglycemia | | |
| **Purpose of Review:** To evaluate the safety and efficacy of the glucagon products including Baqsimi, a new intranasal formulation, and Gvoke, a new prefilled injectable formulation, for formulary consideration. | | |

* Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text

Note: Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## SUMMARY

**Background**

- Hypoglycemia in patients with diabetes can be defined as episodes of abnormally low plasma glucose concentration that expose the individual to potential harm. An alert value for hypoglycemia is defined as blood glucose < 70 mg/dL. Clinically important hypoglycemia is defined as blood glucose < 54 mg/dL, but the physiologic response to low blood glucose can be variable (*American Diabetes Association [ADA] 2019*, *Cryer 2019*).
- Hypoglycemia frequently affects patients with type 1 diabetes (T1DM), in whom the risk of severe hypoglycemia (episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) increases with intensive therapy. Patients with T1DM report an average of up to 3 episodes of severe hypoglycemia per year. Severe hypoglycemia affects patients with type 2 diabetes (T2DM) less commonly; those who are treated with a sulfonylurea, a meglitinide, or insulin are generally at higher risk (*Cryer 2019, Seaquist et al 2013*).
  - The Centers for Disease Control and Prevention (CDC) reported that in 2014, 245,000 episodes of hypoglycemia resulted in emergency department visits (incidence ratio of 11.2 per 1000 patients with diabetes).
- Hypoglycemia causes neurogenic (autonomic) symptoms such as tremor, anxiety, tachycardia, sweating, and hunger as well as neuroglycopenic symptoms such as dizziness, weakness, drowsiness, confusion, and possibly, seizure and coma at lower plasma glucose concentrations. Although extreme, prolonged hypoglycemia can cause brain death, the majority of episodes are reversed after the glucose level is raised. Rare fatal episodes are generally thought to be due to other mechanisms such as ventricular arrhythmia (*Cryer 2019, Seaquist et al 2013*).
- The goal of treatment of hypoglycemia is to normalize the plasma glucose concentration by administering carbohydrates (dietary or parenteral according to the level of consciousness), or in cases of severe hypoglycemia, by administering glucagon (*Cryer 2019*).
  - Patients with symptomatic hypoglycemia should ingest glucose in the form of tablets, juice, milk, other snacks, or a meal.
  - Patients with severe hypoglycemia can usually be treated quickly by giving intravenous (IV) dextrose.
  - In a person with impaired consciousness and no established IV access, administration of glucagon (subcutaneously [SC], intramuscularly [IM], or intranasally [IN]) by a second party will usually lead to recovery of consciousness within approximately 15 minutes, although it may be followed by marked nausea or even vomiting.

- The response to IV glucose and glucagon is transient; therefore, treatment of hypoglycemia often needs to be followed by a continuous infusion of glucose or by intake of food if the patient is able to eat.

- Injectable glucagon has been approved for use in the U.S. for several decades (*Baqsimi FDA News Release 2019*). A few injectable products (ie, GlucaGen and Glucagon Emergency Kits [GEKs] by Lilly [GEK-L] and Fresenius Kabi [GEK-F]) are available for SC or IM administration that require the caregiver to reconstitute the glucagon powder with the diluent prior to injection. A recently approved product, Gvoke (glucagon injection), is available as an auto-injector or prefilled syringe for SC administration and does not require reconstitution. Baqsimi (glucagon nasal powder) is the first IN administered glucagon to be approved; it can be delivered by placing the tip of the device in one nostril and depressing a small plunger that discharges the powder into the nostril without need for inhalation from the patient (*Cryer 2019*).

**Indication**

- Baqsimi is indicated for the treatment of severe hypoglycemia in patients with diabetes ages 4 years and above.
- GEKs are indicated as a treatment for severe hypoglycemia in patients with diabetes mellitus, while GlucaGen is indicated to treat severe hypoglycemia (low blood sugar) reactions which may occur in patients with diabetes mellitus treated with insulin.
  - These products are also indicated for use as a diagnostic aid during radiologic examinations to temporarily inhibit the movement of the gastrointestinal tract. This indication will not be addressed in this review.
- Gvoke is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above.

**Pharmacology**

- Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect.

**Clinical Efficacy**

- Two randomized, open-label (OL), 2-period, crossover (XO), noninferiority studies compared the efficacy of a single 3 mg dose of Baqsimi to a single 1 mg dose of IM glucagon injection (GlucaGen) for treatment of insulin-induced hypoglycemia in adults with diabetes (*Baqsimi Dossier 2019*, *Baqsimi Prescribing Information 2019*, *Rickels et al 2016*). One of the studies included 70 adult patients with T1DM, while the other study included 83 adult patients with T1DM or T2DM. The primary outcome measure was the proportion of patients achieving treatment success, defined as either an increase in blood glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon.
  - In both studies, Baqsimi demonstrated noninferiority to IM glucagon in reversing insulin-induced hypoglycemia (98.8 to 100% for Baqsimi vs 100% for IM glucagon). In one study, the mean time to treatment success was 11.6 minutes for the Baqsimi group vs 9.9 minutes for the IM glucagon group while in the other study, the mean time to treatment success was 15.9 minutes for Baqsimi group vs 12.1 minutes for the IM glucagon group.
- In a pediatric study of 48 patients aged ≥ 4 years with T1DM, similar results for Baqsimi 3 mg vs weight-based (0.5 mg or 1 mg) IM glucagon were observed. The primary endpoint was the percentage of patients with a glucose increase of ≥ 20 mg/dL from glucose nadir within 30 minutes of glucagon administration (*Baqsimi Dossier 2019*, *Baqsimi Prescribing Information 2019*, *Sherr et al 2016*).
  - Across all age groups, all (100%) patients in both treatment arms achieved an increase in glucose ≥ 20 mg/dL from glucose nadir within 20 minutes of glucagon administration. The mean time to reach a glucose increase ≥ 20 mg/dL ranged from 10.8 to 14.2 minutes for Baqsimi and 10.8 to 12.5 minutes for IM glucagon.
- In a comparative usability study (N = 31) evaluating the use of Baqsimi and IM glucagon by individuals in a simulated emergency event, participants were significantly more likely to successfully administer a full dose with Baqsimi (94% of attempts) than with injectable glucagon (13% of attempts) (*Yale et al 2017*).
- In 2 OL, real-world usability studies involving caregivers of adults with T1DM (N = 69) and caregivers of children with T1DM (N = 15), Baqsimi was successful in treating episodes of moderate and severe hypoglycemia in 95.7% of adults and 100% of children. Of note, the trials had serious quality limitations and additional data are needed to validate the results (*Deeb et al 2018, Seaquist et al 2018)*.
- Two randomized, 2-way, XO, noninferiority studies (N = 181) compared the efficacy of Gvoke 1 mg SC to GEK-L 1 mg SC for treatment of insulin-induced hypoglycemia in adults with T1DM (*Gvoke Prescribing Information 2019, Christensen et al 2019 [poster]*). The primary efficacy endpoint was the proportion of patients achieving treatment success, defined as either an increase in plasma glucose from a mean value at the time of glucagon administration to an absolute value ≥ 70 mg/dL or a relative increase of ≥ 20 mg/dL at 30 minutes after receiving study glucagon.
  - In a pooled analysis of both studies, the proportion of patients who achieved treatment success was 99% in the Gvoke group and 100% in the GEK-L group, and the comparison between groups met the prespecified non-inferiority margin.

- An OL study of 31 patients ≥ 2 years of age with T1DM evaluated 2 doses of Gvoke for treatment of insulin-induced hypoglycemia (*Gvoke Prescribing Information 2019*, *Buckingham et al 2018 [poster]*). Patients 2 to < 6 years and 6 to < 12 years received Gvoke 0.5 mg SC while patients ≥ 12 years received either Gvoke 0.5 mg or 1 mg SC.
  - All evaluable patients achieved a target dose of at least 25 mg/dL.
- Two human factors studies evaluated whether the Gvoke prefilled syringe could be effectively administered (*Newswanger et al 2019*). In a formative study (N = 11), there was a 100% success rate while in the validation study (N = 75), 99% of patients successfully administered the full dose. Similarly, 2 human factors studies evaluated whether the Gvoke auto-injector could be effectively administered (*Valentine et al 2019*). In the simulated-use comparative usability study (N = 16), 88% of participants were able to successfully administer a rescue injection using Gvoke compared with 31% with the GEKs. In the validation study (N = 75), 98.7% of patients successfully administered the rescue injection using the Gvoke auto-injector.

**Place in Therapy**

- ADA guidelines recommend that all patients at increased risk of hypoglycemia < 54 mg/dL be prescribed glucagon so that it would be available if needed (*ADA 2019*). Caregivers, school personnel, or family members should know where it is and when and how to administer it.
- The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) guidelines recommend that SC or IM glucagon or IV glucose be given by a trained family member or medical personnel to patients experiencing severe hypoglycemia who are unable to swallow or is unresponsive (*Handelsman et al 2015*).

**Safety**

- All glucagon products are contraindicated in patients with known hypersensitivity to any of the constituents of the formulation, and they all carry a warning for lack of efficacy in patients with decreased hepatic glycogen. They are also contraindicated or have a warning for patients with pheochromocytoma and insulinoma. The injectable products also have a warning for necrolytic migratory erythema (NME) due to postmarketing reports following continuous glucagon infusion.
- The most common adverse events (AEs) with Baqsimi were nausea, vomiting, headache, upper respiratory tract irritation, watery eyes, redness of eyes, and itchy nose, throat and eyes. Common AEs with the injectable products included nausea, vomiting, and injection site reactions.

**Dosing**

- Baqsimi is administered IN via a device containing glucagon nasal powder, and it is available in a 3 mg strength for all patients. Gvoke is administered SC only via a prefilled auto-injector or a prefilled syringe that does not require reconstitution; it is available in 2 strengths (0.5 mg and 1 mg) for age and weight-based dosing. GlucaGen and the GEKs may be given SC, IM, or IV; these kits produce a 1 mg/mL glucagon solution after reconstitution which is used for age and weight-based dosing.
  - An additional dose using a new kit/device may be given while waiting for emergency assistance.
  - When the patient responds to treatment, oral carbohydrates should be given to restore the liver glycogen and prevent recurrence of hypoglycemia.

**Conclusion**

- Severe hypoglycemia is generally defined as a hypoglycemic event that requires assistance from another person to administer carbohydrates or glucagon or take other corrective action. Immediate treatment is necessary to increase blood sugar and prevent serious complications, such as loss of consciousness, seizure, coma, or death. If the patient is unable to swallow or is unresponsive, current treatment options include IV infusion of glucose by a healthcare provider or administration of glucagon by trained caregivers.
- Injectable glucagon in the form of kits containing a prefilled syringe of diluent and a vial of glucagon powder for reconstitution has been approved for use in the U.S. for many years. Recently, 2 new glucagon formulations have been approved that provide additional options for the treatment of severe hypoglycemia in patients with diabetes that may simplify the process of glucagon administration. Gvoke is available in the form of an auto-injector or prefilled syringe that does not require reconstitution, while Baqsimi is the first IN formulation of glucagon.
  - Both Baqsimi and Gvoke were approved based on studies that found them to be comparable to injectable glucagon in terms of increasing plasma glucose in patients with insulin-induced hypoglycemia.
  - In manufacturer-sponsored usability studies, there were higher rates of successful administration with Baqsimi and Gvoke compared with the GEKs.

## INDICATIONS

**Severe hypoglycemia**

- Baqsimi is indicated for the treatment of severe hypoglycemia in patients with diabetes ages 4 years and above.
- GEK-F is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes.

- GEK-L is indicated as a treatment for severe hypoglycemia (low blood sugar) which may occur in patients with diabetes mellitus.
  - Because patients with T1DM may have less of an increase in blood glucose levels compared with a stable T2DM patient, supplementary carbohydrates should be given as soon as possible, especially to a pediatric patient.
- GlucaGen is indicated to treat severe hypoglycemia (low blood sugar) reactions which may occur in patients with diabetes mellitus treated with insulin.
  - Because GlucaGen depletes glycogen stores, the patient should be given supplemental carbohydrates as soon as he/she awakens and is able to swallow, especially children or adolescents. Medical evaluation is recommended for all patients who experience severe hypoglycemia.
- Gvoke is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above.

**Diagnostic aid**

- GlucaGen and the GEKs are indicated for use as a diagnostic aid during radiologic examinations to temporarily inhibit the movement of the gastrointestinal tract. This indication is not addressed in this review.

**PHARMACOLOGY**

- Glucagon increases blood glucose concentration by activating hepatic glucagon receptors, thereby stimulating glycogen breakdown and release of glucose from the liver. Hepatic stores of glycogen are necessary for glucagon to produce an antihypoglycemic effect.
- In a Phase 1 repeated-measures study, the efficacy and pharmacokinetics (PK) of Baqsimi were found to be unaffected by the presence of nasal congestion or the use of decongestant medication. No statistical differences were observed following baseline correction (*Baqsimi Dossier 2019*).
  - Cold symptoms: 1198 pg/mL; 144 mg/dL
  - No congestion: 801.5 pg/mL; 139 mg/dL
  - Decongestant: 868.0 pg/mL; 158 mg/dL

**CLINICAL EFFICACY**

**STUDY DESIGN ABBREVIATIONS: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover**

***Search Strategy**: Studies supporting the FDA-approved indication were identified using search terms "severe hypoglycemia" and "glucagon" through September 11, 2019. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

**Baqsimi**

**Study 1. Sherr et al, *Diabetes Care.* 2016;39(4):555-562. Baqsimi Prescribing Information 2019. Baqsimi Dossier 2019. Data on file, Eli Lilly and Company.**

| **Study Objective: Evaluate the ability of Baqsimi compared with injectable glucagon (GlucaGen HypoKit) to increase blood glucose after insulin-induced reduction in blood glucose in children and adolescents aged 4 to < 17 years with T1DM** | |
|---|---|
| **Study Design, Follow-up** | **Treatment Groups** |
| • Randomized, MC, Phase 1, dose-finding study (N = 48)<br>  ○ Insulin was used to reduce blood glucose levels, and glucagon was given after plasma glucose reached < 80 mg/dL. | Children 4 to < 8 years old (n = 18)<br>• Baqsimi 2 mg and 3 mg IN in a DB, XO fashion during different visits (n = 12)<br>• Weight-based glucagon (< 25 kg: 0.5 mg, ≥ 25 kg: 1 mg) IM (n = 6)<br><br>Children 8 to < 12 years old (n = 18)<br>• Baqsimi 2 mg and 3 mg IN in a DB, XO fashion during different visits (n = 12)<br>• Weight-based glucagon (< 25 kg: 0.5 mg, ≥ 25 kg: 1 mg) IM (n = 6)<br><br>Children 12 to < 17 years old (n = 12) |

| | |
|---|---|
| | • All patients received Baqsimi 3 mg IN and glucagon 1 mg IM in a XO fashion during different visits |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • Children aged 4 to < 17 years with T1DM for at least 1 year and in good general health | • History of a severe hypoglycemic episode in the month prior to enrollment<br>• Pheochromocytoma or insulinoma; history of epilepsy or seizure disorder; cardiovascular, gastrointestinal, liver, or kidney disease<br>• Use of medications such as beta-blockers |
| **Primary Endpoint** | |
| • Percentage of patients with a glucose increase of ≥ 20 mg/dL from glucose nadir within 30 minutes of glucagon administration (primary endpoint in FDA review)<br>○ Glucose nadir was defined as the minimum glucose measurement within 10 minutes after glucagon administration.<br>○ Note: The original primary efficacy measure in the study was the percentage of patients achieving a ≥ 25 mg/dL increase in blood glucose above the blood nadir concentration within 20 minutes of glucagon administration. | |

- **Results:**
  - The mean age in the young children cohort (4 to < 8 years) was 6.5 years. In the children cohort (8 to < 12 years), mean age was 11.1 years and in the adolescents cohort (12 to <17 years), mean age was 14.6 years. In all age cohorts, the population was predominantly male and white.
  - Insulin infusion lowered the mean nadir plasma glucose levels to a range of 67 to 75 mg/dL for the Baqsimi visits and 69 to 72 mg/dL for the IM glucagon visits.
  - It was found that Baqsimi 3 mg was the optimal dose in children and adolescents aged 4 to 17 years; only the results of this FDA-approved dose are reported below.
  - Across all age groups, all (100%) patients in both treatment arms achieved an increase in glucose ≥ 20 mg/dL from glucose nadir within 20 minutes of glucagon administration. The mean time to reach a glucose increase of ≥ 20 mg/dL for Baqsimi and IM glucagon for all age groups is shown in Table 1.

**Table 1. Mean time to reach glucose increase of ≥ 20 mg/dL from nadir in pediatric patients with T1DM**

| Increase from blood glucose nadir | Mean time post-glucagon administration (minutes) | | | | | |
|---|---|---|---|---|---|---|
| | Young children (4 to < 8 years old) | | Children (8 to < 12 years old) | | Adolescents (12 to < 17 years old) | |
| | IM glucagon n = 6 | Baqsimi 3 mg n = 12 | IM glucagon n = 6 | Baqsimi 3 mg n = 12 | IM glucagon n = 12 | Baqsimi 3 mg n = 12 |
| ≥ 20 mg/dL | 10.8 | 10.8 | 12.5 | 11.3 | 12.5 | 14.2 |

  - Common AEs included vomiting (Baqsimi 3 mg: 30.6% vs IM glucagon: 37.5%), headache (25.0% vs 12.5%), nausea (16.7% vs 33.3%), and upper respiratory tract irritation (16.7% vs 0%).
  - Nasal and ocular symptoms were solicited via a patient questionnaire. These AEs were more commonly reported with Baqsimi (eg, watery eyes [Baqsimi: 47.2% vs IM glucagon: 0%], nasal congestion [41.7% vs 0%], nasal itching [27.8% vs 4.2%], runny nose [25.0% vs 0%]).
- **Authors' conclusion:**
  - The results of this study support the potential efficacy of Baqsimi for the treatment of hypoglycemia in youth with T1DM. A single 3 mg IN dose appears to be appropriate for use across the entire age range.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Eli Lilly and Company
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Patients in the 2 younger cohort groups received both the 2 mg and 3 mg Baqsimi doses, allowing for assessment of whether age- or weight-based dosing would be required.
  - **Study limitations:**
    - Hypoglycemia was not induced for ethical reasons, limiting the generalizability of the results to real-world situations during which glucagon would be used.
    - The population was predominantly male and white.

- Patients in the 2 younger cohort groups either received weight-based IM glucagon or Baqsimi, precluding direct comparison of the formulations in each individual patient.
- The study was carried out in a controlled setting, and the drugs were administered by trained professionals.

**Study 2. Baqsimi Prescribing Information 2019. Baqsimi Dossier 2019. Data on file, Eli Lilly and Company.**

| **Study Objective: Evaluate the safety and efficacy of Baqsimi vs IM glucagon (GlucaGen HypoKit) as treatment for insulin-induced hypoglycemia in adults with T1DM** | |
|---|---|
| **Study Design, Follow-up** | **Treatment Groups** |
| • Randomized, MC, OL, 2-period, XO, noninferiority study (N = 70)<br>○ IV insulin was used to reduce blood glucose levels, and glucagon was given after plasma glucose reached < 60 mg/dL. | • Baqsimi 3 mg IN then XO to glucagon 1 mg IM, or vice versa |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • Adults aged 18 to 64 with T1DM of at least 2 years' duration<br>• Receiving daily insulin ≤ 1.5 U/kg<br>• Body mass index (BMI) 18.5 to 35 kg/m$^2$<br>• Glycosylated hemoglobin (HbA1c) ≤ 10% | • History of a severe hypoglycemic episode in the month prior to enrollment<br>• Pheochromocytoma or insulinoma; history of epilepsy or seizure disorder; cardiovascular, liver, gastrointestinal, or kidney disease<br>• Use of medications such as beta-blockers, warfarin, indomethacin, or anticholinergic drugs |
| **Primary Endpoint** | |
| • Proportion of patients achieving treatment success (defined as either an increase in blood glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level)<br>○ Glucose nadir was defined as the minimum glucose measurement at the time of, or within 10 minutes, following glucagon administration.<br>○ Baqsimi was deemed noninferior to injectable glucagon if the upper limit of the 2-sided 95% CI of the mean difference in treatment success rates was < 10%. | |

- **Results:**
  - The mean age was 41.7 years; the mean diabetes duration was 20.1 years; and 39% of the patients were female.
  - The mean nadir blood glucose was 54.5 mg/dL for Baqsimi and 55.8 mg/dL for IM glucagon.
  - Baqsimi demonstrated noninferiority to IM glucagon, with 100% of both groups achieving treatment success within 30 minutes (see Table 2 below).

**Table 2. Adult patients with T1DM meeting treatment success**

| | **T1DM (N = 66)** | |
|---|---|---|
| | **Baqsimi 3 mg** | **IM glucagon 1 mg** |
| **Treatment success n (%)** | 66 (100%) | 66 (100%) |
| **Treatment difference % (2-sided 95% CI)** | 0% (-2.9 to 2.9%) | |
| **Glucose criterion met n (%)** | | |
| **(i) ≥ 70 mg/dL** | 66 (100%) | 66 (100%) |
| **(ii) increase by ≥ 20 mg/dL from nadir** | 66 (100%) | 66 (100%) |
| **Both (i) and (ii)** | 66 (100%) | 66 (100%) |

  - The mean time to treatment success was 11.6 minutes for the Baqsimi group vs 9.9 minutes for the IM glucagon group.
  - Pooled AEs for Studies 2 and 3 are reported below.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Eli Lilly and Company
  - **Study limitations:**
    - The glucagon dosing administration was not blinded, which could have influenced the investigator's approach to the insulin infusion protocol.
    - Glucagon was administered by trained health care professionals under nonemergency conditions; it is unknown whether similar results would be obtained in a real-world setting.

**Study 3. Rickels et al, *Diabetes Care*. 2016;39(2):264-270. Baqsimi Prescribing Information 2019. Baqsimi Dossier 2019. Data on file, Eli Lilly and Company.**

| **Study Objective: Evaluate the safety and efficacy of Baqsimi vs IM glucagon (GlucaGen HypoKit) as treatment for insulin-induced hypoglycemia in adults with T1DM or T2DM** | |
|---|---|
| **Study Design, Follow-up** | **Treatment Groups** |
| • Randomized, MC, OL, 2-period, XO, noninferiority study (N = 83)<br>○ IV insulin was used to reduce blood glucose levels, and glucagon was given after plasma glucose reached < 60 mg/dL. | • Baqsimi 3 mg IN then XO to glucagon 1 mg IM, or vice versa (visits were scheduled 1 to 4 weeks apart) |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • Adults aged 18 to 64<br>• T1DM of at least 2 years' duration (an additional 6 patients with T2DM were enrolled)<br>• Weighing ≥ 50 kg with BMI 20 to 35 kg/m$^2$ | • History of a severe hypoglycemic episode in the month prior to enrollment<br>• Pheochromocytoma or insulinoma; history of epilepsy or seizure disorder; cardiovascular, liver, or kidney disease<br>• Use of medications such as beta-blockers<br>• Consumption of ≥ 3 alcoholic beverages daily |
| **Primary Endpoint** | |
| • Proportion of patients achieving treatment success (defined as either an increase in blood glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon, without receiving additional actions to increase the blood glucose level)<br>○ Glucose nadir was defined as the minimum glucose measurement at the time of, or within 10 minutes, following glucagon administration.<br>○ Baqsimi was deemed noninferior to injectable glucagon if the upper limit of the 2-sided 97.5% CI of the mean difference in treatment success rates was < 10%. | |

- **Results:**
  - In patients with T1DM (n = 77), the mean age was 32.9 years; the mean diabetes duration was 18.1 years; and 58% of the patients were female. In patients with T2DM (n = 6), the mean age was 47.8 years; the mean diabetes duration was 18.8 years; and 67% of the patients were female.
  - The mean nadir blood glucose was 44.2 mg/dL for Baqsimi and 47.2 mg/dL for IM glucagon.
  - Baqsimi demonstrated noninferiority to IM glucagon, with 98.8% of Baqsimi-treated patients and 100% of IM glucagon-treated patients achieving treatment success within 30 minutes (see Table 3 below).

**Table 3. Adult patients with T1DM meeting treatment success**

| | **T1DM and T2DM (N = 80)** | |
|---|---|---|
| | **Baqsimi 3 mg** | **IM glucagon 1 mg** |
| **Treatment success – n (%)** | 79 (98.8%) | 80 (100%) |
| **Treatment difference – % (2-sided 95% CI)** | -1.3% (-4.6 to 2.2%) | |
| **Glucose criterion met – n (%)** | | |
| **(i) ≥ 70 mg/dL** | 77 (96%) | 79 (99%) |
| **(ii) increase by ≥ 20 mg/dL from nadir** | 79 (99%) | 80 (100%) |
| **Both (i) and (ii)** | 77 (96%) | 79 (99%) |

  - The mean time to treatment success was 15.9 minutes for the Baqsimi group vs 12.1 minutes for the IM glucagon group.
  - Common pooled AEs reported in Studies 2 and 3 included nausea (Baqsimi 3 mg: 26.1% vs IM glucagon: 33.8%), headache (18.3% vs 9.3%), vomiting (15.0% vs 13.9%), and upper respiratory tract irritation (12.4% vs 1.3%).
  - Nasal and ocular symptoms were solicited via a patient questionnaire in Studies 2 and 3. These AEs were more commonly reported with Baqsimi (eg, watery eyes [Baqsimi: 58.8% vs IM glucagon: 2.0%], nasal congestion [42.5% vs 6.0%], nasal itching [39.2% vs 4.6%], runny nose [34.6% vs 0%]).
- **Authors' conclusion:**
  - Baqsimi was highly effective in treating patients with insulin-induced hypoglycemia in adults with T1DM. Although the trial was conducted in a controlled setting, the results are applicable to real-world management of severe

hypoglycemia, which occurs owing to excessive therapeutic insulin relative to the impaired or absent endogenous glucagon response.

- **Study Appraisal:**
  - **Study sponsorship:**
    - Eli Lilly and Company
  - **Study rating:**
    - Fair
  - **Study limitations:**
    - The glucagon dosing administration was not blinded, which could have influenced the investigator's approach to the insulin infusion protocol.
    - There was no placebo group to control for spontaneous recovery, but hospital policies precluded not treating hypoglycemia < 40 mg/dL and it would have been unethical to reduce glucose levels to the point of seizure or unconsciousness.
    - Glucagon was administered by trained health care professionals under nonemergency conditions; it is unknown whether similar results would be obtained in a real-world setting.

**Study 4. Yale et al, *Diabetes Technol Ther*. 2017;19(7):423-432.**

- A comparative usability study was conducted to evaluate the relative ability of nonmedical personnel (caregivers [Group 1] and acquaintances [Group 2] of people with diabetes) to administer Baqsimi compared to injectable glucagon (GEK-L) during simulated severe hypoglycemic episodes. A total of 16 instructed caregivers and 15 noninstructed acquaintances administered Baqsimi and injectable glucagon to manikins. Key endpoints included speed and accuracy of dose delivery, percentage of glucagon dose delivered, and ease of use.
  - With Baqsimi, 15 caregivers (94%) and 14 acquaintances (93%) administered a full dose (mean time 0.27 and 0.44 min, respectively). However, 2 caregivers also administered insulin believing it would help the patient.
  - With injectable glucagon, 8 caregivers (50%) injected glucagon (mean time 1.89 min), but only 2 (13%) administered the full dose. Three acquaintances (20%) injected a partial dose of injectable glucagon (mean time 2.40 min); none gave a full dose. Two caregivers and 1 acquaintance injected insulin because they confused insulin with injectable glucagon.
  - When asked which treatment option they would recommend, 81% of caregivers preferred Baqsimi; 6% had no preference, and 13% preferred injectable glucagon. All acquaintances stated that they would recommend Baqsimi. Of the individuals with diabetes, 69% preferred Baqsimi; 19% preferred injectable glucagon; and 13% had no preference.
- **Authors' Conclusion:**
  - Administration of Baqsimi is faster and has a much higher success rate for delivery of the full glucagon dose with fewer errors than injectable glucagon. It was preferred over injectable glucagon by both people with diabetes and caregivers.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Locemia Solutions/Eli Lilly and Company
  - **Study strengths:**
    - This study evaluated the use of both Baqsimi and injectable glucagon.
  - **Study limitations:**
    - The sample size was small. To achieve 95% power, 16 pairs and 16 acquaintances were required to complete the study. Because there were fewer acquaintances than planned, the statistical power for this group was 94% rather than 95%.
    - The simulation may not have fully replicated the experience of treating a patient during a severe hypoglycemic episode.
    - The study design required the caregivers and acquaintances to encounter the emergency situation twice; the second simulation may have been less stressful.
    - There was only a 1 to 2 week delay between instruction and the simulation whereas a real-life delay could be months or years.
    - The manikin was assumed to be an adult, which did not necessitate measuring the dose of injectable glucagon based on age and weight.
    - It is unknown how these simulated administrations would have impacted the outcome of the hypoglycemic event.

**Study 5. Deeb et al, *Pediatr Diabetes*. 2018;19(5):1007-1013.**

- A MC, OL, Phase 3, prospective study was conducted to evaluate the real-world effectiveness and ease of use of Baqsimi in treating moderate (symptoms and/or signs of neuroglycopenia and a blood glucose level of ≤ 70 mg/dL) or severe (severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy) hypoglycemic

events in children and adolescents with T1DM (N = 26). Caregivers were instructed to administer a single dose of Baqsimi 3 mg IN to the patient if a spontaneous severe or moderate hypoglycemic event occurred. The primary outcome was the proportion of patients awakening or returning to normal status within 30 minutes of Baqsimi administration.
  - Of the 26 patients who were enrolled in the study, 11 patients were from a non-compliant site and were excluded from analysis. Of the remaining 15 patients, 14 reported experiencing 33 moderate hypoglycemic events, at which time Baqsimi was administered.
  - All hypoglycemic events (100%) resolved, and patients returned to normal status within 30 minutes after Baqsimi administration; 54.5% of events resolved within 10 minutes.
  - Mean blood glucose levels increased from 55.5 mg/dL (range 42 to 70 mg/dL) at baseline to 113.7 mg/dL (range 79 to 173 mg/dL) within 15 minutes of Baqsimi administration.
  - The most common AEs were nasal discomfort (92.9%), watery eyes (85.7%), headache (71.4%), runny nose (64.3%), nasal congestion (50.0%), sneezing (50.0%), and redness of eyes (42.9%). Three patients withdrew from the study after 3 months due to severe nasal discomfort following treatment.
  - Caregivers reported that the administration of Baqsimi was easy or very easy in 93.9% of hypoglycemic events. Caregivers were able to administer it within 30 seconds in 60.6% of events and within 2 minutes in 100% of events.
- **Authors' Conclusion:**
  - A single 3-mg dose of Baqsimi was effective in treating moderate, symptomatic, hypoglycemic events in children and adolescents with T1DM in a real-world setting. It was easy-to use and reasonably well tolerated.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Eli Lilly and Company
  - **Study strengths:**
    - This study evaluated the use of Baqsimi in a real-world setting.
  - **Study limitations:**
    - The sample size was small, and only 58% (n = 15) were able to be evaluated (11 patients were excluded from a non-compliant study site).
    - There was no comparison group.
    - No patients experienced severe hypoglycemia, the indication for which Baqsimi is FDA-approved.
    - This was not a randomized, controlled study; all data were collected by the patients and caregivers, which may have led to inconsistencies in reporting.

**Study 6. Seaquist et al, *Diabetes Obes Metab*. 2018;20(5):1316-1320.**
- A MC, single-arm, OL, Phase 3, prospective study was conducted to evaluate real-world effectiveness and ease of use of Baqsimi in treating moderate (symptoms and/or signs of neuroglycopenia and a blood glucose level of ≤ 60 mg/dL) or severe (patient is incapacitated and requires third-party assistance) hypoglycemic events in adults with T1DM. The efficacy population included 69 patients (with 157 events) and the safety population included 74 patients (with 179 events. Caregivers were instructed to administer a single dose of Baqsimi 3 mg IN to the patient if a spontaneous severe or moderate hypoglycemic event occurred. The primary outcome was the proportion of patients awakening or returning to normal status within 30 minutes of Baqsimi administration.
  - In the efficacy population, a total of 66 patients (95.7%) awakened or returned to normal status within 30 minutes after Baqsimi administration.
    - A total of 151 events (96.2%) resolved within 30 minutes after Baqsimi administration.
    - In all of the 12 severe hypoglycemic events, patients awakened or returned to normal status within 15 minutes of Baqsimi administration without additional external medical help.
  - Mean blood glucose levels increased from 47.9 mg/dL at the time of Baqsimi administration to 84.4 mg/dL after 15 minutes and continued to increase.
  - The most common AE was nasal irritation, reported by 82.4% of patients; in more than half of these patients, it was short-lasting and resolved within 1 hour. One patient withdrew from the study because of local nasal AEs.
  - The majority of caregivers reported that it was easy to understand the kit instructions (91% of events) and to administer the product (80.5% of events). Caregivers were able to administer Baqsimi within 30 seconds in 70.4% of the events and within 1 minute in 92.7% of the events.
- **Authors' Conclusion:**
  - A single, 3-mg dose of Baqsimi demonstrated real-life effectiveness in treating moderate and severe hypoglycemic events in adults with T1DM. It was well tolerated and easy to use.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Eli Lilly and Company
  - **Study strengths:**

- This study evaluated the use of Baqsimi in a real-world setting.

- **Study limitation:**
  - There was no comparison group (single-arm study).
  - The number of severe hypoglycemic events was low. The hypoglycemic events in which patients required oral carbohydrates, injectable glucagon, and professional medical assistance within 30 minutes and before clinical response, were excluded from the efficacy analysis population.
  - A total 21 patients were considered ineligible for analysis (16 because of a clinical trial material issue resulting in potential under-dose, and 5 because of site termination).
  - This was not a randomized, controlled study.

**Gvoke**

**Study 7 and Study 8. Gvoke Prescribing Information 2019. Christensen et al, Poster presented at American Diabetes Association 79th Scientific Sessions, June 7–11, 2019, San Francisco, CA.**

- Gvoke was evaluated in adult patients aged 18 to 74 years with T1DM in 2 randomized, MC, XO, noninferiority studies. XSGP-301 was a DB study (N = 80) while Study XSGP-303 (N = 81) was a single-blinded study. Insulin was used to induce hypoglycemia, and glucagon was given after glucose reached < 50 mg/dL. Patients were randomized to receive Gvoke 1 mg SC via auto-injector during one session, then GEK-L 1 mg SC during the other session. The primary efficacy endpoint was the proportion of patients achieving treatment success (defined as either an increase in plasma glucose from a mean value at the time of glucagon administration to an absolute value ≥ 70 mg/dL or a relative increase of ≥ 20 mg/dL at 30 minutes after receiving study glucagon).
  - In Study XSGP-301, mean plasma glucose at the time of glucagon administration was 44.8 mg/dL and 45.2 mg/dL for Gvoke and GEK-L, respectively. In Study XSGP-303, mean plasma glucose at the time of glucagon administration was 47.7 mg/dL and 48.7 mg/dL for Gvoke and GEK-L, respectively.
  - In a pooled analysis of both studies, the proportion of patients who achieved treatment success was 99% in the Gvoke group and 100% in the GEK-L group, and the comparison between groups met the prespecified non-inferiority margin (see Table 4 below).

**Table 4. Adults meeting treatment success in Studies XSGP-301 and XSGP-303 combined**

| | XSGP-301 (N = 80) | | XSGP-303 (N = 81) | | Pooled Studies (N = 161) | |
|---|---|---|---|---|---|---|
| | Gvoke | GEK-L | Gvoke | GEK-L | Gvoke | GEK-L |
| **Treatment Success – n (%)** | 76 (97%) | 79 (100%) | 76 (100%) | 78 (100%) | 152 (99%) | 157 (100%) |
| **Glucose criteria met – n (%)** | | | | | | |
| **> 70 mg/dL** | 74 (95%) | 79 (100%) | 76 (100%) | 78 (100%) | 150 (97%) | 157 (100%) |
| **≥ 20 mg/dL increase** | 76 (97%) | 79 (100%) | 76 (100%) | 78 (100%) | 152 (99%) | 157 (100%) |

**Note**: Data obtained from the *Gvoke prescribing information 2019.*

  - The mean time to treatment 'success' was 13.8 minutes in the Gvoke group and 10 minutes in the GEK-L group.
  - The most commonly reported AE considered related to study drug for patients receiving either product was nausea (Gvoke: 29.9% vs GEK-L: 22.9%) followed by vomiting (Gvoke: 16.2% vs GEK-L: 9.6%).
- **Conclusion:**
  - These studies demonstrated that Gvoke consistently corrected insulin-induced severe hypoglycemia in adults with T1DM in a reliable manner, meeting the predefined definition of non-inferiority to GEK-L.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Xeris Pharmaceuticals
  - **Study limitation:**
    - The study was carried out in a controlled setting; it is unknown whether similar results would be obtained in a real-world setting.

**Study 9. Gvoke Prescribing Information 2019. Buckingham et al, Poster presented at: American Diabetes Association 78th Scientific Sessions; Orlando, Florida, June 22–26, 2018.**

- An OL sequential efficacy and safety study (XPS-302) was conducted in 31 children ages 2 to 17 years with T1DM to evaluate 2 doses of Gvoke auto-injector (0.5 mg or 1 mg) for treatment of hypoglycemia (plasma glucose < 80 mg/dL) induced via IV insulin or insulin pump. Patients 2 to < 6 years and 6 to < 12 years received Gvoke 0.5 mg SC while

patients ≥ 12 years received either Gvoke 0.5 mg or 1 mg SC. The primary efficacy endpoint was increase in mean plasma glucose from baseline at 30 minutes following administration of an age-appropriate glucagon dose.
  - All evaluable patients achieved a target dose of at least 25 mg/dL. Plasma glucose over time showed similar responses for patients in each age group (see Table 5).

**Table 5. Pediatric patients with T1DM plasma glucose by age group**

| Age group | Gvoke dose | Plasma glucose (mg/dL) Mean (standard deviation) | | |
|---|---|---|---|---|
| | | Baseline | 30 minutes | Change |
| **2 to < 6 years (n = 7)** | 0.5 mg | 68.1 (8.3) | 149.6 (15.2) | 81.4 (18.3) |
| **6 to < 12 years (n = 13)** | 0.5 mg | 71.6 (7.6) | 155.8 (26.5) | 84.2 (25.3) |
| **12 to < 18 years (n = 11)** | 0.5 mg | 75.2 (2.1) | 128.1 (20.46) | 52.9 (19.88) |
| | 1.0 mg | 74.5 (4.84) | 129.5 (29.5) | 55.0 (27.3) |

**Note**: Data obtained from the *Gvoke prescribing information 2019.*

  - Nausea (45%), hypoglycemia (39%), and vomiting (19%) were the most commonly reported AEs.
- **Conclusion:**
  - This study demonstrated that Gvoke consistently corrected insulin-induced hypoglycemia in pediatric patients with T1DM.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Xeris Pharmaceuticals
  - **Study limitation:**
    - The study was carried out in a controlled setting; it is unknown whether similar results would be obtained in a real-world setting.

**Study 10. Newswanger et al, *Expert Opin Drug Deliv*. 2019;16(9):1015-1025.**

- Two human factors studies were conducted to evaluate whether the Gvoke prefilled syringe could be safely and effectively administered. In a formative study, 11 caregivers of a patient with diabetes (both experienced and naïve to GEKs). During the first session, 3 naïve caregivers were trained on the device while the others were untrained/given time to familiarize themselves with the device. During session 2, all participants performed a single unaided rescue attempt. During the summative human factors validation study, 75 adult and adolescent participants (first responders, experienced caregivers, and naïve caregivers) received training or familiarized themselves with the Gvoke prefilled syringe device before returning a week later to perform a simulated rescue of a patient suffering from a severe hypoglycemic event.
  - In the formative human factors study, no failures or errors were observed. No significant differences in performance were observed between user groups (experienced vs naïve or trained vs untrained). All participants successfully identified/comprehended critical information in the instructions for use, although some suggested minor enhancements.
  - All 75 participants (100%) performed a successful rescue and injected glucagon into the SC tissue at the designated injection site. Seventy-four (99%) participants delivered the full dose. No significant differences were observed between trained or untrained participants. No participants stated difficulty understanding the instructions.
- **Authors' Conclusion:**
  - The Gvoke prefilled syringe provides an easy-to-use alternative to currently marketed lyophilized glucagon kits for treating severe hypoglycemia.
- **Study appraisal:**
  - **Study sponsorship:**
    - Xeris Pharmaceuticals
  - **Study strength:**
    - The validation study included volunteers with differing backgrounds and experience with glucagon administration.
  - **Study limitation:**
    - The study was carried out in a controlled setting; it is unknown whether similar results would be obtained in a real-world setting.

**Study 11. Valentine et al, *Diabetes Technol Ther*. 2019 ;21(9):522-530.**

- Human factors usability and validation studies were conducted to evaluate the Gvoke auto-injector. The simulated-use comparative usability study was conducted with the Gvoke auto-injector vs GEKs and involved 16 participants (8 caregivers of patients with diabetes or first responders who were experienced with using GEKs, and 8 adults with no relationship to a diabetes patient and naive to GEKs). Half of each participant group received training and the other half received no training. The summative human factors validation study included 75 volunteers (first responders,

experienced caregivers, and naïve caregivers); participants were trained on the Gvoke device or given time to self-familiarize themselves with the device before returning a week later to perform a simulated rescue of a patient suffering from a hypoglycemic emergency.
  - In the usability study, 14 of 16 participants (88%) were able to successfully administer a rescue injection using Gvoke compared with 5 of 16 participants (31%) with the GEKs ($p < 0.05$). Mean total rescue time of use was 47.9 seconds with Gvoke vs 109.0 seconds with GEKs ($p < 0.05$).
  - In the validation study, 98.7% successfully administered the rescue injection using Gvoke. Overall, there were no patterns of differences between trained vs untrained participants, between caregivers vs first responders, or between adults vs adolescents.
- **Authors' Conclusion:**
  - Gvoke auto-injector and instructional materials can be correctly, safely, and effectively used by intended user, supporting it as a viable alternative to currently marketed GEKs.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Xeris Pharmaceuticals
  - **Study strengths:**
    - This usability study had a comparison group (GEKs).
    - The validation study included volunteers with differing backgrounds and experience with glucagon administration.
  - **Study limitation:**
    - The study was carried out in a controlled setting; it is unknown whether similar results would be obtained in a real-world setting.

## CLINICAL GUIDELINES

- **ADA – Glycemic Targets: Standards of Medical Care in Diabetes, 2019** (*ADA 2019*)
  - Glucose (15 to 20 g) is the preferred treatment for the conscious individual with blood glucose < 70 mg/dL, although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if self-monitoring of blood glucose (SMBG) shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia (Grade of recommendation: E).
  - Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose < 54 mg/dL, so that it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals (Grade of recommendation: E).
- **AACE/ACE Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan: Executive Summary** (*Handelsman et al 2015*)
- Oral administration of rapidly absorbed glucose should be used to treat hypoglycemia (generally defined as any blood glucose < 70 mg/dL with or without symptoms including anxiety, palpitations, tremor, sweating, hunger, paresthesias, behavioral changes, cognitive dysfunction, seizures, and coma).
- Severe hypoglycemia is defined as any occurrence that requires assistance from another person to administer carbohydrates or glucagon or take other corrective action. If the patient is unable to swallow or is unresponsive, SC or IM glucagon or IV glucose should be given by a trained family member or medical personnel (Grade A; Evidence Level 1).
  - The usual adult dose is 1 mg; for children weighing < 44 lb (20 kg), the dose is 0.5 mg.
  - As soon as the patient is awake and able to swallow, a rapidly absorbed source of carbohydrate should be given followed by a snack or meal containing protein and carbohydrates (Grade C; Best Evidence Level 3).
- **ADA and The Endocrine Society – Hypoglycemia and Diabetes: A Report of a Workgroup of the ADA and ES** (*Seaquist et al 2013*)
  - Although a single threshold value for plasma glucose concentration that defines hypoglycemia in diabetes cannot be assigned, the workgroup suggests an alert value that can be defined that draws the attention of both patients and caregivers to the potential harm associated with hypoglycemia. Patients at risk for hypoglycemia (ie, those treated with a sulfonylurea, meglitinide, or insulin) should be alert to the possibility of developing hypoglycemia at a glucose concentration of ≤ 70 mg/dL.
  - The following classification of hypoglycemia in diabetes is suggested:
    - Severe hypoglycemia: Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
    - Documented symptomatic hypoglycemia: Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL.

- Asymptomatic hypoglycemia: Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL.
- Probable symptomatic hypoglycemia: Probable symptomatic hypoglycemia is an event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL.
- Pseudo-hypoglycemia: Pseudo-hypoglycemia is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration > 70 mg/dL but approaching that level.

## SAFETY

- **Contraindications**
  - Known hypersensitivity to any of the constituents in the product (all products): Allergic reactions have been reported and include generalized rash, and in some cases, anaphylactic shock with breathing difficulties and hypotension.
  - Pheochromocytoma (Baqsimi, GEK-F, GlucaGen, Gvoke; warning for GEK-L): Use of glucagon in patients with pheochromocytoma may stimulate release of catecholamines from the tumor. If the patient develops a dramatic increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, IV phentolamine mesylate has been shown to be effective in lowering blood pressure.
  - Insulinoma (Baqsimi, GEK-F, GlucaGen, Gvoke; warning for GEK-L): In patients with insulinoma, administration of glucagon may produce an initial increase in blood glucose; however, it may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. If a patient develops symptoms of hypoglycemia, oral or IV glucose should be given.
- **Warnings/precautions**
  - Lack of efficacy in patients with decreased hepatic glycogen (all products): Glucagon is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia, may not have adequate levels of hepatic glycogen for glucagon administration to be effective. Patients with these conditions should be treated with glucose.
  - Necrolytic migratory erythema (NME) (GEKs, GlucaGen, Gvoke): NME, a skin rash commonly associated with glucagonomas (glucagon-producing tumors) and characterized by scaly, pruritic erythematous plaques, bullae, and erosions, has been reported postmarketing following continuous glucagon infusion. NME may affect the face, groin, perineum and legs or be more widespread. In the reported cases, NME resolved with discontinuation of the glucagon, and treatment with corticosteroids was not effective.
  - Glucagonoma (GEK-F, Gvoke): Glucagon administered to patients with glucagonoma may cause secondary hypoglycemia. Patients suspected of having glucagonoma should be tested for blood levels of glucagon prior to treatment, and blood glucose levels should be monitored during treatment. If a patient develops hypoglycemia, glucose should be given orally or IV.
- **Adverse effects**
  - The most common AEs (≥ 10%) with Baqsimi were nausea, vomiting, headache, upper respiratory tract irritation (ie, rhinorrhea, nasal discomfort, nasal congestion, cough, and epistaxis), watery eyes, redness of eyes, and itchy nose, throat and eyes.
  - The most common AEs (≥ 5%) with GEK-F were injection site swelling, injection site erythema, vomiting, nausea, decreased blood pressure, asthenia, headache, dizziness, pallor, diarrhea, and somnolence.
  - The most common AEs with GlucaGen and GEK-L were nausea and vomiting.
  - The most common AEs (≥ 2%) with Gvoke were:
    - Adult patients: nausea, vomiting, injection site edema raised ≥ 1 mm, and headache.
    - Pediatric patients: nausea, hypoglycemia, vomiting, headache, abdominal pain, hyperglycemia, injection site discomfort and reaction, and urticaria.
- **Drug Interactions**
  - Beta-blockers: Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given glucagon.
  - Indomethacin: In patients taking indomethacin, glucagon may lose its ability to raise blood glucose or may even produce hypoglycemia.
  - Warfarin: Glucagon may increase the anticoagulant effect of warfarin.

## DOSAGE AND ADMINISTRATION

Baqsimi

- The recommended dose of Baqsimi is 3 mg administered as 1 actuation of the IN device into 1 nostril. If there has been no response after 15 minutes, an additional 3 mg dose from a new device may be administered while waiting for emergency assistance.

- The dose should be administered by inserting the tip into 1 nostril and pressing the device plunger all the way in until the green line is no longer showing. The dose does not need to be inhaled.
- Emergency assistance should be called immediately after administering the dose.
- When the patient responds to treatment, oral carbohydrates should be given to restore the liver glycogen and prevent recurrence of hypoglycemia.
- Baqsimi should not be reused. Each device only contains 1 dose of glucagon and cannot be reused.

GEK-F and GlucaGen

- The product should be reconstituted according to instructions before administration.
  - The supplied prefilled syringe containing diluent should be inserted and emptied into the vial of dry powder.
  - The entire unit (the vial and syringe) should be held in one hand and gently shaken until the powder is completely dissolved.
  - Carefully holding the unit upside down, all of the liquid should be drawn into the syringe.
  - Keeping the needle inside the vial, the syringe should be tapped until any existing bubbles rise to the top; the plunger should then be gently pushed to move only the air bubbles into the vial.
  - Holding the unit as shown in the instructions, the plunger should be gently pushed until it is at the 0.5 mL mark on the syringe in order to obtain the dose for children weighing < 55 lb (25 kg). The content of the full syringe (1 mL) should be used for adults and children weighing > 55 lb (25 kg).
- The recommended dose is 1 mL (adults and children, weighing > 55 lb [25 kg]) or 0.5 mL (children weighing < 55 lb [25 kg]) SC, IM, or IV. If the weight is not known: Children < 6 years should be given 0.5 mL and children ≥ 6 years should be given 1 mL. Common SC/IM injection sites are the upper arms, thighs or buttocks.
  - Emergency assistance should be sought immediately after administering glucagon. The glucagon injection (from a new kit) may be repeated while waiting for emergency assistance.
  - When the patient responds to treatment, oral carbohydrates should be given to restore the liver glycogen and prevent recurrence of hypoglycemia.

GEK-L

- The product should be reconstituted according to instructions before administration.
  - The supplied prefilled syringe containing diluent should be inserted and emptied into the vial of dry powder.
  - The syringe should be removed and the bottle gently swirled until the powder is completely dissolved.
  - Holding the bottle upside down, the same syringe should be inserted and used to gently withdraw either half of the solution (0.5 mg mark) for children weighing < 44 lb or all of the solution (1 mg mark) for adults and children weighing > 44 lb.
- For adults and for pediatric patients weighing > than 44 lb (20 kg), the recommended dose is 1 mg by SC, IM, or IV injection. For pediatric patients weighing < 44 lb (20 kg), the dose is 0.5 mg or a dose equivalent to 20 to 30 mcg/kg. Injection sites include the buttock, arm, or thigh.
  - An unconscious patient will usually awaken within 15 minutes following the injection. If the response is delayed, there is no contraindication to the administration of an additional dose of glucagon; however, emergency aid should be sought so that parenteral glucose can be given.
  - After the patient responds, supplemental carbohydrates should be given to restore liver glycogen and to prevent secondary hypoglycemia.

Gvoke

- Gvoke should be administered by SC injection in the lower abdomen, outer thigh, or outer upper arm according to the instructions.
- The recommended dose for adults and pediatric patients aged ≥ 12 years is 1 mg.
- The recommended dose for pediatric patients aged 2 to < 12 years of age is weight-dependent:
  - For pediatric patients who weigh < 45 kg, the recommended dose is 0.5 mg.
  - For pediatric patients who weigh ≥ 45 kg, the recommended dose is 1 mg.
- Emergency assistance should be called immediately after administering the dose.
- If there has been no response after 15 minutes, an additional weight-appropriate dose from a new device may be administered while waiting for emergency assistance.
- When the patient responds to treatment, oral carbohydrates should be given.

**SPECIFIC POPULATIONS**

- **Geriatrics**
  - Clinical studies of glucagon did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Limited clinical trial experience has not identified differences in responses between the elderly and younger patients.
- **Pediatrics**
  - Baqsimi: Safety and effectiveness have not been established in pediatric patients < than 4 years of age.

- GlucaGen, GEKs: For the treatment of severe hypoglycemia, the use of glucagon in pediatric patients has been reported to be safe and effective.
- Gvoke: Safety and effectiveness have not been established in pediatric patients < 2 years of age.

- **Pregnancy and nursing**
  - Available data from case reports and a small number of observational studies with glucagon use in pregnant women over decades of use have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
  - There is no information available on the presence of glucagon in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. However, glucagon is a peptide and would be expected to be broken down to its constituent amino acids in the infant's digestive tract and is therefore, unlikely to cause harm to an exposed infant.

## APPENDICES

### Appendix A. ADA evidence-grading system

| Level of evidence | Description |
|---|---|
| A | Clear evidence from well-conducted, generalizable RCTs that are adequately powered, including:<br>• Evidence from a well-conducted MC trial<br>• Evidence from a meta-analysis that incorporated quality ratings in the analysis |
| | Compelling nonexperimental evidence, ie, “all or none” rule developed by the Centre for Evidence-Based Medicine at the University of Oxford |
| | Supportive evidence from well-conducted RCTs that are adequately powered, including:<br>• Evidence from a well-conducted trial at 1 or more institutions<br>• Evidence from a meta-analysis that incorporated quality ratings in the analysis |
| B | Supportive evidence from well-conducted cohort studies, including:<br>• Evidence from a well-conducted prospective cohort study or registry<br>• Evidence from a well-conducted meta-analysis of cohort studies |
| | Supportive evidence from a well-conducted case-control study |
| C | Supportive evidence from poorly controlled or uncontrolled studies, including:<br>• Evidence from randomized clinical trials with 1 or more major or 3 or more minor methodological flaws that could invalidate the results<br>• Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)<br>• Evidence from case series or case reports |
| | Conflicting evidence with the weight of evidence supporting the recommendation |
| E | Expert consensus or clinical experience |

### Appendix B. AACE evidence-grading system

- **Recommendation Grades**
  - **A**: Strong
  - **B**: Intermediate
  - **C**: Weak
  - **D**: Not evidenced-based

| Evidence level | Reference methodology |
|---|---|
| **1 (strong evidence)** | Meta-analysis of RCTs; RCTs |
| **2 (intermediate evidence)** | Meta-analysis of nonrandomized prospective or case-controlled trials; nonrandomized controlled trial; prospective cohort study; retrospective case-control study |
| **3 (weak evidence)** | Cross-sectional study; surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database); consecutive case series; single case reports |
| **4 (no evidence)** | No evidence (theory, opinion, consensus, review, or preclinical study) |

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