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# Formulary Changes

**Effective 7/1/2019 (unless otherwise noted)**

Table 1: Summary of Medicaid PDL proposed designation as **Preferred**

| Drug Name | Ingredients | Dosage Form | Strength(s) | Notes |
|---|---|---|---|---|
| **Delstrigo** | Doravirine/Lamivudine/ Tenofovir Disoproxil Fumarate | Tablet | 100-300-300 mg | |
| **Pifeltro** | Doravirine | Tablet | 100 mg | |
| **Epclusa** | Sofosbuvir/Velpatasvir | Tablet | 400-100 mg | **Effective Immediately.** |

Table 2: Summary of Medicaid PDL proposed designation as **Non-Preferred**

| Drug Name | Ingredients | Dosage Form | Strength(s) | Notes |
|---|---|---|---|---|
| **Emgality** | Galcanezumab | Prefilled syringe<br>Auto-injector | 120 mg/mL<br>120 mg/mL | |
| **Aimovig** | Erenumab | Auto-injector | 70 mg/mL | |
| **Ajovy** | Fremanezumab | Prefilled Syringe | 225 mg/1.5 mL | |
| **Mavyret** | Glecaprevir/Pibrentasvir | Tablet | 100-40 mg | |

Table 3: Summary of Medicaid PDL proposed **change in status**

| Drug Name | Ingredients | Dosage Form | Strength(s) | Notes |
|---|---|---|---|---|
| **Copaxone** | Glatiramer Acetate | Prefilled Syringe | 20 mg/mL<br>40 mg/mL | **Remove prior authorization requirement.** |

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# New Drugs

**Reviewed for P&T Meeting March 14, 2019**

**Ajovy™ (fremanezumab-vfrm)**

**Therapeutic Class:** CGRP antagonist
**FDA Indication:** Migraine Prophylaxis
**Formulary Recommendations:** Non-preferred
**Rationale:** In December 2018, The American Society updated their clinical practice guidelines to include the CGRP agents and their place in therapy. Currently, CGRPs should only be used for patients with 4-7 monthly headache days and have an inadequate response to a 6-week trial or inability to tolerate at least 2 of the following classes of medications: topiramte, divalproex/valproate, beta blocker (metoprolol, propranolol, timolol, atenolol, nadolol), tricyclic antidepressant (amitriptyline, nortriptyline), and/or serotonin-norepinephrine reuptake inhibitor (venlafaxine, duloxetine). Additionally, patients should experience at least moderate disability as rated by Migraine Disability Assessment (MIDAS>11) or Headache Impact Test (HIT-6>50). If the patient has 8-14 monthly headache days then the "moderate disability rating" criteria is removed. Lastly, for chronic migraine patients the criteria for CGRP use includes inability to tolerate or inadequate response after 6 weeks to the above agents or inability to tolerate or inadequate response to a minimum of 2 quarterly injections of onabotulinumtoxin A.

**Delstrigo™ (doravirine/lamivudine/tenofovir disoproxil fumarate)**

**Therapeutic Class:** NNRTI/NRTI/NRTI
**FDA Indication:** HIV-1 infection
**Formulary Recommendations:** Preferred
**Rationale:** Doravirine is non-inferior to both efavirenz and darunavir/ritonavir when either were taken in combination with two NRTIs. There are fewer potential drug interactions and efavirenz or rilpivirine, and unlike rilpivirine, virologic effects are note compromised in those with high HIV RNA levels and low CD4 counts. Though first line therapy is an INSTI based regimen, NNRTI, or a PK-enhanced PI regimens can be used in certain clinical situations. For most patients, an INSTI-containing regimen will be effective with fewer adverse effects, and have no significant CYP3A4-associated drug interactions.

**Emgality™ (galcanezumab-gnlm)**

**Therapeutic Class:** CGRP antagonist
**FDA Indication:** Migraine Prophylaxis
**Formulary Recommendations:** Non-preferred
**Rationale:** Based on indirect comparison, the efficacy of all three CGRP inhibitors appeared to be similar, and all were overall well tolerated. The efficacy of Emgality (galcanezumab-gnlm) in EM prevention was demonstrated in up to 24 weeks of treatment in clinical trials, while efficacy data for Aimovig (erenumab-aooe) and Ajovy (fremanezumab-vfrm) were limited to 12 weeks. All three CGRP inhibitors are administered subcutaneously monthly, while Ajovy (fremanezumab-vfrm) can also be administered every 3 months (i.e., quarterly). Compared to other migraine-prophylactic agents such as Botox (onabotulinumtoxinA) and oral agents (i.e., topiramate, divalproex, propranolol, and timolol), CGRP inhibitors including Emgality (galcanezumab-gnlm) are effective for both EM and CM prevention and appear to have a more favorable safety profile. Overall, Emgality (galcanezumab-gnlm) provides an additional option for the prevention of CM or EM.

**Fulphila™ (pegfilgrastim)** [Neulasta biosimilar]

**Therapeutic Class:** Colony stimulating factor (CSF)
**FDA Indication:** Prevention of chemotherapy-induced neutropenia
**Formulary Recommendations:** Non-preferred (approved via e-vote 10/18/2018)
**Rationale:** Fulphila is one of 4 pegfilgrastim agents approved by the FDA, all of which are clinically equivalent.

**Pifeltro (doravirine)**

**Therapeutic Class:** NNRTI
**FDA Indication:** HIV-1 infection
**Formulary Recommendations:** Preferred
**Rationale:** Doravirine is non-inferior to both efavirenz and darunavir/ritonavir when either were taken in combination with two NRTIs. There are fewer potential drug interactions and efavirenz or rilpivirine, and unlike rilpivirine, virologic effects are note compromised in those with high HIV RNA levels and low CD4 counts. Though first line therapy is an INSTI based regimen, NNRTI, or a PK-enhanced PI regimens can be used in certain clinical situations. For most patients, an INSTI-containing regimen will be effective with fewer adverse effects, and have no significant CYP3A4-associated drug interactions.

**Pharmacy & Therapeutics Committee Summary Review**
*Ajovy® (fremanezumab) – Teva Pharmaceutical Industries Ltd.*

**Prepared by:** Aaron Natarus, Jordan Breitigam

**Presentation Date:** March 28, 2019

**Therapeutic Class:** Anti-Migraine Agent, Calcitonin-gene related peptide blocker (CGRP)

**FDA Approval Date:** September 14, 2018

**FDA Indication:** Preventative treatment of migraine in adults

**Comparable Formulary Products:** Aimovig (non-preferred), Emgality (non-preferred)

## Proposed Designation & Rationale

**Recommendation:** Non-preferred

**Clinical Implications/Place in Therapy:**

- Based on the data presented, Ajovy is an effective therapy for prevention of migraines.[1-4] It is comparable to other agents in regards to efficacy, safety, and cost parameters.[1-6]
- In December 2018, The American Society updated their clinical practice guidelines to include the CGRP agents and their place in therapy. Currently, CGRPs should only be used for patients with 4-7 monthly headache days and have an inadequate response to a 6-week trial or inability to tolerate at least 2 of the following classes of medications: topiramte, divalproex/valproate, beta blocker (metoprolol, propranolol, timolol, atenolol, nadolol), tricyclic antidepressant (amitriptyline, nortriptyline), and/or serotonin-norepinephrine reuptake inhibitor (venlafaxine, duloxetine).
- Additionally the patient should experience at least moderate disability as rated by Migraine Disability Assessment (MIDAS>11) or Headache Impact Test (HIT-6>50). If the patient has 8-14 monthly headache days then the "moderate disability rating" criteria is removed. Lastly, for chronic migraine patients the criteria for CGRP use includes inability to tolerate or inadequate response after 6 weeks to the above agents or inability to tolerate or inadequate response to a minimum of 2 quarterly injections of onabotulinumtoxin A.[7]

**References:**


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CVSHealth

# CVS Caremark Pharmacy & Therapeutics
# Drug Monograph

## Ajovy™ (fremanezumab-vfrm) subcutaneous injection
## Teva Pharmaceuticals, Inc.

### INDICATION

Ajovy (fremanezumab-vfrm) is indicated for the preventive treatment of migraine in adults (Ajovy prescribing information, 2018).

### U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Ajovy (fremanezumab-vfrm) was approved by the FDA on September 14, 2018 under a Biologic License Application (BLA) and underwent a Standard Review (FDA, 2018).

### DRUG SUMMARY

| Ajovy (fremanezumab-vfrm) | |
|---|---|
| **Place in Therapy** | • Ajovy is the second CGRP inhibitor indicated for the preventive treatment of migraine in adults.<br>• Aimovig (erenumab-aooe) was the first CGRP inhibitor approved by the FDA for the prevention of migraine in adults, and Emgality (galcanezumab-gnlm) was the third. Other preventive treatment for migraine include Botox (onabotulinumtoxinA), and oral agents (i.e., topiramate, divalproex, propranolol, and timolol).<br>• There is limited guidance in the approach to migraine prevention. The AAN in 2016 recommended Botox for CM but not EM. The AHS/AAN jointly in 2012 considered oral prophylactic agents to be effective for EM prevention. Available guidelines were published prior to the approval of CGRP inhibitors including Ajovy.<br>• Ajovy provides a SC injectable option with the least frequent administration (Q 3 months as well as the monthly administration) compared with Aimovig (administered SC monthly only). Oral agents are dosed daily or twice daily. Botox is the only agent that requires administration by a healthcare provider.<br>• Ajovy and Aimovig are effective in both CM and EM prevention, whereas Botox is only effective for CM. Oral agents are likely only effective for EM prevention; among oral agents, topiramate has shown some efficacy in CM prevention.<br>• Ajovy and Aimovig are well tolerated, whereas Botox has multiple boxed warnings, and oral agents have multiple safety concerns. |
| **Efficacy** | • Two phase III, multinational, randomized, double-blind, placebo-controlled, 12-week trials in patients with migraine who were not treatment-refractory, of which up to 30% of patients were allowed to continue a concomitant migraine-preventive medication in addition to Ajovy:<br>○ In patients with EM (HALO-EM trial):<br>▪ Ajovy reduced MMD by 1.3 days to 1.5 days (placebo-adjusted; $p < 0.001$).<br>▪ 17% to 20% of Ajovy-treated patients achieved ≥ 50% reduction in MMD (placebo-adjusted; $p < 0.001$).<br>○ In patient with CM (HALO-CM trial):<br>▪ Ajovy reduced MHD by 1.8 days to 2.1 days (placebo-adjusted; $p < 0.001$).<br>▪ Ajovy reduced MMD by 1.7 days to 1.8 days (placebo-adjusted; $p < 0.001$).<br>▪ 20% to 23% of Ajovy-treated patients achieved ≥ 50% reduction in MHD (placebo-adjusted; $p < 0.001$). |
| **Safety** | • Contraindicated in patients with severe hypersensitivity to Ajovy<br>• AEs (≥ 2%): injection site reactions (e.g., pain, induration, and erythema) |

AAN = American Academy of Neurology
AE = adverse event
AHS = American Headache Society
CGRP = calcitonin gene-related peptide
CM = chronic migraine
EM = episodic migraine
FDA = Food and Drug Administration
IM = intramuscular
MHD = monthly headache day
MMD = monthly migraine day
Q = every
SC = subcutaneous

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Fremanezumab-vfrm is a fully humanized immunoglobulin G (IgG)-2a monoclonal antibody that specifically binds to the calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the CGRP receptor (Ajovy prescribing information, 2018).

### Pharmacokinetics

**Table 1: Selected Pharmacokinetics of Fremanezumab-vfrm**

| Route of Administration | $T_{max}$ | $T_{ss}$ | Volume of Distribution | Metabolism & Elimination | $T_{1/2}$ |
|---|---|---|---|---|---|
| Subcutaneous | 5 days to 7 days | 168 days (~6 months) | 6 L* | Degraded by enzymatic proteolysis into small peptides and amino acids; not metabolized by cytochrome P450 enzymes | 31 days |

* Minimal distribution to extravascular tissues
$T_{1/2}$ = elimination half-life
$T_{max}$ = time to maximum plasma concentration
$T_{ss}$ = time to steady-state concentration

(Ajovy prescribing information, 2018)

### Pharmacogenomics

No pharmacogenomic data are available at this time for fremanezumab-vfrm.

## CLINICAL EFFICACY

**Table 2: Efficacy of Ajovy (fremanezumab-vfrm) in the Prevention of EM**

| Study, Treatments, and Groups | Study Design, Endpoints, and Criteria | Results | | | |
|---|---|---|---|---|---|
| **Dodick, 2018a**<br><br>**HALO-EM**<br>Evidence level Ib<br><br>**Ajovy (fremanezumab-vfrm) SC monthly:**<br>225 mg with two placebo injections at baseline, 225 mg at week 4, and 225 mg at week 8<br>(n = 290)<br><br>or<br><br>**Ajovy SC quarterly:**<br>675 mg (three 225 mg injections) at baseline, placebo at week 4, and placebo at week 8<br>(n = 291)<br><br>vs.<br><br>**Placebo SC monthly**<br>(n = 294) | (N = 875)<br>**Study Design:**<br>Phase III, multinational, randomized, double-blind, placebo-controlled trial consisting of a 28-day pretreatment period and a 12-week treatment period<br>**Objective:**<br>To evaluate the efficacy and safety of the two dosing regimens of Ajovy for EM prevention<br>**Primary Endpoint:**<br>Mean change in MMD* from baseline to 12 weeks<br>**Secondary Endpoint(s):**<br>• Proportion of patients achieving ≥ 50% reduction in MMD* at 12 weeks<br>• Mean change in monthly days requiring abortive agent (acute migraine treatment) from baseline to 12 weeks<br>• Change in MMD* in patients not receiving concomitant migraine-preventive agent from baseline to 12 weeks<br>**Inclusion Criteria:**<br>• Adults with a history of EM† based on the ICHD-3 beta diagnostic criteria with an onset prior to 50 years of age (mean age: 42 years; ~85% female; ~20 years since diagnosis; baseline MMD*: ~9 days)<br>**Exclusion Criteria:**<br>• Use of Botox (onabotulinumtoxinA) within 4 months prior or migraine intervention/device within 2 months prior to baseline<br>• Failure of ≥ 2 preventive medication classes‡ for ≥ 3 months of use<br>• Use of a concomitant migraine-preventive agent, unless the dosing was stable for ≥ 2 months prior to baseline and without change during study (~19% had prior use of topiramate; ~21% were allowed to continue treatment with one concomitant migraine-preventive agent) | **Endpoint** | **Ajovy monthly** (n = 287)§ | **Ajovy quarterly** (n = 288)§ | **Placebo** (n = 290)§ |
| | | Δ in MMD at 12 weeks | -3.7 | -3.4 | -2.2 |
| | | | Placebo-adjusted: -1.5<br>95% CI -2.01 to -0.93‖ | Placebo-adjusted: -1.3<br>95% CI -1.79 to -0.72‖ | N/A |
| | | ≥ 50% reduction in MMD | 47.7% | 44.4% | 27.9% |
| | | | Placebo-adjusted: 19.8%<br>95% CI 12.0% to 27.6%‖ | Placebo-adjusted: 16.5%<br>95% CI 8.9% to 24.1%‖ | N/A |
| | | Δ in days/month requiring acute treatment | -3.0 | -2.9 | -1.6 |
| | | | Placebo-adjusted: -1.4<br>95% CI -1.84 to -0.89‖ | Placebo-adjusted: -1.3<br>95% CI -1.76 to -0.82‖ | N/A |
| | | **Safety:**<br>• TEAEs occurred in 48% of the Ajovy monthly arm and 47% of the Ajovy quarterly arm vs. 37% in the placebo arm. Equal numbers of patients discontinued therapy due to AEs (1.7% in all three arms).<br>• AEs (> 5%): injection site pain (30% monthly and quarterly vs. 26% placebo), injection site induration (25% monthly and 20% quarterly vs. 15% placebo), injection site erythema (18% monthly and 19% quarterly vs. 14% placebo), upper respiratory infection (6% monthly and 4% quarterly vs. 5% placebo)<br>**Comments/Study Limitations:**<br>• In patients without a concomitant migraine-preventing agent, the changes in MMD were -3.7 days and -3.5 days for Ajovy monthly and quarterly dosing regimens, respectively, compared with -2.4 days for placebo (placebo-adjusted -1.3 days‖ and -1.1 days‖ for Ajovy monthly and quarterly, respectively).<br>• Treatment effect with Ajovy was seen within 4 weeks after the initial dose.<br>• Limitations: the study did not include treatment-refractory patients with ≥ 2 failed preventive-medication classes or patients with comorbidities with compromised blood-brain barrier (e.g., ischemic stroke); short treatment duration and follow up of only 3 months<br>**Conclusions:** Ajovy significantly reduced MMD by a placebo-adjusted 1.3 days to 1.5 days at end of 12 weeks. Ajovy was generally well-tolerated. | | | |

* A migraine day was defined as a calendar day with either ≥ 2 consecutive hours of headache meeting criteria for migraine ± aura, probable migraine (only one migraine criterion absent), or a day when migraine-abortive agent was used (e.g., triptans or ergots).
† EM was defined as a headache frequency occurring between 6 days to 14 days, with ≥ 4 days fulfilling the ICHD-3 beta criteria for migraine with or without aura, probable migraine, or with the use of triptan/ergot derivative.
‡ Medication classes include divalproex/valproate; flunarizine and pizotifen; amitriptyline, nortriptyline, venlafaxine, and duloxetine; and atenolol, nadolol, metoprolol, propranolol, and timolol.
§ The modified intent-to-treat population included patients who received at least one dose of study drug and had at least 10 days of diary data.
‖ $p < 0.001$ vs. placebo
AE = adverse event
CI = confidence interval
Evidence level Ib = randomized, controlled trial
ICHD-3 beta = International Classification of Headache Disorder 3 beta version
MMD = monthly migraine day
N/A = not applicable
SC = subcutaneously
TEAE = treatment-emergent adverse event

(Dodick, 2018a)

**Table 3: Efficacy of Ajovy (fremanezumab-vfrm) in the Prevention of CM**

| Study, Treatments, and Groups | Study Design, Endpoints, and Criteria | Results |
|---|---|---|
| **Silberstein, 2017**<br><br>**HALO-CM**<br>Evidence level Ib<br><br>**Ajovy (fremanezumab-vfrm) SC monthly:**<br>675 mg (three 225 mg injections) at baseline, 225 mg at week 4, and 225 mg at week 8¶<br>(n = 379)<br><br>or<br><br>**Ajovy SC quarterly:**<br>675 mg (three 225 mg injections) at baseline, placebo at week 4, and placebo at week 8<br>(n = 376)<br><br>vs.<br><br>**Placebo SC monthly**<br>(n = 375) | (N = 1,130)<br>**Study Design:**<br>Phase III, multinational, randomized, double-blind, placebo-controlled trial consisting of a 4-week pre-intervention period and 12-week active-intervention period<br>**Objective:** To evaluate the efficacy and safety of the two dosing regimens of Ajovy for CM prevention<br>**Primary Endpoint:** Mean change in MHD* from baseline to 12 weeks<br>**Secondary Endpoint(s):**<br>• Mean change in MMD* from baseline to 12 weeks<br>• Proportion of patients achieving ≥ 50% reduction in MHD* at 12 weeks<br>• Mean change in monthly days requiring abortive agent (acute migraine treatment) from baseline to 12 weeks<br>• Change in MHD* in patients not receiving concomitant migraine-preventive agent from baseline to 12 weeks<br>**Inclusion Criteria:**<br>• Adults with a history of migraine based on the ICHD-3 beta diagnostic criteria for ≥ 12 months and met criteria for CM† during the pre-intervention period (mean age: 41 years; ~88% female; ~20 years since diagnosis; baseline MHD*: ~13 days; baseline MMD*: ~16 days)<br>• Up to 30% of patients using one concomitant migraine-preventive medication, of which the dosing had been stable for ≥ 2 months prior to baseline and remained unchanged during study (~21% were allowed to continue treatment with one concomitant migraine-preventive agent)<br>**Exclusion Criteria:**<br>• Use of Botox (onabotulinumtoxinA) within 4 months prior or migraine intervention/device within 2 months prior to baseline; use of opioid or barbiturate on > 4 days during pre-intervention period<br>• Failure of ≥ 2 classes out of 4 classes of migraine-preventive medication classes‡ for ≥ 3 months of use (~30% had prior use of topiramate; 13% to 18% had prior use of Botox) | **Endpoint** / **Ajovy monthly** (n = 375)§ / **Ajovy quarterly** (n = 375)§ / **Placebo** (n = 371)§<br>Δ in MHD at 12 weeks: -4.6 ± 0.3 / -4.3 ± 0.3 / -2.5<br>Placebo-adjusted: -2.1‖ / Placebo-adjusted: -1.8‖ / N/A<br>Δ in MMD at 12 weeks: -5.0 ± 0.4 / -4.9 ± 0.4 / -3.2<br>Placebo-adjusted: -1.8‖ / Placebo-adjusted: -1.7‖ / N/A<br>≥ 50% reduction in MHD: 41% / 38% / 18%<br>Placebo-adjusted: 23%‖ / Placebo-adjusted: 20%‖ / N/A<br>Δ in days/month requiring acute treatment: -4.2 ± 0.3 / -3.7 ± 0.3 / -1.9<br>Placebo-adjusted: -2.3‖ / Placebo-adjusted: -1.8‖ / N/A<br>**Safety:**<br>• TEAEs occurred in 51% of the Ajovy monthly arm and 49% of the Ajovy quarterly arm vs. 42% in the placebo arm. Similar proportions of patients discontinued therapy due to AEs (1% to 2% in all three arms).<br>• AEs (> 5%): injection site pain (26% monthly and 30% quarterly vs. 28% placebo), injection site induration (24% monthly and 20% quarterly vs. 18% placebo), and injection site erythema (20% monthly and 21% quarterly vs. 16% placebo).<br>**Comments/Study Limitations:**<br>• In patients without a concomitant migraine-preventing agent, the changes in MHD were -4.8 days and -4.6 days for Ajovy monthly and quarterly dosing regimens, respectively, compared with -2.6 days for placebo (placebo-adjusted -2.2 days‖ and -1.9 days‖ for Ajovy monthly and quarterly, respectively).<br>• Treatment effect with Ajovy was seen within 4 weeks after the initial dose.<br>• Limitations: the study did not include treatment-refractory patients with ≥ 2 failed preventive-medication classes or patients with comorbidities; short treatment duration and follow up of only 3 months<br>**Conclusions:** Ajovy significantly reduced MHD by a placebo-adjusted 1.8 days to 2.1 days and MMD by a placebo-adjusted 1.7 days to 1.8 days at end of 12 weeks. Ajovy was generally well-tolerated. |

* MHD was defined as days in which headache pain lasted ≥ 4 consecutive hours with peak severity of ≥ moderate level or days requiring migraine-abortive agent (e.g., triptans or ergots). For MMD, a migraine day was defined as a calendar day in which headache pain lasted ≥ 4 consecutive hours and met criteria for migraine ± aura, probable migraine (only one migraine criterion absent), or a day when migraine-abortive agent was used (e.g., triptans or ergots).
† CM was defined as headaches of any duration of severity with a frequency of ≥ 15 days per month and headache meeting the ICHD-3 beta criteria for migraine on ≥ 8 days per month.
‡ Medication classes include divalproex/valproate; topiramate; amitriptyline, nortriptyline, and venlafaxine; and atenolol, nadolol, metoprolol, propranolol, and timolol.
§ The modified intent-to-treat population included patients who received at least one dose of study drug and had at least 10 days of diary data.
‖ $p < 0.001$ vs. placebo
¶ The Food and Drug Administration-approved dosing regimens of Ajovy are 675 mg (administered as three consecutive injections of 225 mg each) quarterly or 225 mg monthly.
AE = adverse event
CM = chronic migraine
Evidence level Ib = randomized, controlled trial
ICHD-3 beta = International Classification of Headache Disorder 3 beta version
MHD = monthly headache day
MMD = monthly migraine day
N/A = not applicable
SC = subcutaneously
TEAE = treatment-emergent adverse event

(Ajovy prescribing information, 2018; Silberstein, 2017)

## SAFETY

### Contraindications and Warnings

Ajovy (fremanezumab-vfrm) is contraindicated for use in patients with serious hypersensitivity to fremanezumab-vfrm (Ajovy prescribing information, 2018). In the Ajovy (fremanezumab-vfrm) clinical trials, hypersensitivity reactions (e.g., rash, drug hypersensitivity, and urticaria) have been reported. Although most reactions were mild to moderate, some required corticosteroid treatment or resulted in the discontinuation of Ajovy (fremanezumab-vfrm) treatment. Most hypersensitivity reactions occurred within hours to one month after administration.

### Reproductive Risk

There are limited data to inform the developmental risk associated with the use of fremanezumab-vfrm in pregnant women (Ajovy prescribing information, 2018). Fremanezumab-vfrm has a long half-life of 31 days, which should be taken into consideration during therapy selection for women who are pregnant or plan to become pregnant. In animal studies, the administration of fremanezumab-vfrm during the period of organogenesis and throughout pregnancy and lactation did not result in adverse developmental effect.

### Nursing Mothers

There are no data on the presence of fremanezumab-vfrm in human milk, the effects on the breastfed infant, or the effects on milk production (Ajovy prescribing information, 2018).

### Pediatric Use

Safety and effectiveness of Ajovy (fremanezumab-vfrm) have not been established in pediatric patients (Ajovy prescribing information, 2018).

### Geriatric Use

Clinical trials of Ajovy (fremanezumab-vfrm) did not include sufficient numbers of patients 65 years of age or older to determine whether older patients respond differently from younger patients (Ajovy prescribing information, 2018).

### Drug Interactions

Fremanezumab-vfrm is not metabolized by cytochrome P450 (CYP) enzymes (Ajovy prescribing information, 2018). Therefore, fremanezumab-vfrm is unlikely to interact with CYP substrates, inducers, or inhibitors. Additionally, acute migraine treatments (i.e., analgesics, ergots, and triptans) and migraine prophylactic treatments did not alter the exposure of fremanezumab-vfrm in a population pharmacokinetic model.

### Adverse Events

**Table 4: Adverse Events Occurring in ≥ 2% of Ajovy (fremanezumab-vfrm)-treated Patients and ≥ 2% More Common than with Placebo in Clinical Trials***

| Adverse Event | Ajovy (fremanezumab-vfrm) | | Placebo monthly (n = 668) |
|---|---|---|---|
| | 225 mg SC monthly (n = 290) | 675 mg SC quarterly (n = 667) | |
| Injection site reactions (e.g., injection site pain, induration, and erythema) | 43% | 45% | 38% |

* Safety data from phase III trials (i.e., HALO-EM and HALO-CM)
SC = subcutaneously

(Ajovy prescribing information, 2018)

### Immunogenicity

In the 3-month placebo-controlled trials, treatment-emergent anti-drug antibodies (ADA) responses were observed in six of 1,701 Ajovy (fremanezumab-vfrm)-treated patients (0.4%) (Ajovy prescribing information, 2018). Of these six patients, one patient developed anti-fremanezumab-vfrm neutralizing antibodies at day 84. In the ongoing, open-label, long-term study, ADA were detected in 30 out of 1,888 Ajovy (fremanezumab-vfrm)-treated patients (1.6%). Of these 30 patients, 17 patients developed neutralizing antibodies. Available data do not demonstrate an impact on efficacy of safety by the ADA development; however, available data are too limited to draw a conclusion.

## PRODUCT AVAILABILITY

Ajovy (fremanezumab-vfrm) is available as a single-dose 225 mg/1.5 mL prefilled syringe for subcutaneous injection and is supplied as individual cartons containing one syringe each (Ajovy prescribing information, 2018). Storage of Ajovy (fremanezumab-vfrm) requires refrigeration at 2° C to 8° C (36° F to 46° F) in the original carton to protect from light. Ajovy (fremanezumab-vfrm) may be kept in the original carton at room temperature up to 25° C (77° F) for a maximum of 24 hours. Ajovy (fremanezumab-vfrm) launched on September 17, 2018 (RxPipeline, 2018).

## DOSAGE AND ADMINISTRATION

Ajovy (fremanezumab-vfrm) has two subcutaneous dosing options (Ajovy prescribing information, 2018). Ajovy (fremanezumab-vfrm) 225 mg as a single injection is administered monthly. Ajovy (fremanezumab-vfrm) 675 mg is administered as three consecutive 225 mg injections every 3 months. Multiple injections may share the same body site but not the exact location of the previous injection.

Ajovy (fremanezumab-vfrm) may be administered by a healthcare provider, patient, or caregivers after proper training on the preparation and administration technique of the prefilled syringes. Prior to administration, the prefilled syringe of Ajovy (fremanezumab-vfrm) should be allowed to warm up in room temperature for 30 minutes after the removal from the refrigerator. Ajovy (fremanezumab-vfrm) should be discarded if it has been at room temperature for 24 hours or longer.

## APPROACHES TO TREATMENT

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches and reversible neurological or systemic symptoms (Dodick, 2018b). In 2015, migraine was ranked the second largest contributor of disability-adjusted life years (DALY) at 13.1%, second to stroke at 47.3% (Global Burden of Disease [GBD] 2015 Neurological Disorder Collaborator Group, 2017). In 2016, migraine affected over one billion people worldwide, with an incidence of about 110,000 cases per year (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Migraine often begins at puberty, but it most commonly affects those between 35 years and 45 years of age (World Health Organization [WHO], 2016). Migraine is about twice as common in women than men, which is likely due to hormonal influences.

A migraine attack may start with the premonitory phase, which is characterized by the presence of aura prior to experience of pain (Dodick, 2018b). The premonitory phase may be caused by the spontaneous activation of certain regions in the brain, which can be triggered by alteration in homeostasis, stress, or visual stimuli, and followed by a massive release of glutamate resulting in the activation of trigeminovascular system, which leads to the headache phase. About half of patients with migraine report unilateral, throbbing or pulsating headache. Migraine occurs more often during sleep, upon awakening, or shortly after rising in the morning. In addition to pain, over half of patients with migraine also experience photophobia, phonophobia, cutaneous allodynia, nausea/vomiting, and dizziness. Shortly after the resolution of headache pain, the majority of patients also experience postdromal symptoms, such as fatigue and somnolence.

The International Classification of Headache Disorder, 3rd Edition (ICHD-3), by the International Headache Society (IHS) classifies migraine headaches into migraine with aura, migraine without aura, and chronic migraine (CM), among other migraine diagnoses (IHS, 2018). In general, a diagnosis of migraine is made based on ICHD-3 criteria and by ruling out differential diagnoses, such as transient ischemic attack, tension-type headache, or other systemic or intracranial disease (Dodick, 2018b). A diagnosis of CM is based on the presence of 15 or more headache days per month, of which at least 8 days meet the diagnostic criteria for migraine with or without aura or headache that was relieved by a triptan or ergot derivative, and the frequency of headache days was maintained for longer than 3 months (IHS, 2018). The prevalence of CM in the general population is between 1.4% and 2.2%, and CM accounts for about 8% of all migraine cases (Dodick, 2018b; Schwedt, 2014). The diagnosis of episodic migraine (EM) is not specifically outlined in the ICHD-3, but it is generally defined by the presence of fewer than 15 migraine headache days per month (Dodick, 2018b). About 2.5% to 3.0% of patients with EM transform to CM annually (Dodick, 2018b). The mechanism of transformation from EM to CM may be attributed to atypical modulation of pain, sensitization of the trigeminal system from recurrent migraine attacks, cortical hyperexcitability, and neurogenic inflammation due to the release of vasoactive neuropeptides (e.g., CGRP) (Schwedt, 2014). CM results in substantially greater disability than EM; people with CM have lower incomes and are less likely to be employed full time. However, patients with CM may revert back to EM; about 40% of patients transition in and out of CM.

Preventive treatment of migraine can reduce the frequency, severity, and duration of attacks in patients with frequent migraine (Dodick, 2018b). Migraine prophylactic agents that are approved by the Food and Drug Administration (FDA) include Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), Botox (onabotulinumtoxinA), propanolol, timolol, topiramate, and divalproex (FDA, 2018). The decision to start prophylactic therapy should be based on the frequency and severity of the attacks as well as patient responsiveness to acute treatments (Charles, 2017). The selection of a migraine prophylactic agent should be based on the patient's comorbidities, tolerance of adverse events associated with the agent, and the potential for pregnancy in women of childbearing age. Since attack frequency is a risk factor for progression from EM to CM, preventive migraine medications should be considered in patients with four or more migraine attacks per month or at least eight headache days per month. However, studies have reported poor adherence to migraine-preventive treatments. Currently, there is limited guidance on the approach to migraine prevention, and the available guidelines were published prior to the approval of CGRP inhibitors including Ajovy (fremanezumab-vfrm). The American Academy of Neurology (AAN) recommends Botox (onabotulinumtoxinA) for adult patients with CM but not for EM (Simpson, 2016). The American Headache Society (AHS) and AAN jointly in 2012 considered divalproex, propranolol, timolol, and topiramate to be effective for migraine prevention in adult patients with EM (Loder, 2012; Silberstein, 2012). Of note, an update to the 2012 joint AHS/AAN guideline for pharmacological and non-pharmacological treatment and prevention of migraine headache in adults is in development without an expected publication date (AAN, 2018).

**National Institute for Health and Care Excellence (NICE)**

The NICE guidance recommends topiramate or propranolol for migraine prevention based on patient's preference, comorbidities, risk of adverse events, and childbearing potential (NICE, 2015). The NICE guidance also recommends botulinum toxin type A for prevention of CM in patients who did not respond to ≥ 3 migraine prophylactic agents, but botulinum toxin should be discontinued if the patient fails to achieve ≥ 30% reduction in MMD after two treatment cycles or if CM transitions to EM for three consecutive months (NICE, 2012a). Migraine prophylactic agents should be reviewed 6 months after treatment initiation, and treatment should be continued if the prophylactic agent is well tolerated (NICE, 2012b; NICE, 2015). The appraisal for Aimovig (erenumab-aooe) and Ajovy (fremanezumab-vfrm) for migraine prevention is currently in development without an expected publication date (NICE, 2018a; NICE, 2018b)

**Institute for Clinical and Economic Review (ICER)**

ICER recently published the final evidence report on CGRP inhibitors as preventive treatments for patients with EM and CM (Ellis, 2018). In their review of comparative clinical effectiveness, the use of Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Botox (onabotulinumtoxinA), and topiramate in patients with CM was associated with greater reductions in migraine days, headache days, and days using acute medication per month compared with placebo, and the use of Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), and oral preventive agents in patients with EM was also associated with greater reductions in migraine days, higher odds of 50% response, and greater reductions in monthly days requiring acute migraine medications compared with placebo. There was no statistical difference between CGRP inhibitors and other preventive therapies for the previously listed endpoints. When evaluating the incremental direct cost-effectiveness ratio, the quality-adjusted life year (QALY) is a well-established benchmark which evaluates the impact of treatment on lengthening life and/or improving the quality of life (ICER, 2017). ICER generally sets a value-based price benchmark range of $100,000 per QALY to $150,000 per QALY; incremental cost-effectiveness ratios below $50,000 per QALY are presumed to be "high value", while ratios above $175,000 per QALY are deemed to be "low value". The results of ICER analyses are summarized in Table 5. Based on the analyses, Ajovy (fremanezumab-vfrm) has a higher cost per QALY gained compared with Aimovig (erenumab-aooe) in patients with CM and in patients with EM who are eligible to receive oral preventive agents. Ajovy (fremanezumab-vfrm) and Aimovig (erenumab-aooe) were projected to have similar costs per QALY gained compared with no preventive treatments in patients with EM who have failed oral preventive agents. ICER concluded that the class of CGRP inhibitors provide some clinical benefit in patients with EM or CM, and few harms were seen in these short-term trials (Ellis, 2018). ICER noted several limitations to their analysis, including the variation of clinical trial population from the general patient population and that price estimates may not reflect actual market price.

**Table 5: Results of ICER Analysis on CGRP Inhibitors in Migraine Prevention**

| Agent | Patient Population | ICER Evidence Rating (Rationale) | Approximate Incremental Direct Cost-Effectiveness Ratio (per QALY gained) |
|---|---|---|---|
| Aimovig (erenumab-aooe)<br>Ajovy (fremanezumab-vfrm) | Patients with CM who are eligible to receive preventive therapy (i.e., oral agents or Botox [onabotulinumtoxinA]) | **Insufficient**<br>(Not available) | Compared with current preventive treatment (not conditional on prior treatment failure):<br>• Aimovig: $345,000<br>• Ajovy: $12.78 million |
| | Patients with CM for whom prior preventive therapy has failed | **C+**<br>(Uncertainties about harms vs. need for CGRP inhibitors in patients with frequent migraine and no other preventive options) | Compared with no preventive treatment:<br>• Aimovig: $90,000†<br>• Ajovy: $120,000† |
| Aimovig<br>Ajovy<br>Emgality (galcanezumab-gnlm)* | Patients with EM who are eligible to receive preventive therapy (i.e., oral agents) | **Insufficient**<br>(Not available) | Compared with current preventive treatment (not conditional on prior treatment failure):<br>• Aimovig: $395,000<br>• Ajovy: $1.02 million<br>• Emgality: $389,000 |
| Aimovig<br>Ajovy | Patients with EM for whom oral preventive therapy has failed | **Promising, but inconclusive**<br>(Uncertainties about harms vs. need for CGRP inhibitors in those without other preventive options but with less frequent migraine than in the CM population) | Compared with no preventive treatment:<br>$150,000 (for both CGRP inhibitors)† |
| Emgality* | All other populations and comparisons | **Insufficient**<br>(Limited data available) | Not available |

* Emgality (galcanezumab-gnlm) is projected to launch in the fourth quarter of 2018
† Based on base-case analysis from a health system payer perspective, which focuses on the direct medical care costs only
CGRP = calcitonin gene-related peptide
CM = chronic migraine
EM = episodic migraine
FDA = Food and Drug Administration
ICER = Institute for Clinical and Economic Review
QALY = quality-adjusted life year

(Ellis, 2018; RxPipeline, 2018)

**Table 6: Comparison of Migraine Prophylactic Agents**

| Product | Advantages | Disadvantages |
|---|---|---|
| **Injectable Agents** | | |
| Injectable agents as a class | • Less frequent administration (monthly or every 3 months) | • Injectable dosing |
| Aimovig (erenumab-aooe) | • Efficacy demonstrated in both CM and EM<br>• Favorable safety profile<br>• Self-administered SC injection monthly | • Limited clinical experience<br>• Requires refrigeration |
| Ajovy (fremanezumab-vfrm) | • Efficacy demonstrated in both CM and EM<br>• Favorable safety profile<br>• Self-administered SC injection monthly or every 3 months | • Limited clinical experience<br>• Requires refrigeration |
| Botox (onabotulinumtoxinA) | • Multiple additional indications<br>• Retreatment every 3 months | • Indicated for CM only<br>• Efficacy not demonstrated in EM<br>• Requires multiple IM injections per session by a healthcare provider<br>• Boxed warning of distant spread of toxin effect<br>• Increased risk of AE with pre-existing neuromuscular disorders, dysphagia, and breathing difficulties<br>• Risk of viral transmission by human albumin |
| Emgality (galcanezumab-gnlm) | • Efficacy demonstrated in both CM and EM<br>• Efficacy demonstrated in EM for up to 24 weeks vs. up to only 12 weeks with Aimovig and Ajovy<br>• Favorable safety profile<br>• Self-administered SC injection monthly | • Limited clinical experience<br>• Requires refrigeration |
| **Oral Agents** | | |
| Oral agents as a class | • Oral dosing<br>• Most agents generically available | • Efficacy mostly in EM prevention only<br>• Daily or twice-daily dosing |
| Antiepileptic: divalproex<br>**Depakote (divalproex DR)**<br>**Depakote ER (divalproex ER)** | • Also indicated for seizure and psychiatric disorders | • Boxed warnings of hepatotoxicity, pancreatitis, and fetal toxicity; Contraindicated in certain metabolic disorders and pregnancy<br>• High frequency of AEs (including weight gain) |
| Antiepileptic: topiramate<br>**Topamax (topiramate)**<br>Qudexy XR (topiramate ER)<br>**Trokendi XR (topiramate ER)** | • Indicated in pediatric patients ≥ 12 years of age<br>• Also indicated for seizure and psychiatric disorders | • ER formulations are contraindicated for use in metabolic acidosis or with recent alcohol use<br>• Risk of fetal toxicity<br>• High frequency of AEs (including weight loss and neuropsychiatric AEs) |
| Beta-blockers:<br>**Inderal LA (propranolol ER)**<br>**propranolol**<br>**timolol** | • Multiple additional indications | • Boxed warning of angina pectoris and exacerbation of heart disease<br>• Contraindicated in bradycardia, cardiogenic shock, bronchial asthma, and severe COPD<br>• Can mask symptoms (e.g., tachycardia) of hypoglycemia or hyperthyroidism |

**Boldface** indicates generic availability
AE = adverse event
CM = chronic migraine
COPD = chronic pulmonary obstructive disease
DR/ER = delayed release/extended release
EM = episodic migraine
IM = intramuscular
SC = subcutaneous

## FORMULARY CONSIDERATIONS

Ajovy (fremanezumab-vfrm) is a CGRP inhibitor indicated for the preventive treatment of migraine in adults. The efficacy of Ajovy (fremanezumab-vfrm) administered monthly or quarterly was demonstrated in two phase III trials. Both dosing regimens of Ajovy (fremanezumab-vfrm) were superior to placebo in reducing monthly migraine and/or headache days in patients with EM or CM. Both dosing regimens of Ajovy (fremanezumab-vfrm) were also superior to placebo in terms of achieving at least 50% reduction in monthly migraine or headache days and reducing days requiring acute migraine-abortive agents. Ajovy (fremanezumab-vfrm) is the second CGRP inhibitor approved by the FDA for migraine prevention, with Aimovig (erenumab-aooe) being the first, and Emgality (galcanezumab-gnlm) being the third. Based on indirect comparison, the efficacy of the three CGRP inhibitors appear to be similar, and all agents are generally well tolerated. All three agents are administered subcutaneously monthly, while Ajovy (fremanezumab-vfrm) can also be administered every 3 months (i.e., quarterly). Compared to other migraine-prophylactic agents such as Botox (onabotulinumtoxinA) and oral agents (i.e., topiramate, divalproex, propranolol, and timolol), Ajovy (erenumab-aooe) is effective for both EM and CM prevention and has a more favorable safety profile. Overall, Ajovy (fremanezumab-vfrm) provides an additional option for the prevention of CM or EM.

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**DRUG MONOGRAPH PREPARED BY:**

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October 4, 2018

**This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client’s formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.**

 

**Pharmacy & Therapeutics Committee Summary Review**

*Delstrigo™ (doravirine, lamivudine, tenofovir disoproxil fumarate) – Merck & Co., Inc.*

**Prepared by:** Jordan Breitigam, FormularyDecisions.com

**Presentation Date:** March 28, 2019

**Therapeutic Class:** NNRTI/NRTI, single tablet regimen

**FDA Approval Date:** August 31, 2018

**FDA Indication:** Treatment naïve HIV-1 infection

**Comparable Formulary Products:** Atripla, Complera, Odefsey, Symfi, Symtuza

## Proposed Designation & Rationale

**Recommendation:** Preferred with quantity limit (1 tablet/day)

**Clinical Implications/Place in Therapy:**

- Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) to be used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs)
- New Department of Health and Human Services Guidelines released in March 2018 now recommend that antiretroviral regimens for initial therapy include an integrase inhibitor
    - Combinations of a boosted protease inhibitor + 2 NRTIs and an NNRTI + 2 NRTIs are now recommended initial regimens in certain clinical situations and not recommended initial regimens for most people with HIV
    - Given these new recommendations, Delstrigo and Pifeltro use should be reserved for those certain clinical situations that the DHHS guidelines describe

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3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services adults and adolescents antiretroviral guidelines panel classifies a fixed-dose combination product of bictegravir/tenofovir alafenamide/emtricitabine as one of the recommended initial regimens for most people with HIV. Department of Health and Human Services. Available at https://aidsinfo.nih.gov/news/2044/adult-arv-panel-classifies-bic-taf-ftc-as-recommended-initial-regimen-for-hiv. Published March 27, 2018. Accessed August 31, 2018.

# Delstrigo (doravirine, lamivudine, and tenofovir disoproxil fumarate) Monograph

Last modified – Jan 12, 2019

## Product Overview

| Product Overview | |
|---|---|
| **Generic name & manufacturer** | doravirine, lamivudine, and tenofovir disoproxil fumarate<br>Merck & Co., Inc. |
| **PDUFA date (or FDA Approval Date)** | Aug 31, 2018 |
| **Indication** | DELSTRIGO is a three-drug combination of doravirine (a non-nucleoside reverse transcriptase inhibitor [NNRTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside analogue reverse transcriptase inhibitors) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history. (1) |
| **Pharmacology/MOA** | In a Phase 2 trial evaluating doravirine over a dose range of 0.25 to 2 times the recommended dose of doravirine in DELSTRIGO (in combination with FTC/TDF) in HIV-1 infected subjects with no antiretroviral treatment history, no exposure-response relationship for efficacy was identified for doravirine.<br>Cardiac Electrophysiology<br>At a doravirine dose of 1200 mg, which provides approximately 4 times the peak concentration observed following the recommended dose of doravirine in DELSTRIGO does not prolong the QT interval to any clinically relevant extent. |
| **Dose and administration** | **Strengths Available:**<br>• Tablets: 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate. (3)<br>**Dosage Frequency:** |

| | |
|---|---|
| | • Testing: Prior to or when initiating DELSTRIGO, test for HBV infection. Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.(2.1)<br>• Recommended dosage: One tablet taken orally once daily with or without food in adult patients. (2.2)<br>• Renal impairment: Not recommended in patients with estimated creatinine clearance below 50 mL per minute. (2.3)<br>• Dosage adjustment with rifabutin: Take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine 100 mg (PIFELTRO) approximately 12 hours after the dose of DELSTRIGO. (2.4) |
| **Common adverse events** | Most common adverse reactions (incidence greater than or equal to 5%, all grades) are dizziness, nausea, and abnormal dreams. (6.1)<br><br>To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. |

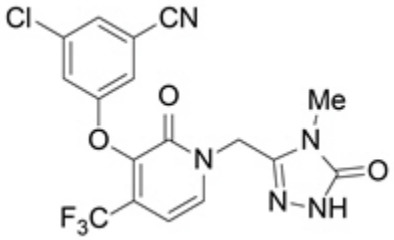
## Appendix: Package Insert Highlights

For the complete Product Insert click here.

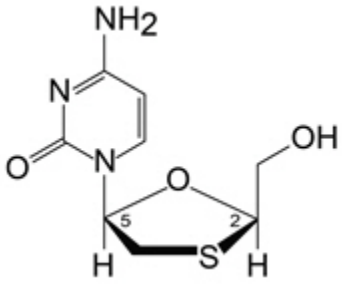
### Product Description

DELSTRIGO is a fixed-dose combination, film-coated tablet, containing doravirine, lamivudine, and TDF for oral administration.
Doravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI).
Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine and is an HIV-1 nucleoside analogue reverse transcriptase inhibitor.
TDF (a prodrug of tenofovir) is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir.In vivoTDF is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir is an HIV-1 reverse transcriptase inhibitor.
Each tablet contains 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil) as active ingredients. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium stearyl fumarate. The tablets are film coated with a coating material containing the following inactive ingredients: hypromellose, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin. The coated tablets are polished with carnauba wax.
Doravirine:

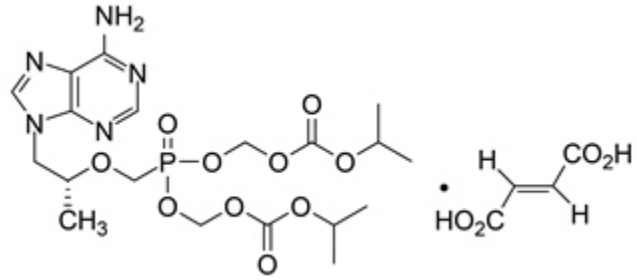
The chemical name for doravirine is 3-chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1H-1,2,4-triazol-3-yl)methyl]-1,2-dihydro-2-oxo-4-(trifluoromethyl)-3-pyridinyl]oxy]benzonitrile.
It has a molecular formula of C17H11ClF3N5O3and a molecular weight of 425.75.
It has the following structural formula:




Doravirine is practically insoluble in water.
Lamivudine:
The chemical name for lamivudine is (-)-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine.
It has a molecular formula of C8H11N3O3S and a molecular weight of 229.26.
It has the following structural formula:




Lamivudine is soluble in water.
TDF:
The chemical name for TDF is 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]-methoxy]propyl]adenine fumarate (1:1).
It has a molecular formula of C19H30N5O10P·C4H4O4and a molecular weight of 635.52.
It has the following structural formula:




TDF is slightly soluble in water.

## Indications and Usage

DELSTRIGO™ is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history.

## Dosage and Administration

DELSTRIGO film-coated tablets are yellow, oval-shaped tablets, debossed with the corporate logo and 776 on one side and plain on the other side. Each tablet contains 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

2.1 Testing When Initiating and During Treatment with DELSTRIGO

Prior to or when initiating DELSTRIGO, test patients for HBV infection[see Warnings and Precautions (5.1)].

Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus[see Warnings and Precautions (5.2)].

2.2 Recommended Dosage

DELSTRIGO is a fixed-dose combination product containing 100 mg of doravirine (DOR), 300 mg of lamivudine (3TC), and 300 mg of TDF. The recommended dosage of DELSTRIGO in adults is one tablet taken orally once daily with or without food[see Clinical Pharmacology (12.3)].

2.3 Renal Impairment

Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and TDF cannot be adjusted, DELSTRIGO is not recommended in patients with estimated creatinine clearance less than 50 mL/min[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)].

2.4 Dosage Adjustment with Rifabutin

If DELSTRIGO is co-administered with rifabutin, take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine 100 mg (PIFELTRO) approximately 12 hours after the dose of DELSTRIGO for the duration of rifabutin co-administration[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)].

## Adverse Reactions

The following adverse reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV[see Warnings and Precautions (5.1)]
- New Onset or Worsening Renal Impairment[see Warnings and Precautions (5.2)]
- Bone Loss and Mineralization Defects[see Warnings and Precautions (5.4)]
- Immune Reconstitution Syndrome[see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adults with No Prior Antiretroviral Treatment History

The safety assessment of DELSTRIGO is based on Week 48 data from two Phase 3, randomized, international, multicenter, double-blind, active-controlled trials. A total of 747 subjects received doravirine either as the single entity in combination with other antiretroviral drugs as background regimens (n=383) or as the fixed-dose DELSTRIGO (n=364), and a total of 747 subjects were randomized to control arms.

In DRIVE-AHEAD (Protocol 021), 728 adult subjects received either DELSTRIGO (n=364) or EFV/FTC/TDF once daily (n=364). By Week 48, 3% in the DELSTRIGO group and 6% in the EFV/FTC/TDF group had adverse events leading to discontinuation of study medication.

Adverse reactions reported in greater than or equal to 5% of subjects in any treatment group in DRIVE-AHEAD are presented in Table 1.

Table 1: Adverse ReactionsFrequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator. (All Grades) Reported in ≥5%No adverse reactions of Grade 2 or higher (moderate or severe) occurred in ≥2% of subjects treated with DELSTRIGO. of Subjects in Any Treatment Group in Adults with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

| | **DELSTRIGO Once Daily N=364** | **EFV/FTC/TDF Once Daily N=364** |
|---|---|---|
| Dizziness | 7% | 32% |
| Nausea | 5% | 7% |
| Abnormal Dreams | 5% | 9% |
| Insomnia | 4% | 5% |
| Diarrhea | 3% | 5% |
| Somnolence | 3% | 7% |
| RashRash: includes rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic. | 2% | 12% |

The majority (65%) of adverse reactions associated with DELSTRIGO occurred at severity Grade 1 (mild).

Neuropsychiatric Adverse Events

For DRIVE-AHEAD, the analysis of subjects with neuropsychiatric adverse events by Week 48 is presented in Table 2. The proportion of subjects who reported one or more neuropsychiatric adverse events was 24% and 57% in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

A statistically significantly lower proportion of DELSTRIGO-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric adverse events by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium.

Table 2: DRIVE-AHEAD - Analysis of Subjects with Neuropsychiatric Adverse EventsAll causality and all grade events were included in the analysis. (Week 48)

| | **DELSTRIGO Once Daily N=364** | **EFV/FTC/TDF Once Daily N=364** | **Treatment Difference (DELSTRIGO - EFV/FTC/TDF) Estimate (95% CI)The 95% CIs were calculated using Miettinen and Nurminen's method. Categories pre-specified for statistical testing were dizziness (p <0.001), sleep disorders and disturbances (p <0.001), and altered sensorium (p=0.033).** |
|---|---|---|---|
| Sleep disorders and disturbancesPredefined using MedDRA preferred terms including: abnormal dreams, hyposomnia, initial insomnia, | 12% | 26% | -13.5 (-19.1, -7.9) |

| | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 | Treatment Difference (DELSTRIGO - EFV/FTC/TDF) Estimate (95% CI)The 95% CIs were calculated using Miettinen and Nurminen's method. Categories pre-specified for statistical testing were dizziness (p <0.001), sleep disorders and disturbances (p <0.001), and altered sensorium (p=0.033). |
|---|---|---|---|
| insomnia, nightmare, sleep disorder, somnambulism. | | | |
| Dizziness | 9% | 37% | -28.3 (-34.0, -22.5) |
| Altered sensoriumPredefined using MedDRA preferred terms including: altered state of consciousness, lethargy, somnolence, syncope. | 4% | 8% | -3.8 (-7.6, -0.3) |

Neuropsychiatric adverse events in the pre-defined category of depression and suicide/self-injury were reported in 4% and 7% of subjects, in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

In DRIVE-AHEAD through 48 weeks of treatment, the majority of subjects who reported neuropsychiatric adverse events reported events that were mild to moderate in severity (97% [83/86] and 96% [198/207], in the DELSTRIGO and EFV/FTC/TDF groups, respectively) and the majority of subjects reported these events in the first 4 weeks of treatment (72% [62/86] in the DELSTRIGO group and 86% [177/207] in the EFV/FTC/TDF group).

Neuropsychiatric adverse events led to treatment discontinuation in 1% (2/364) and 1% (5/364) of subjects in the DELSTRIGO and EFV/FTC/TDF groups, respectively. The proportion of subjects who reported neuropsychiatric adverse events through Week 4 was 17% (62/364) in the DELSTRIGO group and 49% (177/364) in the EFV/FTC/TDF group. At Week 48, the prevalence of neuropsychiatric adverse events was 12% (44/364) in the DELSTRIGO group and 22% (81/364) in the EFV/FTC/TDF group.

Laboratory Abnormalities

The percentages of subjects with selected laboratory abnormalities (that represent a worsening from baseline) who were treated with DELSTRIGO or EFV/FTC/TDF in DRIVE-AHEAD are presented in Table 3.

Table 3: Selected Laboratory Abnormalities Reported in Adult Subjects with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

| Laboratory Parameter Preferred Term (Unit)/Limit | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 |
|---|---|---|
| **Blood Chemistry** | | |
| Total bilirubin | | |
| 1.1 - <1.6 × ULN | 4% | 0% |
| 1.6 - <2.6 × ULN | 2% | 0% |
| ≥2.6 × ULN | <1% | <1% |
| Creatinine (mg/dL) | | |

| Laboratory Parameter Preferred Term (Unit)/Limit | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 |
|---|---|---|
| **Blood Chemistry** | | |
| >1.3 - 1.8 × ULN or Increase of >0.3 mg/dL above baseline | 2% | 1% |
| >1.8 × ULN or Increase of ≥1.5 × above baseline | 2% | 1% |
| Aspartate aminotransferase (IU/L) | | |
| 2.5 - <5.0 × ULN | 2% | 2% |
| ≥5.0 × ULN | <1% | 2% |
| Alanine aminotransferase (IU/L) | | |
| 2.5 - <5.0 × ULN | 3% | 4% |
| ≥5.0 × ULN | <1% | 2% |
| Alkaline phosphatase (IU/L) | | |
| 2.5 - <5.0 × ULN | 0% | <1% |
| ≥5.0 × ULN | 0% | <1% |
| Lipase | | |
| 1.5 - <3.0 × ULN | 5% | 4% |
| ≥3.0 × ULN | 1% | 2% |
| Creatine kinase (IU/L) | | |
| 6.0 - <10.0 × ULN | 2% | 2% |
| ≥10.0 × ULN | 2% | 3% |
| Cholesterol, fasted (mg/dL) | | |
| ≥300 mg/dL | <1% | <1% |
| LDL cholesterol, fasted (mg/dL) | | |
| ≥190 mg/dL | <1% | 2% |
| Triglycerides, fasted (mg/dL) | | |
| >500 mg/dL | <1% | 3% |

Change in Lipids from Baseline

For DRIVE-AHEAD, changes from baseline at Week 48 in LDL-cholesterol, non-HDL-cholesterol, total cholesterol, triglycerides, and HDL-cholesterol are shown in Table 4.

The LDL and non-HDL comparisons were pre-specified and are summarized in Table 4. The differences were statistically significant, showing superiority of DELSTRIGO for both parameters. The clinical benefit of these findings has not been demonstrated.

Table 4: Mean Change from Baseline in Fasting Lipids in Adult Subjects with No Antiretroviral Treatment History in DRIVE-AHEAD (Week 48)

| Laboratory Parameter Preferred Term | DELSTRIGO Once Daily N=320 | | EFV/FTC/TDF Once Daily N=307 | | Difference Estimates (DELSTRIGO - EFV/FTC/TDF) |
|---|---|---|---|---|---|
| | Baseline | Change | Baseline | Change | Difference (95% CI) |
| LDL-Cholesterol (mg/dL)P-value for the pre-specified hypothesis testing for treatment difference was <0.0001. | 91.7 | -2.1 | 91.3 | 8.3 | -10.2 (-13.8, -6.7) |
| Non-HDL Cholesterol (mg/dL) | 114.7 | -4.1 | 115.3 | 12.7 | -16.9 (-20.8, -13.0) |
| Total Cholesterol (mg/dL) Not pre-specified for hypothesis testing. | 156.8 | -2.2 | 156.8 | 21.1 | - |
| Triglycerides (mg/dL) | 118.7 | -12.0 | 122.6 | 21.6 | - |
| HDL-Cholesterol (mg/dL) | 42.1 | 1.8 | 41.6 | 8.4 | - |

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving lamivudine- or TDF-containing regimens. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Lamivudine:

Body as a Whole:redistribution/accumulation of body fat

Endocrine and Metabolic:hyperglycemia

General:Weakness

Hemic and Lymphatic:anemia (including pure red cell aplasia and severe anemias progressing on therapy)

Hepatic and Pancreatic: lactic acidosis and hepatic steatosis, posttreatment exacerbations of hepatitis B

Hypersensitivity:anaphylaxis, urticaria

Musculoskeletal:muscle weakness, CPK elevation, rhabdomyolysis

Skin:alopecia, pruritus

TDF:

Immune System Disorders:allergic reaction, including angioedema

Metabolism and Nutrition Disorders:lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic,and Mediastinal Disorders:dyspnea

Gastrointestinal Disorders:pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders:hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders:rash

Musculoskeletal and Connective Tissue Disorders:rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders:acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions:asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

## Clinical Trials Results

14.1 Adult Subjects with No Antiretroviral Treatment History

The efficacy of DELSTRIGO is based on the analyses of 48-week data from a randomized, multicenter, double-blind, active controlled Phase 3 trial (DRIVE-AHEAD, NCT02403674) in HIV-1 infected subjects with no antiretroviral treatment history (n=728).

Subjects were randomized and received at least 1 dose of either DELSTRIGO or EFV 600 mg/FTC 200 mg/TDF 300 mg once daily. At baseline, the median age of subjects was 31 years, 15% were female, 52% were non-white, 3% had hepatitis B or C coinfection, 14% had a history of AIDS, 21% had HIV-1 RNA greater than 100,000 copies/mL, and 88% had CD4+ T-cell count greater than 200 cells/mm3; these characteristics were similar between treatment groups. Week 48 outcomes for DRIVE-AHEAD are provided in Table 8.

Mean CD4+ T-cell counts in the DELSTRIGO and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm3, respectively.

Table 8: Virologic Outcome in DRIVE-AHEAD at Week 48 in HIV-1 Adult Subjects with No Antiretroviral Treatment History

| Outcome | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 |
|---|---|---|
| HIV-1 RNA <50 copies/mL | 84% | 81% |
| Treatment Difference (95% CI) The 95% CI for the treatment difference was calculated using stratum-adjusted Mantel-Haenszel method. | 3.5% (-2.0%, 9.0%) | |
| HIV-1 RNA ≥ 50 copies/mLIncludes subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (relative day 295-378). | 11% | 10% |
| No Virologic Data at Week 48 Window | 5% | 9% |
| Discontinued study due to AE or DeathIncludes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data in the Week 48 window. | 2% | 7% |
| Discontinued study for Other ReasonsOther reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, withdrawal by subject. | 2% | 2% |
| On study but missing data in window | 0 | <1% |
| Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline and Demographic Category | | |
| Gender | | |
| Male | 84% (n = 305) | 80% (n = 311) |
| Female | 85% (n = 59) | 83% (n = 53) |
| Race | | |

| Outcome | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 |
|---|---|---|
| White | 84% (n = 177) | 81% (n = 170) |
| Non-White | 84% (n = 187) | 80% (n = 194) |
| Ethnicity | | |
| Hispanic or Latino | 83% (n = 126) | 84% (n = 120) |
| Not Hispanic or Latino | 85% (n = 236) | 79% (n = 238) |
| Baseline HIV-1 RNA (copies/mL) | | |
| ≤100,000 copies/mL | 86% (n = 291) | 83% (n = 282) |
| >100,000 copies/mL | 77% (n = 73) | 72% (n = 82) |
| CD4+ T-cell Count (cells/mm3) | | |
| ≤200 cells/mm3 | 66% (n = 44) | 78% (n = 46) |
| >200 cells/mm3 | 87% (n = 320) | 81% (n = 318) |
| Viral SubtypeViral subtype was not available for two subjects. | | |
| Subtype B | 84% (n = 232) | 80% (n = 253) |
| Subtype Non-B | 85% (n = 130) | 83% (n = 111) |

## Clinical Pharmacology

In a Phase 2 trial evaluating doravirine over a dose range of 0.25 to 2 times the recommended dose of doravirine in DELSTRIGO (in combination with FTC/TDF) in HIV-1 infected subjects with no antiretroviral treatment history, no exposure-response relationship for efficacy was identified for doravirine.
Cardiac Electrophysiology
At a doravirine dose of 1200 mg, which provides approximately 4 times the peak concentration observed following the recommended dose of doravirine in DELSTRIGO does not prolong the QT interval to any clinically relevant extent.

## *Mechanism of Action*

DELSTRIGO is a fixed-dose combination of the antiretroviral drugs doravirine, lamivudine, and TDF[see Microbiology (12.4)].

## *Pharmacokinetics*

Single-dose administration of one DELSTRIGO tablet to healthy subjects provided comparable exposures of doravirine, lamivudine, and tenofovir to administration of doravirine tablets (100 mg) plus lamivudine tablets (300 mg) plus TDF tablets (300 mg). Doravirine pharmacokinetics are similar in healthy subjects and HIV-1-infected subjects. Pharmacokinetic properties of the components of DELSTRIGO are provided in Table 6.

Table 6: Pharmacokinetic Properties of the Components of DELSTRIGO

| Parameter | Doravirine | Lamivudine | Tenofovir |
|---|---|---|---|
| General | | | |
| Steady State ExposurePresented as geometric mean (%CV: geometric coefficient of variation) or mean ± SD. | | | |
| AUC0-24 (mcg·h/mL) | 16.1 (29)Doravirine 100 mg once daily to HIV-1 infected subjects. | 8.87 ± 1.83Lamivudine 300 mg once daily for 7 days to 60 healthy subjects. | 2.29 ± 0.69Single 300 mg dose of TDF to HIV-1-infected subjects in the fasted state. |
| Cmax (mcg/mL) | 0.962 (19) | 2.04 ± 0.54 | 0.30 ± 0.09 |
| C24 (mcg/mL) | 0.396 (63) | NA | NA |
| Absorption | | | |
| Absolute Bioavailability | 64% | 86% | 25% |
| Tmax(h) | 2 | NA | 1 |
| Effect of FoodGeometric mean ratio [high-fat meal/fasting] and (90% confidence interval) for PK parameters. High fat meal is approximately 1000 kcal, 50% fat. The effect of food is not clinically relevant. | | | |
| AUC Ratio | 1.10 (1.01, 1.20) | 0.93 (0.84, 1.03) | 1.27 (1.17, 1.37) |
| CmaxRatio | 0.95 (0.80, 1.12) | 0.81 (0.65, 1.01) | 0.88 (0.74, 1.04) |
| C24Ratio | 1.26 (1.13, 1.41) | NA | NA |
| Distribution | | | |
| VdssBased on IV dose. | 60.5 L | 1.3 L/kg | 1.3 L/kg |

| Parameter | Doravirine | Lamivudine | Tenofovir |
|---|---|---|---|
| Plasma Protein Binding | 76% | < 36% | <0.7% |
| Elimination | | | |
| t1/2(h) | 15 | 5-7 | 17 |
| CL/F (mL/ min) | 106 (35.2) | 398.5 ± 69.1 | 1,043.7 ± 115.4 |
| CLrenal(mL/ min) | 9.3 (18.6) | 199.7 ± 56.9 | 243.5 ± 33.3 |
| Metabolism | | | |
| Primary Pathway(s) | CYP3A | Minor | No CYP Metabolism |
| Excretion | | | |
| Major route of elimination | Metabolism | Glomerular filtration and active tubular secretion | Glomerular filtration and active tubular secretion |
| Urine (unchanged) | 6% | 71% | 70-80% |
| Biliary/Fecal (unchanged) | Minor | NA | NA |

Specific Populations

No clinically significant differences in the pharmacokinetics of certain DELSTRIGO components were observed based on age ≥ 65 years (for doravirine), sex (for doravirine, lamivudine, TDF), and race/ethnicity (for doravirine, lamivudine). The effects of age (≥ 65 years) on the pharmacokinetics of lamivudine, TDF and the effect of race on the pharmacokinetics of TDF are unknown. The pharmacokinetics of doravirine in patients <18 years of age is unknown.

Patients with Renal Impairment

Doravirine:No clinically significant difference in the pharmacokinetics of doravirine were observed in subjects with mild to severe renal impairment (creatinine clearance (CLcr) >15 mL/min, estimated by Cockcroft-Gault). Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis.

Lamivudine:The AUCinf, Cmax, and half-life of lamivudine increased and CL/F decreased to a clinically significant extent with diminishing renal function (CLcr 111 to < 10 mL/min).

TDF:A clinically significant increase in the Cmaxand AUC of tenofovir was observed in subjects with CLcr < 50 mL/min or with end stage renal disease requiring dialysis[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)].

Patients with Hepatic Impairment

Doravirine:No clinically significant difference in the pharmacokinetics of doravirine was observed in subjects with moderate hepatic impairment (Child-Pugh score B) compared to subjects without hepatic impairment. Doravirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C).

Lamivudine:No clinically significant differences in lamivudine pharmacokinetics were observed with diminishing hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

TDF:No clinically significant differences in tenofovir pharmacokinetics were observed between subjects with any degree of hepatic impairment and healthy subjects.

Drug Interaction Studies

DELSTRIGO is a complete regimen for the treatment of HIV-1 infection; therefore, DELSTRIGO is not recommended to be administered with other HIV-1 antiretroviral medications. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided.

The drug interaction trials described were conducted with doravirine, lamivudine and/or TDF, as single entities; no drug interaction trials have been conducted using the combination of doravirine, lamivudine, and TDF. No clinically relevant drug interactions were observed between doravirine, lamivudine, and TDF.
Doravirine:Doravirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of doravirine. Co-administration of doravirine and drugs that induce CYP3A may result in decreased plasma concentrations of doravirine. Co-administration of doravirine and drugs that inhibit CYP3A may result in increased plasma concentrations of doravirine.
Doravirine is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes. Doravirine did not inhibit major drug metabolizing enzymesin vitro, including CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and UGT1A1 and is not likely to be an inducer of CYP1A2, 2B6, or 3A4. Based onin vitroassays, doravirine is not likely to be an inhibitor of OATP1B1, OATP1B3, P-glycoprotein, BSEP, OAT1, OAT3, OCT2, MATE1, and MATE2K. Drug interaction studies were performed with doravirine and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. The effects of co-administration with other drugs on the exposure (Cmax, AUC, and C24) of doravirine are summarized in Table 7. A single doravirine 100 mg dose was administered in these studies unless otherwise noted.
Table 7: Drug Interactions: Changes in Pharmacokinetic Parameter Values of Doravirine in the Presence of Co-administered Drug

| **Co-administered Drug** | **Regimen of Co-administered Drug** | **N** | **Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)** | | |
|---|---|---|---|---|---|
| | | | **AUCAUCinffor single-dose, AUC0-24for once daily.** | **Cmax** | **C24** |
| Azole Antifungal Agents | | | | | |
| ketoconazoleChanges in doravirine pharmacokinetic values are not clinically relevant. | 400 mg QD | 10 | 3.06 (2.85, 3.29) | 1.25 (1.05, 1.49) | 2.75 (2.54, 2.98) |
| Antimycobacterials | | | | | |
| rifampin | 600 mg QD | 10 | 0.12 (0.10, 0.15) | 0.43 (0.35, 0.52) | 0.03 (0.02, 0.04) |
| rifabutin | 300 mg QD | 12 | 0.50 (0.45, 0.55) | 0.99 (0.85, 1.15) | 0.32 (0.28, 0.35) |
| HIV Antiviral Agents | | | | | |
| ritonavir,A single doravirine 50 mg dose (0.5 times the recommended approved dose) was administered. | 100 mg BID | 8 | 3.54 (3.04, 4.11) | 1.31 (1.17, 1.46) | 2.91 (2.33, 3.62) |
| efavirenz | 600 mg QDThe first day following the cessation of efavirenz therapy and | 17 | 0.38 (0.33, 0.45) | 0.65 (0.58, 0.73) | 0.15 (0.10, 0.23) |

| Co-administered Drug | Regimen of Co-administered Drug | N | Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00) | | |
|---|---|---|---|---|---|
| | | | AUCAUCinffor single-dose, AUC0-24for once daily. | Cmax | C24 |
| | initiation of doravirine 100 mg QD. | | | | |
| | 600 mg QD14 days following the cessation of efavirenz therapy and initiation of doravirine 100 mg QD. | 17 | 0.68 (0.58, 0.80) | 0.86 (0.77, 0.97) | 0.50 (0.39, 0.64) |

Based on drug interaction studies conducted with doravirine, no clinically significant drug interactions have been observed following the co-administration of doravirine and the following drugs: dolutegravir, TDF, lamivudine, elbasvir and grazoprevir, ledipasvir and sofosbuvir, ketoconazole, ritonavir, aluminum hydroxide/magnesium hydroxide/simethicone containing antacid, pantoprazole, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, and midazolam.
Lamivudine:
Trimethoprim/Sulfamethoxazole:Co-administration of TMP/SMX with lamivudine resulted in an increase of 43% ±23% (mean ±SD) in lamivudine AUC∞, a decrease of 29% ±13% in lamivudine oral clearance, and a decrease of 30% ±36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by co-administration with lamivudine.
Sorbitol (Excipient):Co-administration of lamivudine with a single dose of 3.2 grams, 10.2 grams, or 13.4 grams of sorbitol resulted in dose-dependent decreases of 14%, 32%, and 36% in the AUC∞; and 28%, 52%, and 55% in the Cmax of lamivudine, respectively.
TDF:
No clinically significant changes in exposure were observed for tenofovir when co-administered with tacrolimus or entecavir.
No clinically significant changes in exposure were observed for the following drugs when co-administered with tenofovir: tacrolimus, entecavir, methadone, or ethinyl estradiol/norgestimate.

## Drug Interactions

7.1 Concomitant Use with Other Antiretroviral Medications
Because DELSTRIGO is a complete regimen for the treatment of HIV-1 infection, co-administration with other antiretroviral medications for treatment of HIV-1 infection is not recommended. Information regarding potential drug-drug interactions with other antiretroviral medications is not provided.
7.2 Effect of Other Drugs on DELSTRIGO
Co-administration of DELSTRIGO with a CYP3A inducer decreases doravirine plasma concentrations, which may reduce DELSTRIGO efficacy[see Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)].
Co-administration of DELSTRIGO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

Table 5 shows the significant drug interactions with the components of DELSTRIGO. The drug interactions described are based on studies conducted with either DELSTRIGO or the components of DELSTRIGO as individual agents.

Table 5: Drug Interactions with DELSTRIGOThis table is not all-inclusive

| Concomitant Drug Class: Drug Name | Effect on Concentration | Clinical Comment |
|---|---|---|
| Androgen Receptors | | |
| enzalutamide | ↓ doravirine | Co-administration is contraindicated with enzalutamide.<br>At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO. |
| Anticonvulsants | | |
| carbamazepine<br>oxcarbazepine<br>phenobarbital<br>phenytoin | ↓ doravirine | Co-administration is contraindicated with these anticonvulsants.<br>At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO. |
| Antimycobacterials | | |
| rifampinThe interaction between doravirine and the concomitant drug was evaluated in a clinical study.<br>rifapentine | ↓ doravirine | Co-administration is contraindicated with rifampin or rifapentine.<br>At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO. |
| rifabutin | ↓ doravirine | If DELSTRIGO is co-administered with rifabutin, one tablet of doravirine (PIFELTRO) should be taken approximately 12 hours after the dose of DELSTRIGO [see Dosage and Administration (2.4)].<br>At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO. |
| Cytotoxic Agents | | |
| mitotane | ↓ doravirine | Co-administration is contraindicated with mitotane.<br>At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO. |
| Hepatitis C Antiviral Agents | | |
| ledipasvir/sofosbuvir<br>sofosbuvir/velpatasvir | ↑ tenofovir | Monitor for adverse reactions associated with TDF. |
| Herbal Products | | |
| St. John's wort | ↓ doravirine | Co-administration is contraindicated with St. John's wort.<br>At least a 4-week cessation period is recommended prior to initiation of DELSTRIGO. |
| Other Agents | | |

| Concomitant Drug Class: Drug Name | Effect on Concentration | Clinical Comment |
|---|---|---|
| sorbitol | ↓ lamivudine | Co-administration of single doses of lamivudine and sorbitol resulted in a sorbitol dose-dependent reduction in lamivudine exposures. When possible, avoid use of sorbitol-containing medicines with lamivudine-containing medicines. |

Co-administration of DELSTRIGO with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of lamivudine, tenofovir, and/or other renally eliminated drugs. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].

No clinically significant changes in concentration were observed for doravirine when co-administered with the following agents: TDF, lamivudine, elbasvir and grazoprevir, ledipasvir and sofosbuvir, ritonavir, ketoconazole, aluminum hydroxide/magnesium hydroxide/simethicone containing antacid, pantoprazole, or methadone[see Clinical Pharmacology (12.3)].

No clinically significant changes in concentration were observed for tenofovir when co-administered with tacrolimus or entecavir[see Clinical Pharmacology (12.3)].

7.3 Effect of DELSTRIGO on Other Drugs

No clinically significant changes in concentration were observed for the following agents when co-administered with doravirine: lamivudine, TDF, elbasvir and grazoprevir, ledipasvir and sofosbuvir, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, or midazolam.

No clinically significant drug interactions have been observed between TDF and the following medications: entecavir, methadone, oral contraceptives, sofosbuvir, or tacrolimus in studies conducted in healthy subjects. Lamivudine is not significantly metabolized by CYP enzymes nor does it inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur through these pathways[see Clinical Pharmacology (12.3)].

## Contraindications

- DELSTRIGO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO[see Warnings and Precuations (5.3), Drug Interactions (7.2), and Clinical Pharmacology (12.3)]. These drugs include, but are not limited to, the following:
    - -the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
    - -the androgen receptor inhibitor enzalutamide
    - -the antimycobacterials rifampin, rifapentine
    - -the cytotoxic agent mitotane
    - -St. John's wort (Hypericum perforatum)
- DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine.

## Use in Specific Populations

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DELSTRIGO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There is insufficient prospective pregnancy data from the APR to adequately assess the risk of birth defects and miscarriage. Doravirine use in individuals during pregnancy has not been evaluated; however, lamivudine and TDF use during pregnancy has been evaluated in a limited number of individuals reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for lamivudine and TDF compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (see Data).The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates individuals and infants from the limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

In animal reproduction studies, oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemic exposure (AUC) similar to the recommended clinical dose; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (Cmax) 35 times the recommended clinical dose.

No adverse developmental effects were observed when doravirine and TDF were administered separately at doses/exposures ≥8 (doravirine) and ≥14 (TDF) times those of the recommended human dose (RHD) of DELSTRIGO (see Data).

Data

Human Data

Lamivudine:The APR has received a total of over 12,000 prospective reports with follow-up data of possible exposure to lamivudine-containing regimens; over 5,400 reports in the first trimester; over 5,500 reports in the second trimester; and over 1,800 reports in the third trimester. Birth defects occurred in 151 of 5,008 (3.0%, 95% CI: 2.6% to 3.5%) live births for lamivudine-containing regimens (first trimester exposure); and 210 of 7,356 (2.9%, 95% CI: 2.5% to 3.3%) live births for lamivudine-containing regimens (second/third trimester exposure). Among pregnant mothers in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between lamivudine and overall birth defects observed in the APR.

TDF:The APR has received a total of over 5,500 prospective reports with follow-up data of possible exposure to tenofovir disoproxil-containing regimens; over 3,900 reports in the first trimester; over 1,000 reports in the second trimester; and over 500 reports in the third trimester. Birth defects occurred in 82 of 3,535 (2.3%, 95% CI: 1.9% to 2.9%) live births for TDF-containing regimens (first trimester exposure); and 35 of 1,570 (2.2%, 95% CI: 1.6% to 3.1%) live births for TDF-containing regimens (second/third trimester exposure). Among pregnant mothers in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between tenofovir and overall birth defects observed in the APR.

Animal Data

Doravirine:Doravirine was administered orally to pregnant rabbits (up to 300 mg/kg/day on gestation days (GD) 7 to 20) and rats (up to 450 mg/kg/day on GD 6 to 20 and separately from GD 6 to lactation/postpartum day 20). No significant toxicological effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at exposures (AUC) approximately 9 times (rats) and 8 times (rabbits) the exposure in humans at the RHD. Doravirine was transferred to the fetus through the placenta in embryo-fetal

studies, with fetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on gestation day 20.
Lamivudine:Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300, and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (Cmax) approximately 35 times higher than human exposure at the recommended daily dose. Evidence of early embryolethality was seen in the rabbit at system exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (Cmax) 35 times higher than human exposure at the recommended daily dose. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of lamivudine.
TDF:Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of harm to the fetus.
8.2 Lactation
Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking potential transmission of HIV-1 infection.
Based on limited published data, both lamivudine and tenofovir are present in human milk. It is unknown whether doravirine is present in human milk, but doravirine is present in the milk of lactating rats (see Data). It is not known whether DELSTRIGO or the components of DELSTRIGO affects human milk production, or has effects on the breastfed infant. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving DELSTRIGO.
Data
Doravirine: Doravirine was excreted into the milk of lactating rats following oral administration (450 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations approximately 1.5 times that of maternal plasma concentrations observed 2 hours post dose on lactation day 14.
8.4 Pediatric Use
Safety and efficacy of DELSTRIGO have not been established in pediatric patients less than 18 years of age.
8.5 Geriatric Use
Clinical trials of doravirine, lamivudine, or TDF did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of DELSTRIGO in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy[see Clinical Pharmacology (12.3)].
8.6 Renal Impairment
Because DELSTRIGO is a fixed-dose combination tablet and the dosage of lamivudine and TDF, both components of DELSTRIGO, cannot be altered, DELSTRIGO is not recommended in patients with estimated creatinine clearance less than 50 mL/min[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].
8.7 Hepatic Impairment
No dosage adjustment of DELSTRIGO is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. DELSTRIGO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C)[see Clinical Pharmacology (12.3)].

## References

Delstrigo Prescribing information. Accessed Jan 12, 2019.

**Pharmacy & Therapeutics Committee Summary Review**
*Emgality™ (galcanezumab-gnlm)– Eli Lilly & Co.*

**Prepared by:** Jordan Breitigam, CVS

**Presentation Date:** March 28, 2019

**Therapeutic Class:** CGRP antagonists

**FDA Approval Date:** September 27, 2018

**FDA Indication:** Migraine prophylaxis

**Comparable Formulary Products:** Botox

## Proposed Designation & Rationale

**Recommendation:** Non-preferred

**Clinical Implications/Place in Therapy:**

- Emgality is the third CGRP inhibitor indicated for the preventive treatment of migraine in adults
- Aimovig (erenumab-aooe) was the first and Ajovy (fremanezumab-vfrm) was the second CGRP inhibitor approved by the FDA for the prevention of migraine in adults. Other preventive treatment for migraine include Botox (onabotulinumtoxinA), and oral agents (i.e., topiramate, divalproex, propranolol, and timolol)
- There is limited guidance in the approach to migraine prevention. The AAN in 2016 recommended Botox for chronic migraine but not episodic. The AHS/AAN jointly in 2012 considered oral prophylactic agents to be effective for episodic migraine prevention. Available guidelines were published prior to the approval of CGRP inhibitors including Emgality
- Emgality provides an additional SC monthly injectable option, similar to Aimovig and Ajovy, while Ajovy can also be administered Q 3 months. Oral agents are dosed daily or twice daily. Botox is the only agent that requires administration by a healthcare provider
- All CGRP inhibitors including Emgality are effective in both CM and EM prevention, whereas Botox is only effective for CM. Oral agents are likely only effective for EM prevention; among oral agents, topiramate has shown some efficacy in CM prevention
- All CGRP inhibitors including Emgality are well tolerated, whereas Botox has multiple boxed warnings, and oral agents have multiple safety concerns

**References:**


1. Emgality (galcanezumab-gnlm) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; September 2018.
2. Levin M, Silberstein SD, Gilbert R, Lucas S, Munsie L, Garrelts A, Kennedy K, Everman N, Pearlman E. Basic considerations for the use of monoclonal antibodies in migraine. Headache. 2018; 58(1): 1689-1696. Doi: 10.1111/head.13439
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CVSHealth

# CVS Caremark Pharmacy & Therapeutics
# Drug Monograph

## Emgality™ (galcanezumab-gnlm) subcutaneous injection
## Eli Lilly and Company

### INDICATION

Emgality (galcanezumab-gnlm) is indicated for the preventive treatment of migraine in adults (Emgality prescribing information, 2018).

### U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Emgality (galcanezumab-gnlm) was approved by the FDA on September 27, 2018 under a Biologic License Application (BLA) and underwent a Standard Review (FDA, 2018).

### DRUG SUMMARY

| Emgality (galcanezumab-gnlm) | |
|---|---|
| **Place in Therapy** | • Emgality is the third CGRP inhibitor indicated for the preventive treatment of migraine in adults.<br>• Aimovig (erenumab-aooe) was the first and Ajovy (fremanezumab-vfrm) was the second CGRP inhibitors approved by the FDA for the prevention of migraine in adults. Other preventive treatment for migraine include Botox (onabotulinumtoxinA), and oral agents (i.e., topiramate, divalproex, propranolol, and timolol).<br>• There is limited guidance in the approach to migraine prevention. The AAN in 2016 recommended Botox for CM but not EM. The AHS/AAN jointly in 2012 considered oral prophylactic agents to be effective for EM prevention. Available guidelines were published prior to the approval of CGRP inhibitors including Emgality.<br>• Emgality provides an additional SC monthly injectable option, similar to Aimovig and Ajovy, while Ajovy can also be administered Q 3 months. Oral agents are dosed daily or twice daily. Botox is the only agent that requires administration by a healthcare provider.<br>• All CGRP inhibitors including Emgality are effective in both CM and EM prevention, whereas Botox is only effective for CM. Oral agents are likely only effective for EM prevention; among oral agents, topiramate has shown some efficacy in CM prevention.<br>• All CGRP inhibitors including Emgality are well tolerated, whereas Botox has multiple boxed warnings, and oral agents have multiple safety concerns. |
| **Efficacy** | • Three phase III, multinational, randomized, double-blind, placebo-controlled trials:<br>○ In patients with EM at 24 weeks (EVOLVE-1 and EVOLVE-2; 24-week trials):<br>▪ Emgality 120 mg reduced MMD by 1.9 days to 2.0 days (placebo-adjusted; $p < 0.001$).<br>▪ About 23% of patients treated with Emgality 120 mg achieved ≥ 50% reduction in MMD (placebo-adjusted; $p < 0.001$).<br>○ In patient with CM at 12 weeks (REGAIN; 12-week trial):<br>▪ Emgality 120 mg reduced MMD by 2.1 days (placebo-adjusted; $p < 0.001$).<br>▪ About 12% of patients treated with Emgality 120 mg achieved ≥ 50% reduction in MMD (placebo-adjusted; $p < 0.001$).<br>• Although two dosing regimens (i.e., 240 mg and 120 mg) of Emgality were studied in the clinical trials, the FDA only approved the 120 mg monthly dosing regimen of Emgality. |
| **Safety** | • Contraindicated in patients with severe hypersensitivity to Emgality<br>• AEs (≥ 2%): injection site reactions (e.g., rash, urticaria, and dyspnea) |

AAN = American Academy of Neurology
AE = adverse event
AHS = American Headache Society
CGRP = calcitonin gene-related peptide
CM = chronic migraine
EM = episodic migraine
FDA = Food and Drug Administration
MMD = monthly migraine day
Q = every
SC = subcutaneous

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Galcanezumab-gnlm is a humanized immunoglobulin G (IgG)-4 monoclonal antibody that specifically binds to the calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the CGRP receptor (Emgality prescribing information, 2018).

### Pharmacokinetics

**Table 1: Selected Pharmacokinetics of Galcanezumab-gnlm**

| Route of Administration | $T_{max}$ | Volume of Distribution | Metabolism & Elimination | $T_{1/2}$ |
|---|---|---|---|---|
| Subcutaneous | 5 days | 7.3 L | Degraded into small peptides and amino acids via catabolic pathways; not metabolized by cytochrome P450 enzymes | 27 days |

$T_{1/2}$ = elimination half-life
$T_{max}$ = time to maximum plasma concentration

(Emgality prescribing information, 2018)

### Pharmacogenomics

No pharmacogenomic data are available at this time for galcanezumab-gnlm.

## CLINICAL EFFICACY

**Table 2: Efficacy of Emgality (galcanezumab-gnlm) in the Prevention of EM**

| **Study**<br>Evidence level Ib | **EVOLVE-1** (N = 843)<br>**Stauffer, 2018** | | | **EVOLVE-2** (N = 915)<br>**Skljarevski, 2018** | | |
|---|---|---|---|---|---|---|
| **Study Design** | Phase III, multicenter (EVOLVE-1: North America; EVOLVE-2: international), randomized, double-blind, placebo-controlled trial consisting of a 1-month screening period, a 1-month baseline period, a 6-month double-blind treatment period, and a 4-month posttreatment follow-up period | | | | | |
| **Inclusion Criteria** | Adults with ≥ 1-year history of EM* with an onset prior to 50 years of age<br>• Mean age: ~41 years; ~85% female; ~20 years since diagnosis; baseline MMD†: ~9 days | | | | | |
| | • ~60% had prior preventive treatment<br>• ~19% failed ≥ 1 prior preventive treatment due poor efficacy | | | • 65% to 68% had prior preventive treatment<br>• ~14% failed ≥ 2 prior preventive treatments | | |
| **Exclusion Criteria** | Failure of ≥ 3 preventive medication classes‡, use of Botox (onabotulinumtoxinA) within 4 months or migraine intervention/device within 30 days prior to the baseline period, use of opioids or barbiturates > 2 or 3 times per month, exposure to therapeutic antibody in the past 12 months, pregnancy, or suicide ideation | | | | | |
| **Treatments** | **Emgality 240 mg SC monthly** (n = 208) | **Emgality 120 mg‖ SC monthly** (n = 210) | **Placebo** (n = 425) | **Emgality 240 mg SC monthly** (n = 223) | **Emgality 120 mg‖ SC monthly** (n = 231) | **Placebo** (n = 461) |
| **Results** **Δ in MMD† at 24 weeks** | -4.6 | -4.7 | -2.8 | -4.2 | -4.3 | -2.3 |
| | Placebo-adjusted: -1.8§ | Placebo-adjusted: -1.9§ | N/A | Placebo-adjusted: -1.9§ | Placebo-adjusted: -2.0§ | N/A |
| **≥ 50% reduction in MMD†** | 60.9% | 62.3% | 38.6% | 56.5% | 59.3% | 36.0% |
| | Placebo-adjusted: 22.3%<br>OR: 2.5§; 95% CI 1.9 to 3.2 | Placebo-adjusted: 23.7%<br>OR: 2.6§; 95% CI 2.0 to 3.4 | N/A | Placebo-adjusted: 20.5%§ | Placebo-adjusted: 23.3%§ | N/A |
| **Δ in days/month requiring acute treatment** | -3.8 | -4.0 | -2.2 | -3.6 | -3.7 | -1.9 |
| | Placebo-adjusted: -1.6§ | Placebo-adjusted: -1.8§ | N/A | Placebo-adjusted: -1.7§ | Placebo-adjusted: -1.8§ | N/A |
| **Safety** | • TEAEs in EVOLVE-1: Emgality 240 mg and 120 mg (72% and 65%, respectively) vs. placebo 62%; TEAEs in EVOLVE-2: 72% and 65% vs. 62%.<br>• Discontinuations due to AEs were rare in EVOLVE-1 and were statistically similar between Emgality and placebo in EVOLVE-2.<br>• Most common TEAE (> 5%): injection site pain (Emgality 16% to 21% vs. placebo 17% in EVOLVE-1; ~9% in all three arms in EVOLVE-2), injection site reactions (Emgality 3%§ to 8%§ vs. placebo 0% in EVOLVE-2), nasopharyngitis (up to 9%), and urinary tract infection (up to 6%). | | | | | |
| **Comments** | • In EVOLVE-1, Emgality-treated patients were also more likely to achieve ≥ 75% reduction (Emgality 120 mg: OR 2.7§) and 100% reduction (Emgality 120 mg: OR 2.8§) in MMD vs. placebo. In EVOLVE-2, greater proportions of Emgality-treated patients achieved ≥ 75% reduction (Emgality 120 mg: placebo-adjusted 16%§) and 100% reduction (Emgality 120 mg: placebo-adjusted 6%§) in MMD vs. placebo.<br>• A subgroup analysis in those who failed two prior preventive therapies reported MMD reductions for Emgality 240 mg, 120 mg, and placebo to be 3.85 days, 3.45 days, and 0.81 days, respectively (placebo-adjusted MMD reductions of 3.04 days for Emgality 240 mg and 2.64 days for Emgality 120 mg) (Zhang, 2018).<br>• Limitations: exclusion of treatment-refractory patients (failed ≥ 3 classes) or patients with serious medical or psychiatric condition; patients were not allowed to have a concurrent preventive medication to determine whether Emgality can be used as an adjunctive preventive treatment. | | | | | |
| **Conclusions** | Emgality‖ significantly reduced MMD by a placebo-adjusted 1.8 days to 2.0 days at the end of 24 weeks in patients with EM. Emgality was well tolerated. | | | | | |

* EM was defined as a headache frequency between 4 days to 14 days, with ≥ 2 migraine attacks per month fulfilling the ICHD-3 beta criteria for migraine with or without aura or probable migraine
† A migraine day was defined as a calendar day with a headache meeting criteria for migraine ± aura or probable migraine (only one migraine criterion absent)
‡ Medication classes recommended by the 2012 American Academy of Neurology guideline for EM prevention include antiepileptics (i.e., divalproex, valproate, and topiramate), beta-blockers (i.e., metoprolol, propranolol, timolol, atenolol, and nadolol), triptans (i.e., frovatriptan, naratriptan, and zolmitriptan), and antidepressants (i.e., amitriptyline and venlafaxine) (Silberstein, 2012)
§ $p < 0.001$ vs. placebo
‖ The Food and Drug Administration only approved the 120 mg monthly dosing regimen of Emgality (galcanezumab-gnlm), which consisted of a loading dose of 240 mg followed by 120 mg monthly. In the EVOLVE trials, both dosing regimens of Emgality started with a loading dose of 240 mg (two 120 mg injections) followed by either two injections (240 mg total) or one injection (120 mg) monthly.
AE = adverse event
CI = confidence interval
EM = episodic migraine
ICHD-3 beta = International Classification of Headache Disorder 3 beta version
MMD = monthly migraine day
OR = odds ratio
N/A = not applicable
SC = subcutaneously
TEAE = treatment-emergent adverse event

(Silberstein, 2012; Skljarevski, 2018; Stauffer, 2018; Zhang, 2018)

**Table 3: Efficacy of Emgality (galcanezumab-gnlm) in the Prevention of CM**

| Study, Treatments, and Groups | Study Design, Endpoints, and Criteria | Results |
|---|---|---|
| **REGAIN**<br>Evidence level Ib<br>**Emgality (galcanezumab-gnlm) 240 mg SC monthly:**<br>240 mg (two 120 mg injections) at baseline, week 4, and week 8 (n = 277)<br><br>or<br><br>**Emgality 120 mg SC monthly*:**<br>240 mg (two 120 mg injections) at baseline, 120 mg plus one placebo injection at week 4 and week 8 (n = 278)<br><br>vs.<br><br>**Placebo SC monthly**<br>(n = 558) | (N = 1,113)<br>**Study Design:**<br>Unpublished, phase III, randomized, double-blind, placebo-controlled trial consisting of a 4-week pre-intervention period, a 3-month of double-blind intervention period, a 9-month open-label extension period, and a 4-month follow-up period regardless of entry into open-label extension<br>**Objective:** To determine if Emgality is superior to placebo for CM prevention at 120 mg or 240 mg per month<br>**Primary Endpoint(s):** Mean change in MMD from baseline to 12 weeks<br>**Secondary Endpoint(s):**<br>• Proportion of patients achieving ≥ 50%, ≥ 70%, and 100% reduction in MMD at 12 weeks<br>• Mean change in monthly days requiring abortive agent (acute migraine treatment) from baseline to 12 weeks<br>**Inclusion Criteria:**<br>• Adults with a history of CM† (i.e., ≥ 15 MMD) (mean age: ~40 years; 82% to 87% were female; ~80% were white; ~20 years since diagnosis; baseline MMD: ~19 days; 76% to 79% received prior preventive therapy‡; 24% to 35% failed ≥ 2 preventive therapies‡; ~14% used one concomitant migraine-preventive medication‡ during the intervention period)<br>**Exclusion Criteria:**<br>• Patients with electrocardiogram abnormalities compatible with an acute cardiovascular event, patients with a history of stroke, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism within 6 months of screening | **Endpoint** / **Emgality 240 mg** (n = 274)§ / **Emgality 120 mg*** (n = 273)§ / **Placebo** (n = 538)§<br>Δ in MMD at 12 weeks: -4.62 / -4.83 / -2.74<br>Placebo-adjusted: -1.88 ± 0.42‖ / Placebo-adjusted: -2.09 ± 0.42‖ / N/A<br>≥ 50% reduction in MMD: 27.5% / 27.6% / 15.4%<br>Placebo-adjusted: 12.1%‖ / Placebo-adjusted: 12.2%‖ / N/A<br>Δ in days/month requiring acute treatment: -4.25 / -4.74 / -2.23<br>Placebo-adjusted: -2.02‖ / Placebo-adjusted: -2.51‖ / N/A<br><br>**Safety**<br>• TEAEs occurred in 57% and 58% of the Emgality arms vs. 50% in the placebo arm. Four patients in the Emgality 240 mg arm and one patient in the Emgality 120 mg arm discontinued therapy due to AEs compared with six patients in the placebo arm.<br>• AEs (> 5%): injection site pain (7% with the 240 mg and 6% with the 120 mg vs. 4% placebo), nasopharyngitis (3% with the 240 mg and 6% with the 120 mg vs. 5% placebo), and injection site reaction (5% with 240 mg and 3% with 120 mg vs. 2% placebo).<br>**Comments/Study Limitations:**<br>• Treatment effect with Emgality was seen within 4 weeks after the initial dose.<br>• Higher proportions of patients in the Emgality 240 mg arm (placebo-adjusted: 4.3%; $p < 0.001$) and Emgality 120 mg arm (placebo-adjusted: 2.5%; $p < 0.05$) achieved ≥ 75% reduction in MMD compared with the placebo arm.<br>• Based on the subgroup analysis in those who failed ≥ 2 prior preventive therapies, the reductions in MMD for Emgality 240 mg, 120 mg, and placebo were 3.30 days, 5.91 days, and 1.44 days, respectively (a placebo-adjusted MMD reduction of 1.86 days for Emgality 240 mg and 4.47 days for Emgality 120 mg) (Zhang, 2018).<br>• Limitations: data were unpublished; available data did not address the prior migraine-prevention history of the study population; short treatment duration of only 3 months<br>**Conclusions:** Emgality* significantly reduced MMD by a placebo-adjusted 1.9 days to 2.1 days at end of 12 weeks in patients with CM. Emgality was overall well tolerated. |

* The Food and Drug Administration only approved the 120 mg monthly dosing regimen of Emgality (galcanezumab-gnlm), which consisted of a loading dose of 240 mg followed by 120 mg monthly.
† CM was defined as a headache frequency of ≥ 15 headache days per month, of which ≥ 8 headache days with a headache that met the criteria for migraine.
‡ The unpublished sources of available data did not provide details regarding the types of preventive therapies the study population were receiving, had received, and/or failed in the past.
§ The study population who completed the 3-month of double-blind intervention.
‖ $p < 0.001$ vs. placebo
AE = adverse event
CM = chronic migraine
Evidence level Ib = randomized, controlled trial
MMD = monthly migraine day
N/A = not applicable
SC = subcutaneously
TEAE = treatment-emergent adverse event

(Detke, 2017; Eli Lilly, 2017; Emgality prescribing information, 2018; Zhang, 2018)

## SAFETY

### Contraindications and Warnings

Emgality (galcanezumab-gnlm) is contraindicated for use in patients with serious hypersensitivity to galcanezumab-gnlm (Emgality prescribing information, 2018). In the Emgality (galcanezumab-gnlm) clinical trials, hypersensitivity reactions (e.g., rash, urticaria, and dyspnea) have been reported. If a serious or serious hypersensitivity reaction occurs, Emgality (galcanezumab-gnlm) should be discontinued and patients should be advised to seek immediate medical attention. Hypersensitivity reactions can occur days after administration and may be prolonged.

### Reproductive Risk

There are limited data to inform the developmental risk associated with the use of galcanezumab-gnlm in pregnant women (Emgality prescribing information, 2018). In animal reproductive studies, the administration of galcanezumab-gnlm during the period of organogenesis and throughout pregnancy and lactation did not result in adverse developmental effects.

### Nursing Mothers

There are no data on the presence of galcanezumab-gnlm in human milk, the effects on the breastfed infant, or the effects on milk production (Emgality prescribing information, 2018).

### Pediatric Use

Safety and effectiveness of Emgality (galcanezumab-gnlm) have not been established in pediatric patients (Emgality prescribing information, 2018).

### Geriatric Use

In clinical trials of Emgality (galcanezumab-gnlm), there was an insufficient number of patients 65 years of age or older to determine whether older patients respond differently from younger patients (Emgality prescribing information, 2018).

### Drug Interactions

Galcanezumab-gnlm is not metabolized by cytochrome P450 (CYP) enzymes (Emgality prescribing information, 2018). Therefore, galcanezumab-gnlm is unlikely to interact with CYP substrates, inducers, or inhibitors.

### Adverse Events

**Table 4: Adverse Events Occurring in Adults with Migraine in ≥ 2% of Emgality (galcanezumab-gnlm)-Treated Patients and ≥ 2% More Common than with Placebo in Clinical Trials**

| Adverse Event | Emgality 120 mg subcutaneously monthly N = 705 | Placebo N = 1,452 |
|---|---|---|
| Injection site reactions | 18% | 13% |

* Includes injection site pain, erythema, and pruritus

(Emgality prescribing information, 2018)

### Immunogenicity

In controlled trials up to 6 months, treatment-emergent anti-drug antibodies (ADA) responses were observed in 33 of 688 Emgality (galcanezumab-gnlm)-treated patients (4.8%), with 32 out of the 33 patients having in vitro neutralizing activity (Emgality prescribing information, 2018). In a 12 month, open-label study, 16 out of 128 Emgality (galcanezumab-gnlm)-treated patients (12.5%) developed ADA, most of whom tested positive for neutralizing antibodies. Available data do not demonstrate an impact on the pharmacokinetics, efficacy, or safety by the ADA development; however, available data are too limited to draw a conclusion.

## PRODUCT AVAILABILITY

Emgality (galcanezumab-gnlm) will be available as a single-dose 120 mg/mL prefilled syringe and pen for subcutaneous injection and will be supplied as cartons containing one or two syringes or pens (Emgality prescribing information, 2018). Storage of Emgality (galcanezumab-gnlm) requires refrigeration at 2° C to 8° C (36° F to 46° F) in the original carton to protect from light. Emgality (galcanezumab-gnlm) may be stored out of the refrigerator in the original carton at temperatures up to 30° C (86° F) for a maximum of 7 days. Emgality is projected to launch in the fourth quarter of 2018 (RxPipeline, 2018).

## DOSAGE AND ADMINISTRATION

Emgality (galcanezumab-gnlm) is administered as two consecutive subcutaneous injections (120 mg each) for a total dose of 240 mg once as a loading dose, followed by 120 mg subcutaneously monthly (Emgality prescribing information, 2018). Emgality (galcanezumab-gnlm) is intended for patient self-administration after proper training by a healthcare provider. Prior to administration, the prefilled syringe of Emgality (galcanezumab-gnlm) should be allowed to warm up in room temperature for 30 minutes after the removal from the refrigerator.

## APPROACHES TO TREATMENT

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches and reversible neurological or systemic symptoms (Dodick, 2018). In 2015, migraine was ranked the second largest contributor of disability-adjusted life years (DALY) at 13.1%, second to stroke at 47.3% (Global Burden of Disease [GBD] 2015 Neurological Disorder Collaborator Group, 2017). In 2016, migraine affected over one billion people worldwide, with an incidence of about 110,000 cases per year (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Migraine often begins at puberty, but it most commonly affects those between 35 years and 45 years of age (World Health Organization [WHO], 2016). Migraine is about twice as common in women than men, which is likely due to hormonal influences.

A migraine attack may start with the premonitory phase, which is characterized by the presence of aura prior to experience of pain (Dodick, 2018). The premonitory phase may be caused by the spontaneous activation of certain regions in the brain, which can be triggered by alteration in homeostasis, stress, or visual stimuli, and followed by a massive release of glutamate resulting in the activation of trigeminovascular system, which leads to the headache phase. About half of patients with migraine report unilateral, throbbing or pulsating headache. Migraine occurs more often during sleep, upon awakening, or shortly after rising in the morning. In addition to pain, over half of patients with migraine also experience photophobia, phonophobia, cutaneous allodynia, nausea/vomiting, and dizziness. Shortly after the resolution of headache pain, the majority of patients also experience postdromal symptoms, such as fatigue and somnolence.

The International Classification of Headache Disorder, 3rd Edition (ICHD-3), by the International Headache Society (IHS) classifies migraine headaches into migraine with aura, migraine without aura, and chronic migraine (CM), among other migraine diagnoses (IHS, 2018). In general, a diagnosis of migraine is made based on ICHD-3 criteria and by ruling out differential diagnoses, such as transient ischemic attack, tension-type headache, or other systemic or intracranial disease (Dodick, 2018). A diagnosis of CM is based on the presence of 15 or more headache days per month, of which at least 8 days meet the diagnostic criteria for migraine with or without aura or headache that was relieved by a triptan or ergot derivative, and the frequency of headache days was maintained for longer than 3 months (IHS, 2018). The prevalence of CM in the general population is between 1.4% and 2.2%, and CM accounts for about 8% of all migraine cases (Dodick, 2018; Schwedt, 2014). The diagnosis of episodic migraine (EM) is not specifically outlined in the ICHD-3, but it is generally defined by the presence of fewer than 15 migraine headache days per month (Dodick, 2018). About 2.5% to 3.0% of patients with EM transform to CM annually (Dodick, 2018). The mechanism of transformation from EM to CM may be attributed to atypical modulation of pain, sensitization of the trigeminal system from recurrent migraine attacks, cortical hyperexcitability, and neurogenic inflammation due to the release of vasoactive neuropeptides (e.g., CGRP) (Schwedt, 2014). CM results in substantially greater disability than EM; people with CM have lower incomes and are less likely to be employed full time. However, patients with CM may revert back to EM; about 40% of patients transition in and out of CM.

Preventive treatment of migraine can reduce the frequency, severity, and duration of attacks in patients with frequent migraine (Dodick, 2018). Migraine prophylactic agents that are approved by the Food and Drug Administration (FDA) include Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Botox (onabotulinumtoxinA), Emgality (galcanezumab-gnlm), topiramate, divalproex, propanolol, and timolol (FDA, 2018). The decision to start prophylactic therapy should be based on the frequency and severity of the attacks as well as patient responsiveness to acute treatments (Charles, 2017). The selection of a migraine prophylactic agent should be based on the patient's comorbidities, tolerance of adverse events associated with the agent, and the potential for pregnancy in women of childbearing age. Since attack frequency is a risk factor for progression from EM to CM, preventive migraine medications should be considered in patients with four or more migraine attacks per month or at least eight headache days per month. However, studies have reported poor adherence to migraine-preventive treatments. Currently, there is limited guidance on the approach to migraine prevention, and the available guidelines were published prior to the approval of CGRP inhibitors including Emgality (galcanezumab-gnlm). The American Academy of Neurology (AAN) recommends Botox (onabotulinumtoxinA) for adult patients with CM but not for EM (Simpson, 2016). The American Headache Society (AHS) and AAN jointly in 2012 considered divalproex, propranolol, timolol, and topiramate to be effective for migraine prevention in adult patients with EM (Loder, 2012; Silberstein, 2012). Of note, an update to the 2012 joint AHS/AAN guideline for pharmacological and non-pharmacological treatment and prevention of migraine headache in adults is in development without an expected publication date (AAN, 2018).

**National Institute for Health and Care Excellence (NICE)**

The NICE guidance recommends topiramate or propranolol for migraine prevention based on patient's preference, comorbidities, risk of adverse events, and childbearing potential (NICE, 2015). The NICE guidance also recommends botulinum toxin type A for prevention of CM in patients who did not respond to ≥ 3 migraine prophylactic agents, but botulinum toxin should be discontinued if the patient fails to achieve ≥ 30% reduction in MMD after two treatment cycles or if CM transitions to EM for three consecutive months (NICE, 2012a). Migraine prophylactic agents should be reviewed 6 months after treatment initiation, and treatment should be continued if the prophylactic agent is well tolerated (NICE, 2012b; NICE, 2015). As of October 3, 2018, there is no appraisal or appraisal guidance in development for Emgality (galcanezumab-gnlm). However, the appraisals of two similar CGRP inhibitors, Aimovig (erenumab-aooe) and Ajovy (fremanezumab-vfrm), for migraine prevention are currently in development without an expected publication date (NICE, 2018a; NICE, 2018b).

**Institute for Clinical and Economic Review (ICER)**

ICER recently published the final evidence report on CGRP inhibitors as preventive treatments for patients with EM and CM (Ellis, 2018). In their review of comparative clinical effectiveness, the use of Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), and oral preventive agents in patients with EM was also associated with greater reductions in migraine days, higher odds of 50% response, and greater reductions in monthly days requiring acute migraine medications compared with placebo. There was no statistical difference between CGRP inhibitors and other preventive therapies for the previously listed endpoints. When evaluating the incremental direct cost-effectiveness ratio, the quality-adjusted life year (QALY) is a well-established benchmark which evaluates the impact of treatment on lengthening life and/or improving the quality of life (ICER, 2017). ICER generally sets a value-based price benchmark range of $100,000 per QALY to $150,000 per QALY; incremental cost-effectiveness ratios below $50,000 per QALY are presumed to be "high value", while ratios above $175,000 per QALY are deemed to be "low value". The results of ICER analyses are summarized in Table 5. Based on the analyses, Emgality (galcanezumab-gnlm) was projected to have a lower cost per QALY gained compared with Aimovig (erenumab-aooe) and Ajovy (fremanezumab-vfrm) in patients with EM who are eligible to receive oral preventive agents. However, the ICER conducted analyses prior to the availability of Emgality (galcanezumab-gnlm) trial data, and therefore ICER indicated that there is insufficient information to provide an evidence rating for Emgality (galcanezumab-gnlm). In general, ICER concluded that the class of CGRP inhibitors provide some clinical benefit in patients with EM or CM, and few harms were seen in these short-term trials. ICER noted several limitations to their analysis, including the variation of clinical trial population from the general patient population and that price estimates may not reflect actual market price.

**Table 5: Results of ICER Analysis on CGRP Inhibitors in Migraine Prevention**

| Agent | Patient Population | ICER Evidence Rating (Rationale) | Approximate Incremental Direct Cost-Effectiveness Ratio (per QALY gained) |
|---|---|---|---|
| Aimovig (erenumab-aooe)<br>Ajovy (fremanezumab-vfrm) | Patients with CM who are eligible to receive preventive therapy (i.e., oral agents or Botox [onabotulinumtoxinA]) | **Insufficient**<br>(Not available) | Compared with current preventive treatment (not conditional on prior treatment failure):<br>• Aimovig: $345,000<br>• Ajovy: $12.78 million |
| | Patients with CM for whom prior preventive therapy has failed | **C+**<br>(Uncertainties about harms vs. need for CGRP inhibitors in patients with frequent migraine and no other preventive options) | Compared with no preventive treatment:<br>• Aimovig: $90,000†<br>• Ajovy: $120,000† |
| Aimovig<br>Ajovy<br>Emgality (galcanezumab-gnlm)* | Patients with EM who are eligible to receive preventive therapy (i.e., oral agents) | **Insufficient**<br>(Not available) | Compared with current preventive treatment (not conditional on prior treatment failure):<br>• Aimovig: $395,000<br>• Ajovy: $1.02 million<br>• Emgality: $389,000 |
| Aimovig<br>Ajovy | Patients with EM for whom oral preventive therapy has failed | **Promising, but inconclusive**<br>(Uncertainties about harms vs. need for CGRP inhibitors in those without other preventive options but with less frequent migraine than in the CM population) | Compared with no preventive treatment:<br>$150,000 (for both CGRP inhibitors)† |
| Emgality* | All other populations and comparisons | **Insufficient**<br>(Limited data available) | Not available |

* Emgality (galcanezumab-gnlm) is projected to launch in the fourth quarter of 2018
† Based on base-case analysis from a health system payer perspective, which focuses on the direct medical care costs only
CGRP = calcitonin gene-related peptide
CM = chronic migraine
EM = episodic migraine
ICER = Institute for Clinical and Economic Review
QALY = quality-adjusted life year

(Ellis, 2018; RxPipeline, 2018)

**Table 6: Comparison of Migraine Prophylactic Agents**

| Product | Advantages | Disadvantages |
|---|---|---|
| **Injectable Agents** | | |
| Injectable agents as a class | • Less frequent administration (monthly or every 3 months) | • Injectable dosing |
| Aimovig (erenumab-aooe) | • Efficacy demonstrated in both CM and EM<br>• Favorable safety profile<br>• Self-administered SC injection monthly | • Limited clinical experience<br>• Requires refrigeration |
| Ajovy (fremanezumab-vfrm) | • Efficacy demonstrated in both CM and EM<br>• Favorable safety profile<br>• Self-administered SC injection monthly or every 3 months | • Limited clinical experience<br>• Requires refrigeration |
| Botox (onabotulinumtoxinA) | • Multiple additional indications<br>• Retreatment every 3 months | • Indicated for CM only<br>• Efficacy not demonstrated in EM<br>• Requires multiple IM injections per session by a healthcare provider<br>• Boxed warning of distant spread of toxin effect<br>• Increased risk of AE with pre-existing neuromuscular disorders, dysphagia, and breathing difficulties<br>• Risk of viral transmission by human albumin |
| Emgality (galcanezumab-gnlm) | • Efficacy demonstrated in both CM and EM<br>• Efficacy demonstrated in EM for up to 24 weeks vs. up to only 12 weeks with Aimovig and Ajovy<br>• Favorable safety profile<br>• Self-administered SC injection monthly | • Limited clinical experience<br>• Requires refrigeration |
| **Oral Agents** | | |
| Oral agents as a class | • Oral dosing<br>• Most agents generically available | • Efficacy mostly in EM prevention only<br>• Daily or twice-daily dosing |
| Antiepileptic: divalproex<br>**Depakote (divalproex DR)**<br>**Depakote ER (divalproex ER)** | • Also indicated for seizure and psychiatric disorders | • Boxed warnings of hepatotoxicity, pancreatitis, and fetal toxicity; Contraindicated in certain metabolic disorders and pregnancy<br>• High frequency of AEs (including weight gain) |
| Antiepileptic: topiramate<br>**Topamax (topiramate)**<br>Qudexy XR (topiramate ER)<br>**Trokendi XR (topiramate ER)** | • Indicated in pediatric patients ≥ 12 years of age<br>• Also indicated for seizure and psychiatric disorders | • ER formulations are contraindicated for use in metabolic acidosis or with recent alcohol use<br>• Risk of fetal toxicity<br>• High frequency of AEs (including weight loss and neuropsychiatric AEs) |
| Beta-blockers:<br>**Inderal LA (propranolol ER)**<br>**propranolol**<br>**timolol** | • Multiple additional indications | • Boxed warning of angina pectoris and exacerbation of heart disease<br>• Contraindicated in bradycardia, cardiogenic shock, bronchial asthma, and severe COPD<br>• Can mask symptoms (e.g., tachycardia) of hypoglycemia or hyperthyroidism |

**Boldface** indicates generic availability
AE = adverse event
CM = chronic migraine
COPD = chronic pulmonary obstructive disease
DR/ER = delayed release/extended release
EM = episodic migraine
IM = intramuscular
SC = subcutaneous

## FORMULARY CONSIDERATIONS

Emgality (galcanezumab-gnlm) is a CGRP inhibitor indicated for the preventive treatment of migraine in adults. The efficacy of Emgality (galcanezumab-gnlm) 120 mg administered monthly was demonstrated in three phase III trials. While both dosing regimens (i.e., 120 mg and 240 mg monthly) of Emgality (galcanezumab-gnlm) were superior to placebo in reducing MMD, achieving at least 50% reduction in MMD, and reducing days requiring acute migraine-abortive agents in patients with EM or CM, the FDA only approved the 120 mg monthly dosing regimen of Emgality (galcanezumab-gnlm). Emgality (galcanezumab-gnlm) is the third CGRP inhibitor approved by the FDA for migraine prevention, following Aimovig (erenumab-aooe) and Ajovy (fremanezumab-vfrm). Based on indirect comparison, the efficacy of all three CGRP inhibitors appeared to be similar, and all were overall well tolerated. The efficacy of Emgality (galcanezumab-gnlm) in EM prevention was demonstrated in up to 24 weeks of treatment in clinical trials, while efficacy data for Aimovig (erenumab-aooe) and Ajovy (fremanezumab-vfrm) were limited to 12 weeks. All three CGRP inhibitors are administered subcutaneously monthly, while Ajovy (fremanezumab-vfrm) can also be administered every 3 months (i.e., quarterly). Compared to other migraine-prophylactic agents such as Botox (onabotulinumtoxinA) and oral agents (i.e., topiramate, divalproex, propranolol, and timolol), CGRP inhibitors including Emgality (galcanezumab-gnlm) are effective for both EM and CM prevention and appear to have a more favorable safety profile. Overall, Emgality (galcanezumab-gnlm) provides an additional option for the prevention of CM or EM.

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**DRUG MONOGRAPH PREPARED BY:**

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October 4, 2018

**This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client’s formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.**

**Pharmacy & Therapeutics Committee Summary Review**
*Fulphila™ (pegfilgrastim) [Neulasta biosimilar] – Mylan/Biocon*

**Prepared by:** Jordan Breitigam, FormularyDecisions.com

**Presentation Date:** March 28, 2019

**Therapeutic Class:** Hematopoietic colony stimulating factor

**FDA Approval Date:** June 4, 2018

**FDA Indication:** Prevention of febrile neutropenia

**Policy approved via e-vote 10/18/2018**

**Comparable Formulary Products:** Neulasta

## Proposed Designation & Rationale

**Recommendation:** Non-preferred
For initial authorization:

1. Member has a non-myeloid malignancy; AND
2. Medication will not be administered less than 14 days before OR less than 24 hours after chemotherapy; AND
3. Chart notes with length of chemotherapy cycle, the days of the cycle on which chemotherapy will be administered, and the day of the cycle on which the Fulphila will be administered, are submitted with prior authorization request; AND
4. Member has a documented history of febrile neutropenia (defined as an ANC < 1000/mm3 and temperature > 38.2°C) following a previous course of chemotherapy and is receiving myelosuppressive chemotherapy; OR
5. Member is receiving myelosuppressive anti-cancer drugs associated with a high risk (> 20%, see Appendix for description) for incidence of febrile neutropenia; OR
6. Member is receiving myelosuppressive anti-cancer drugs associated with at intermediate risk (10- 20%, see Appendix for description) for incidence of febrile neutropenia including one of the following:
    a. Previous chemotherapy or radiation therapy;
    b. Persistent neutropenia;
    c. Bone marrow involvement with tumor;
    d. Recent surgery and/or open wounds;
    e. Liver dysfunction (bilirubin > 2.0);
    f. Renal dysfunction (creatinine clearance < 50);
    g. Age > 65 years receiving full chemotherapy dose intensity.
7. Dosage allowed: Up to 6 mg per chemotherapy cycle, beginning at least 24 hours after completion of chemotherapy.

Note: Fulphila is not indicated for hematopoietic syndrome of acute radiation syndrome.
If member meets all the requirements listed above, the medication will be approved for 6 months.

For reauthorization:

1. Member must be in compliance with all other initial criteria.

If member meets all the reauthorization requirements above, the medication will be approved for an additional 12 months.

**Clinical Implications/Place in Therapy:**

- Fulphila is the 3rd pegfilgrastim product to become available, following Neulasta and Neulasta Onpro, and preceding Udenyca (PDUFA November 2018), all of which are clinically equivalent

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# Fulphila (pegfilgrastim biosimilar) Monograph

Last modified – Jan 20, 2019

## Product Overview

| Product Overview | |
|---|---|
| **Generic name & manufacturer** | pegfilgrastim biosimilar<br>Mylan Institutional |
| **PDUFA date (or FDA Approval Date)** | Jun 04, 2018 |
| **Indication** | Fulphila is a leukocyte growth factor indicated to<br>• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. (1.1)<br>Limitations of Use<br>Fulphila is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation. |
| **Pharmacology/MOA** | Animal data and clinical data in humans suggest a correlation between pegfilgrastim products exposure and the duration of severe neutropenia as a predictor of efficacy. Selection of the dosing regimen of Fulphila is based on reducing the duration of severe neutropenia. |
| **Dose and administration** | **Strengths Available:**<br>• Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only. (3)<br>**Dosage Frequency:**<br>• Patients with cancer receiving myelosuppressive chemotherapy<br>  ○ o6 mg administered subcutaneously once per chemotherapy cycle. (2.1) |

| | |
|---|---|
| | ○ oDo not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)<br>○ oUse weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.2) |
| **Common adverse events** | Most common adverse reactions (≥ 5% difference in incidence compared to placebo) are bone pain and pain in extremity. (6.1)<br><br>*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.<br>Biosimilarity of Fulphila has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.<br><br>To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. |

## Appendix: Package Insert Highlights

For the complete Product Insert click here.

### Product Description

Pegfilgrastim-jmdb is a covalent conjugate of recombinant methionyl human G-CSF and monomethoxypolyethylene glycol. Recombinant methionyl human G-CSF is a water-soluble 175 amino acid protein with a molecular weight of approximately 19 kilodaltons (kD). Recombinant methionyl human G-CSF is obtained from the bacterial fermentation of a strain ofE coli transformed with a genetically engineered plasmid containing the human G-CSF gene. To produce pegfilgrastim-jmdb a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of recombinant methionyl human G-CSF. The average molecular weight of pegfilgrastim-jmdb is approximately 39 kD.
Fulphila (pegfilgrastim-jmdb) injection is intended for subcutaneous use only and is supplied in a single-dose prefilled syringe with a 29 gauge needle, with UltraSafe Passive Plus™Needle Guard. The prefilled syringe does not bear graduation marks and is designed to deliver the entire contents of the syringe (6 mg/0.6 mL).
The delivered 0.6 mL dose from the prefilled syringe contains 6 mg pegfilgrastim-jmdb (based on protein mass only) in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.7 mg), D-sorbitol (30 mg), polysorbate 20 (0.024 mg) and sodium (0.01 mg) in Water for Injection, USP.

## Indications and Usage

1.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy
Fulphila is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia[see Clinical Studies (14.1)].
Limitations of Use
Fulphila is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

## Dosage and Administration

Fulphila is a clear, colorless, preservative-free solution available as:

- Injection: 6 mg/0.6 mL in a single-dose prefilled syringe for manual use only.

2.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The recommended dosage of Fulphila is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle. For dosing in pediatric patients weighing less than 45 kg, refer to Table 1. Do not administer Fulphila between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

2.2 Administration

Fulphila is administered subcutaneously via a single-dose prefilled syringe for manual use.

Prior to use, remove the carton from the refrigerator and allow the Fulphila prefilled syringe to reach room temperature for a minimum of 30 minutes. Discard any prefilled syringe left at room temperature for greater than 72 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer Fulphila if discoloration or particulates are observed.

Pediatric Patients weighing less than 45 kg

The Fulphila prefilled syringe is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). The syringe does not bear graduation marks, which are necessary to accurately measure doses of Fulphila less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors. Refer to Table 1.

Table 1. Dosing of Fulphila for pediatric patients weighing less than 45 kg

| Body Weight | Fulphila Dose | Volume to Administer |
|---|---|---|
| Less than 10 kgFor pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of Fulphila. | See below | See below |

| | | |
|---|---|---|
| 10 to 20 kg | 1.5 mg | 0.15 mL |
| 21 to 30 kg | 2.5 mg | 0.25 mL |
| 31 to 44 kg | 4 mg | 0.4 mL |

## Adverse Reactions

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture[See Warnings and Precautions (5.1)]
- Acute Respiratory Distress Syndrome[See Warnings and Precautions (5.2)]
- Serious Allergic Reactions[See Warnings and Precautions (5.3)]
- Use in Patients with Sickle Cell Disorders[See Warnings and Precautions (5.4)]
- Glomerulonephritis[See Warnings and Precautions (5.5)]
- Leukocytosis[See Warnings and Precautions (5.6)]
- Capillary Leak Syndrome[See Warnings and Precautions (5.7)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells[See Warnings and Precautions (5.8)]
- Aortitis [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pegfilgrastim clinical trials safety data are based upon 932 patients receiving pegfilgrastim in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received pegfilgrastim after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m2every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg pegfilgrastim (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other.

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity.

Table 2. Adverse Reactions with ≥ 5% Higher Incidence in Pegfilgrastim Patients Compared to Placebo in Study 3

| Body System<br>Adverse Reaction | Placebo<br>(N = 461) | Pegfilgrastim 6 mg SC on Day 2<br>(N = 467) |
|---|---|---|
| Musculoskeletal and connective tissue disorders | | |
| Bone pain | 26% | 31% |
| Pain in extremity | 4% | 9% |

Leukocytosis
In clinical studies, leukocytosis (WBC counts > 100 x 109/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving pegfilgrastim. No complications attributable to leukocytosis were reported in clinical studies.
6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to pegfilgrastim in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.
6.3 Postmarketing Experience
The following adverse reactions have been identified during post approval use of pegfilgrastim products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Splenic rupture and splenomegaly (enlarged spleen)[see Warnings and Precautions (5.1)]
- Acute respiratory distress syndrome (ARDS)[see Warnings and Precautions (5.2)]
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema, and flushing[see Warnings and Precautions (5.3)]
- Sickle cell crisis[see Warnings and Precautions (5.4)]
- Glomerulonephritis[see Warnings and Precautions (5.5)]
- Leukocytosis[see Warnings and Precautions (5.6)]
- Capillary Leak Syndrome[see Warnings and Precautions (5.7)]
- Injection site reactions
- Sweet's syndrome, (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Aortitis [see Warnings and Precautions (5.9)]

## Clinical Trials Results

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy
Pegfilgrastim was evaluated in three randomized, double-blind, controlled studies. Studies 1 and 2 were active-controlled studies that employed doxorubicin 60 mg/m2and docetaxel 75 mg/m2administered every 21 days for up to 4 cycles for the treatment of metastatic breast cancer. Study 1 investigated the utility of a fixed dose of pegfilgrastim. Study 2 employed a weight-adjusted dose. In the absence of growth factor support, similar chemotherapy regimens have been reported to result in a 100% incidence of severe neutropenia (ANC < 0.5 x 109/L) with a mean duration of 5 to 7 days and a 30% to 40% incidence of febrile neutropenia. Based on the correlation between the duration of severe neutropenia and the incidence of febrile neutropenia found in studies with filgrastim, duration of severe neutropenia was chosen as the primary endpoint in both studies, and the efficacy of pegfilgrastim was demonstrated by establishing comparability to filgrastim-treated patients in the mean days of severe neutropenia.
In Study 1, 157 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (6 mg) on day 2 of each chemotherapy cycle or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each

chemotherapy cycle. In Study 2, 310 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (100 mcg/kg) on day 2 or daily subcutaneous filgrastim (5 mcg/kg/day) beginning on day 2 of each chemotherapy cycle.
Both studies met the major efficacy outcome measure of demonstrating that the mean days of severe neutropenia of pegfilgrastim-treated patients did not exceed that of filgrastim-treated patients by more than 1 day in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 1 were 1.8 days in the pegfilgrastim arm compared to 1.6 days in the filgrastim arm [difference in means 0.2 (95% CI -0.2, 0.6)] and in Study 2 were 1.7 days in the pegfilgrastim arm compared to 1.6 days in the filgrastim arm [difference in means 0.1 (95% CI -0.2, 0.4)].
A secondary endpoint in both studies was days of severe neutropenia in cycles 2 through 4 with results similar to those for cycle 1.
Study 3 was a randomized, double-blind, placebo-controlled study that employed docetaxel 100 mg/m2administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. In this study, 928 patients were randomized to receive a single subcutaneous injection of pegfilgrastim (6 mg) or placebo on day 2 of each chemotherapy cycle. Study 3 met the major trial outcome measure of demonstrating that the incidence of febrile neutropenia (defined as temperature ≥ 38.2°C and ANC ≤ 0.5 x109/L) was lower for pegfilgrastim-treated patients as compared to placebo-treated patients (1% versus 17%, respectively, $p < 0.001$). The incidence of hospitalizations (1% versus 14%) and IV anti-infective use (2% versus 10%) for the treatment of febrile neutropenia was also lower in the pegfilgrastim-treated patients compared to the placebo-treated patients.
Study 4 was a multicenter, randomized, open-label study to evaluate the efficacy, safety, and pharmacokinetics[see Clinical Pharmacology (12.3)] of pegfilgrastim in pediatric and young adult patients with sarcoma. Patients with sarcoma receiving chemotherapy age 0 to 21 years were eligible. Patients were randomized to receive subcutaneous pegfilgrastim as a single-dose of 100 mcg/kg (n = 37) or subcutaneous filgrastim at a dose 5 mcg/kg/day (n = 6) following myelosuppressive chemotherapy. Recovery of neutrophil counts was similar in the pegfilgrastim and filgrastim groups. The most common adverse reaction reported was bone pain.

## Clinical Pharmacology

Animal data and clinical data in humans suggest a correlation between pegfilgrastim products exposure and the duration of severe neutropenia as a predictor of efficacy. Selection of the dosing regimen of Fulphila is based on reducing the duration of severe neutropenia.

### *Mechanism of Action*

Pegfilgrastim products are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation.

### *Pharmacokinetics*

The pharmacokinetics of pegfilgrastim was studied in 379 patients with cancer. The pharmacokinetics of pegfilgrastim was nonlinear, and clearance decreased with increases in dose. Neutrophil receptor binding is an important component of the clearance of pegfilgrastim, and serum clearance is directly related to the number of neutrophils. In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with

higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed. The half-life of pegfilgrastim ranged from 15 to 80 hours after subcutaneous injection.

Specific Populations

No gender-related differences were observed in the pharmacokinetics of pegfilgrastim, and no differences were observed in the pharmacokinetics of geriatric patients (≥ 65 years of age) compared with younger patients (< 65 years of age)[see Use in Specific Populations (8.5)].

Renal Impairment

In a study of 30 subjects with varying degrees of renal dysfunction, including end stage renal disease, renal dysfunction had no effect on the pharmacokinetics of pegfilgrastim.

Pediatric Patients with Cancer Receiving Myelosuppressive Chemotherapy

The pharmacokinetics and safety of pegfilgrastim were studied in 37 pediatric patients with sarcoma in Study 4[see Clinical Studies 14.1]. The mean (± standard deviation [SD]) systemic exposure (AUC0-inf) of pegfilgrastim after subcutaneous administration at 100 mcg/kg was 47.9 (± 22.5) mcg·hr/mL in the youngest age group (0 to 5 years, n = 11), 22.0 (± 13.1) mcg·hr/mL in the (6 to 11 years age group (n = 10), and 29.3 (± 23.2) mcg·hr/mL in the 12 to 21 years age group (n = 13). The terminal elimination half-lives of the corresponding age groups were 30.1 (± 38.2) hours, 20.2 (± 11.3) hours, and 21.2 (± 16.0) hours, respectively.

## Drug Interactions

No formal drug interaction studies between pegfilgrastim products and other drugs have been performed. Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

## Contraindications

Fulphila is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products[see Warnings and Precautions (5.3)]. Reactions have included anaphylaxis[see Warnings and Precautions (5.3)].

## Use in Specific Populations

8.1 Pregnancy

Risk Summary

Although available data with Fulphila or pegfilgrastim product use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from published studies in pregnant women exposed to filgrastim products. These studies have not established an association of filgrastim product use during pregnancy with major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area). In pregnant rabbits, increased embryolethality and spontaneous abortions occurred at 4 times the maximum recommended human dose simultaneously with signs of maternal toxicity (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S.

general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Retrospective studies indicate that exposure to pegfilgrastim is without significant adverse effect on fetal outcomes and neutropenia. Preterm deliveries have been reported in some patients.

Animal Data

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), the treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

8.2 Lactation

Risk Summary

There are no data on the presence of pegfilgrastim in human milk, the effects on the breastfed child, or the effects on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Fulphila and any potential adverse effects on the breastfed child from Fulphila or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of pegfilgrastim have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature.

Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)].

8.5 Geriatric Use

Of the 932 patients with cancer who received pegfilgrastim in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

## References

Fulphila Prescribing information. Accessed Jan 20, 2019.

**Pharmacy & Therapeutics Committee Summary Review**
*Pifeltro™ (doravirine) – Merck & Co., Inc.*

**Prepared by:** Jordan Breitigam, FormularyDecisions.com **Presentation Date:** March 28, 2019

**Therapeutic Class:** NNRTI **FDA Approval Date:** August 31, 2018

**FDA Indication:** Treatment naïve HIV-1 infection

**Comparable Formulary Products:** Intelence (etravirine), Rescriptor (delavirdine), Sustiva (efavirenz), Viramune (nevirapine)

## Proposed Designation & Rationale

**Recommendation:** Preferred

**Clinical Implications/Place in Therapy:**

- Doravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) to be used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs)
- New Department of Health and Human Services Guidelines released in March 2018 now recommend that antiretroviral regimens for initial therapy include an integrase inhibitor
    - Combinations of a boosted protease inhibitor + 2 NRTIs and an NNRTI + 2 NRTIs are now recommended initial regimens in certain clinical situations and not recommended initial regimens for most people with HIV
    - Given these new recommendations, Delstrigo and Pifeltro use should be reserved for those certain clinical situations that the DHHS guidelines describe

**References:**


1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Updated March 27, 2018. Accessed August 31, 2018.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services adults and adolescents antiretroviral guidelines panel classifies a fixed-dose combination product of bictegravir/tenofovir alafenamide/emtricitabine as one of the recommended initial regimens for most people with HIV. Department of Health and Human Services. Available at https://aidsinfo.nih.gov/news/2044/adult-arv-panel-classifies-bic-taf-ftc-as-recommended-initial-regimen-for-hiv. Published March 27, 2018. Accessed August 31, 2018.
3. Pifeltro (doravirine) [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; August 2018.

# Pifeltro (doravirine ) Monograph

Last modified – Feb 23, 2019

## Product Overview

| Product Overview | |
|---|---|
| **Generic name & manufacturer** | doravirine<br>Merck & Co., Inc. |
| **FDA Approval Date** | Aug 31, 2018 |
| **Indication** | PIFELTRO, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history. (1) |
| **Pharmacology/MOA** | In a Phase 2 trial evaluating doravirine over a dose range of 0.25 to 2 times the recommended dose of PIFELTRO, (in combination with FTC/TDF) in HIV-1 infected subjects with no antiretroviral treatment history, no exposure-response relationship for efficacy was identified for doravirine.<br>Cardiac Electrophysiology<br>At a doravirine dose of 1200 mg, which provides approximately 4 times the peak concentration observed following the recommended dose of PIFELTRO, doravirine does not prolong the QT interval to any clinically relevant extent. |
| **Dose and administration** | **Strengths Available:**<br>• Tablets: 100 mg doravirine. (3)<br>**Dosage Frequency:**<br>• Recommended dosage: One tablet taken orally once daily with or without food in adult patients. (2.1)<br>• Dosage adjustment with rifabutin: One tablet taken twice daily (approximately 12 hours apart). (2.2) |

| | |
|---|---|
| **Common adverse events** | Most common adverse reactions (incidence greater than or equal to 5%, all grades) are nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, and abnormal dreams. (6.1)<br><br>To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. |

## Package Insert Highlights

For the complete Product Insert click here.

### Product Description

PIFELTRO is a film-coated tablet containing doravirine for oral administration.

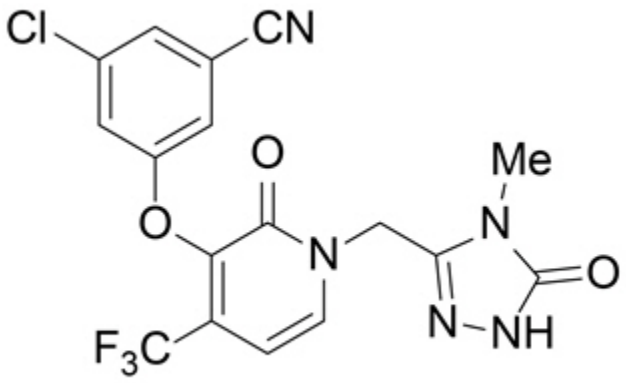
Doravirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI).

Each tablet contains 100 mg of doravirine as the active ingredient. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film coated with a coating material containing the following inactive ingredients: hypromellose, lactose monohydrate, titanium dioxide, and triacetin. The coated tablets are polished with carnauba wax.

The chemical name for doravirine is 3-chloro-5-[[1-[(4,5-dihydro-4-methyl-5-oxo-1H-1,2,4-triazol-3-yl)methyl]-1,2-dihydro-2-oxo-4-(trifluoromethyl)-3-pyridinyl]oxy]benzonitrile.

It has a molecular formula of C17H11ClF3N5O3and a molecular weight of 425.75.

It has the following structural formula:



Doravirine is practically insoluble in water.

## Indications and Usage

PIFELTRO™is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history.

## Dosage and Administration

PIFELTRO film-coated tablets are white, oval-shaped tablets, debossed with the corporate logo and 700 on one side and plain on the other side. Each tablet contains 100 mg doravirine.

2.1 Recommended Dosage

The recommended dosage regimen of PIFELTRO in adults is one 100 mg tablet taken orally once daily with or without food[see Clinical Pharmacology (12.3)].

2.2 Dosage Adjustment with Rifabutin

If PIFELTRO is co-administered with rifabutin, increase PIFELTRO dosage to one tablet twice daily (approximately 12 hours apart) for the duration of rifabutin co-administration [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

## Adverse Reactions

The following adverse reactions are discussed in other sections of the labeling:

- Immune Reconstitution Syndrome[see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adults with No Prior Antiretroviral Treatment History

The safety assessment of PIFELTRO used in combination with other antiretroviral agents is based on Week 48 data from two Phase 3, randomized, international, multicenter, double-blind, active-controlled trials (DRIVE-FORWARD (Protocol 018) and DRIVE-AHEAD (Protocol 021)).

In DRIVE-FORWARD, 766 adult subjects received either PIFELTRO 100 mg (n=383) or darunavir 800 mg + ritonavir 100 mg (DRV+r) (n=383) once daily, each in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC). By Week 48, 2% in the PIFELTRO group and 3% in the DRV+r group had adverse events leading to discontinuation of study medication.

In DRIVE-AHEAD, 728 adult subjects received either DELSTRIGO [doravirine (DOR)/3TC/TDF] (n=364) or efavirenz (EFV)/FTC/TDF once daily (n=364). By Week 48, 3% in the DELSTRIGO group and 6% in the EFV/FTC/TDF group had adverse events leading to discontinuation of study medication.

Adverse reactions reported in greater than or equal to 5% of subjects in any treatment group in DRIVE-FORWARD and DRIVE-AHEAD are presented in Table 1.

Table 1: Adverse ReactionsFrequencies of adverse reactions are based on all adverse events attributed to trial drugs by the investigator. (All Grades) Reported in ≥5%No adverse reactions of Grade 2 or higher (moderate or

severe) occurred in ≥ 2% of subjects treated with doravirine. of Subjects in Any Treatment Group in Adults with No Antiretroviral Treatment History in DRIVE-FORWARD and DRIVE-AHEAD (Week 48)

| | DRIVE-FORWARD | | DRIVE-AHEAD | |
|---|---|---|---|---|
| | PIFELTRO+2 NRTIsNRTI = nucleoside reverse transcriptase inhibitor. Once Daily N=383 | DRV+r+2 NRTIs Once Daily N=383 | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 |
| Nausea | 7% | 8% | 5% | 7% |
| Headache | 6% | 3% | 4% | 4% |
| Fatigue | 6% | 3% | 4% | 4% |
| Diarrhea | 5% | 13% | 3% | 5% |
| Abdominal Pain | 5% | 2% | 1% | 2% |
| Dizziness | 3% | 2% | 7% | 32% |
| Rash | 2% | 3% | 2% | 12% |
| Abnormal Dreams | 1% | <1% | 5% | 9% |
| Insomnia | 1% | 2% | 4% | 5% |
| Somnolence | 0% | <1% | 3% | 7% |

The majority (72%) of adverse reactions associated with doravirine occurred at severity Grade 1 (mild).

Neuropsychiatric Adverse Events

For DRIVE-AHEAD, the analysis of subjects with neuropsychiatric adverse events by Week 48 is presented in Table 2. The proportion of subjects who reported one or more neuropsychiatric adverse events was 24% and 57% in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

A statistically significantly lower proportion of DELSTRIGO-treated subjects compared to EFV/FTC/TDF-treated subjects reported neuropsychiatric adverse events by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium.

Table 2: DRIVE-AHEAD - Analysis of Subjects with Neuropsychiatric Adverse EventsAll causality and all grade events were included in the analysis. (Week 48)

| | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 | Treatment Difference DELSTRIGO - EFV/FTC/TDF Estimate (95% CI)The 95% CIs were calculated using Miettinen and Nurminen's method. Categories pre-specified for statistical testing were dizziness (p <0.001), sleep disorders and disturbances (p <0.001), and altered sensorium (p=0.033). |
|---|---|---|---|
| Sleep disorders and disturbancesPredefined using MedDRA preferred terms, including: abnormal dreams, hyposomnia, initial insomnia, | 12% | 26% | -13.5 (-19.1, -7.9) |

| | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 | Treatment Difference DELSTRIGO - EFV/FTC/TDF Estimate (95% CI)The 95% CIs were calculated using Miettinen and Nurminen's method. Categories pre-specified for statistical testing were dizziness (p <0.001), sleep disorders and disturbances (p <0.001), and altered sensorium (p=0.033). |
|---|---|---|---|
| insomnia, nightmare, sleep disorder, somnambulism. | | | |
| Dizziness | 9% | 37% | -28.3 (-34.0, -22.5) |
| Altered sensoriumPredefined using MedDRA preferred terms, including: altered state of consciousness, lethargy, somnolence, syncope. | 4% | 8% | -3.8 (-7.6, -0.3) |

Neuropsychiatric adverse events in the pre-defined category of depression and suicide/self-injury were reported in 4% and 7% of subjects, in the DELSTRIGO and EFV/FTC/TDF groups, respectively.

In DRIVE-AHEAD through 48 weeks of treatment, the majority of subjects who reported neuropsychiatric adverse events reported events that were mild to moderate in severity (97% [83/86] and 96% [198/207], in the DELSTRIGO and EFV/FTC/TDF groups, respectively) and the majority of subjects reported these events in the first 4 weeks of treatment (72% [62/86] in the DELSTRIGO group and 86% [177/207] in the EFV/FTC/TDF group).

Neuropsychiatric adverse events led to treatment discontinuation in 1% (2/364) and 1% (5/364) of subjects in the DELSTRIGO and EFV/FTC/TDF groups, respectively. The proportion of subjects who reported neuropsychiatric adverse events through Week 4 was 17% (62/364) in the DELSTRIGO group and 49% (177/364) in the EFV/FTC/TDF group. At Week 48, the prevalence of neuropsychiatric adverse events was 12% (44/364) in the DELSTRIGO group and 22% (81/364) in the EFV/FTC/TDF group.

Laboratory Abnormalities

The percentages of subjects with selected laboratory abnormalities (that represent a worsening from baseline) who were treated with PIFELTRO or DRV+r in DRIVE-FORWARD, or DELSTRIGO or EFV/FTC/TDF in DRIVE-AHEAD are presented in Table 3.

Table 3: Selected Laboratory Abnormalities Reported in Adult Subjects with No Antiretroviral Treatment History in DRIVE-FORWARD and DRIVE-AHEAD (Week 48)

| | DRIVE-FORWARD | | DRIVE-AHEAD | |
|---|---|---|---|---|
| Laboratory Parameter Preferred Term (Unit)/Limit | PIFELTRO+2 NRTIs Once Daily N=383 | DRV+r+2 NRTIs Once Daily N=383 | DELSTRIGO Once Daily N=364 | EFV/FTC/TDF Once Daily N=364 |
| **Blood Chemistry** | | | | |
| Total bilirubin | | | | |
| 1.1 - < 1.6 × ULN | 5% | 1% | 4% | 0% |
| 1.6 - <2.6 × ULN | 2% | <1% | 2% | 0% |

| | DRIVE-FORWARD | | DRIVE-AHEAD | |
|---|---|---|---|---|
| **Laboratory Parameter Preferred Term (Unit)/Limit** | **PIFELTRO+2 NRTIs Once Daily N=383** | **DRV+r+2 NRTIs Once Daily N=383** | **DELSTRIGO Once Daily N=364** | **EFV/FTC/TDF Once Daily N=364** |
| **Blood Chemistry** | | | | |
| ≥2.6 × ULN | 0% | 0% | <1% | <1% |
| Creatinine (mg/dL) | | | | |
| >1.3 - 1.8 × ULN or Increase of >0.3 mg/dL above baseline | 3% | 4% | 2% | 1% |
| >1.8 × ULN or Increase of ≥1.5 × above baseline | 2% | 3% | 2% | 1% |
| Aspartate aminotransferase (IU/L) | | | | |
| 2.5 - <5.0 × ULN | 4% | 3% | 2% | 2% |
| ≥5.0 × ULN | <1% | 2% | <1% | 2% |
| Alanine aminotransferase (IU/L) | | | | |
| 2.5 - <5.0 × ULN | 3% | 2% | 3% | 4% |
| ≥5.0 × ULN | 1% | 2% | <1% | 2% |
| Alkaline phosphatase (IU/L) | | | | |
| 2.5 - <5.0 × ULN | <1% | <1% | 0% | <1% |
| ≥5.0 × ULN | 0% | 0% | 0% | <1% |
| Lipase | | | | |
| 1.5 - <3.0 × ULN | 4% | 5% | 5% | 4% |
| ≥3.0 × ULN | 3% | 2% | 1% | 2% |
| Creatine kinase (IU/L) | | | | |
| 6.0 - <10.0 × ULN | 2% | 3% | 2% | 2% |
| ≥10.0 × ULN | 3% | 4% | 2% | 3% |
| Cholesterol, fasted (mg/dL) | | | | |
| ≥300 mg/dL | 0% | <1% | <1% | <1% |
| LDL cholesterol, fasted (mg/dL) | | | | |
| ≥190 mg/dL | <1% | 3% | <1% | 2% |
| Triglycerides, fasted (mg/dL) | | | | |
| >500 mg/dL | <1% | 1% | <1% | 3% |

Change in Lipids from Baseline

For DRIVE-FORWARD and DRIVE-AHEAD, changes from baseline at Week 48 in LDL-cholesterol, non-HDL-cholesterol, total cholesterol, triglycerides, and HDL-cholesterol are shown in Table 4.

The LDL and non-HDL comparisons were pre-specified and are summarized in Table 4. The differences were statistically significant, showing superiority for doravirine for both parameters. The clinical benefit of these findings has not been demonstrated.

Table 4: Mean Change from Baseline in Fasting Lipids in Adult Subjects with No Antiretroviral Treatment History in DRIVE-FORWARD and DRIVE-AHEAD (Week 48)

| | DRIVE-FORWARD | | | | |
|---|---|---|---|---|---|
| | PIFELTRO+2 NRTIsOnce DailyN=320 | | DRV+r+2 NRTIsOnce DailyN=311 | | |
| Laboratory Parameter Preferred Term | Baseline | Change | Baseline | Change | Difference Estimates (95% CI) |
| LDL-Cholesterol (mg/dL)p-values for the pre-specified hypothesis testing for treatment difference were <0.0001 in both DRIVE-FORWARD and DRIVE-AHEAD. | 91.4 | -4.6 | 92.3 | 9.5 | -14.4 (-18.0, -10.8) |
| Non-HDL Cholesterol (mg/dL) | 113.6 | -5.4 | 114.5 | 13.7 | -19.4 (-23.4, -15.4) |
| Total Cholesterol (mg/dL) Not pre-specified for hypothesis testing. | 157.2 | -1.4 | 157.8 | 18.0 | - |
| Triglycerides (mg/dL) | 111.0 | -3.1 | 113.7 | 24.5 | - |
| HDL-Cholesterol (mg/dL) | 43.6 | 4.0 | 43.3 | 4.3 | - |
| DRIVE-AHEAD | | | | | |
| | DELSTRIGO Once DailyN=320 | | EFV/FTC/TDF Once DailyN=307 | | |
| Laboratory Parameter Preferred Term | Baseline | Change | Baseline | Change | Difference Estimates (95% CI) |
| LDL-Cholesterol (mg/dL) | 91.7 | -2.1 | 91.3 | 8.3 | -10.2 (-13.8, -6.7) |
| Non-HDL Cholesterol (mg/dL) | 114.7 | -4.1 | 115.3 | 12.7 | -16.9 (-20.8, -13.0) |
| Total Cholesterol (mg/dL) | 156.8 | -2.2 | 156.8 | 21.1 | - |
| Triglycerides (mg/dL) | 118.7 | -12.0 | 122.6 | 21.6 | - |
| HDL-Cholesterol (mg/dL) | 42.1 | 1.8 | 41.6 | 8.4 | - |

## Clinical Trials Results

14.1 Adult Subjects with No Antiretroviral Treatment History

The efficacy of PIFELTRO is based on the analyses of 48-week data from two randomized, multicenter, double-blind, active controlled Phase 3 trials (DRIVE-FORWARD, NCT02275780 and DRIVE-AHEAD, NCT02403674) in HIV-1 infected subjects with no antiretroviral treatment history (n=1494).

In DRIVE-FORWARD, 766 subjects were randomized and received at least 1 dose of either PIFELTRO once daily or darunavir 800 mg + ritonavir 100 mg (DRV+r) once daily each in combination with emtricitabine/tenofovir DF (FTC/TDF) or abacavir/lamivudine (ABC/3TC) selected by the investigator. At baseline, the median age of subjects was 33 years, 16% were female, 27% were non-white, 4% had hepatitis B and/or C virus co-infection, 10% had a history of AIDS, 20% had HIV-1 RNA greater than 100,000 copies/mL, 86% had CD4+ T-cell count greater than 200 cells/mm3, 13% received ABC/3TC, and 87% received FTC/TDF; these characteristics were similar between treatment groups.

In DRIVE-AHEAD, 728 subjects were randomized and received at least 1 dose of either DELSTRIGO (DOR/3TC/TDF) or EFV 600 mg/FTC 200 mg/TDF 300 mg once daily. At baseline, the median age of subjects was 31 years, 15% were female, 52% were non-white, 3% had hepatitis B or C co-infection, 14% had a history of AIDS, 21% had HIV-1 RNA greater than 100,000 copies/mL, and 88% had CD4+ T-cell count greater than 200 cells/mm3; these characteristics were similar between treatment groups.

Week 48 outcomes for DRIVE-FORWARD and DRIVE-AHEAD are provided in Table 8. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

In DRIVE-FORWARD, the mean CD4+ T-cell counts in the PIFELTRO and DRV+r groups increased from baseline by 193 and 186 cells/mm3, respectively.

In DRIVE-AHEAD, the mean CD4+ T-cell counts in the DELSTRIGO and EFV/FTC/TDF groups increased from baseline by 198 and 188 cells/mm3, respectively.

Table 8: Virologic Outcome in DRIVE-FORWARD and DRIVE-AHEAD at Week 48 in HIV-1 Adults with No Antiretroviral Treatment History

| Outcome | DRIVE-FORWARD | | DRIVE-AHEAD | |
|---|---|---|---|---|
| | PIFELTRO + 2 NRTIs Once Daily | DRV+r + 2 NRTIs Once Daily | DELSTRIGO Once Daily | EFV/FTC/TDF Once Daily |
| | N=383 | N=383 | N=364 | N=364 |
| HIV-1 RNA <50 copies/mL | 84% | 80% | 84% | 81% |
| Treatment Differences (95% CI) The 95% CIs for the treatment differences were calculated using stratum-adjusted Mantel-Haenszel method. | 3.9% (-1.6%, 9.4%) | | 3.5% (-2.0%, 9.0%) | |
| HIV-1 RNA ≥ 50 copies/mLIncludes subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (relative day 295-378). | 11% | 13% | 11% | 10% |
| No Virologic Data at Week 48 Window | 5% | 7% | 5% | 9% |
| Discontinued study due to AE or DeathIncludes subjects who discontinued because of adverse event (AE) or death if this resulted in no virologic data in the Week 48 window. | 1% | 3% | 2% | 7% |

| Outcome | DRIVE-FORWARD | | DRIVE-AHEAD | |
|---|---|---|---|---|
| | PIFELTRO + 2 NRTIs Once Daily | DRV+r + 2 NRTIs Once Daily | DELSTRIGO Once Daily | EFV/FTC/TDF Once Daily |
| | N=383 | N=383 | N=364 | N=364 |
| Discontinued study for Other ReasonsOther Reasons include: lost to follow-up, non-compliance with study drug, physician decision, pregnancy, protocol deviation, screen failure, withdrawal by subject. | 3% | 4% | 2% | 2% |
| On study but missing data in window | <1% | <1% | 0 | <1% |
| Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline and Demographic Category | | | | |
| Gender | | | | |
| Male | 84% (n = 319) | 82% (n = 326) | 84% (n = 305) | 80% (n = 311) |
| Female | 81% (n = 64) | 67% (n = 57) | 85% (n = 59) | 83% (n = 53) |
| Race | | | | |
| White | 87% (n = 280) | 83% (n = 280) | 84% (n = 177) | 81% (n = 170) |
| Non-White | 75% (n = 103) | 73% (n = 103) | 84% (n = 187) | 80% (n = 194) |
| Ethnicity | | | | |
| Hispanic or Latino | 88% (n = 93) | 81% (n = 86) | 83% (n = 126) | 84% (n = 120) |
| Not Hispanic or Latino | 82% (n = 284) | 79% (n = 290) | 85% (n = 236) | 79% (n = 238) |
| NRTI Background Therapy | | | | |
| FTC/TDF | 83% (n = 333) | 81% (n = 335) | - | - |
| ABC/3TC | 86% (n = 50) | 75% (n = 48) | - | - |
| Baseline HIV-1 RNA (copies/mL) | | | | |
| ≤100,000 copies/mL | 86% (n = 300) | 81% (n = 308) | 86% (n = 291) | 83% (n = 282) |
| >100,000 copies/mL | 77% (n = 83) | 74% (n = 74) | 77% (n = 73) | 72% (n = 82) |

| Outcome | DRIVE-FORWARD | | DRIVE-AHEAD | |
|---|---|---|---|---|
| | PIFELTRO + 2 NRTIs Once Daily | DRV+r + 2 NRTIs Once Daily | DELSTRIGO Once Daily | EFV/FTC/TDF Once Daily |
| | N=383 | N=383 | N=364 | N=364 |
| CD4+ T-cell Count (cells/mm3) | | | | |
| ≤200 cells/mm3 | 81% (n = 42) | 66% (n = 67) | 66% (n = 44) | 78% (n = 46) |
| >200 cells/mm3 | 84% (n = 341) | 83% (n = 316) | 87% (n = 320) | 81% (n = 318) |
| Viral SubtypeViral subtype was not available for two subjects in DRIVE-AHEAD. | | | | |
| Subtype B | 84% (n = 266) | 82% (n = 272) | 84% (n = 232) | 80% (n = 253) |
| Subtype Non-B | 83% (n = 117) | 76% (n = 111) | 85% (n = 130) | 83% (n = 111) |

## Clinical Pharmacology

In a Phase 2 trial evaluating doravirine over a dose range of 0.25 to 2 times the recommended dose of PIFELTRO, (in combination with FTC/TDF) in HIV-1 infected subjects with no antiretroviral treatment history, no exposure-response relationship for efficacy was identified for doravirine.
Cardiac Electrophysiology
At a doravirine dose of 1200 mg, which provides approximately 4 times the peak concentration observed following the recommended dose of PIFELTRO, doravirine does not prolong the QT interval to any clinically relevant extent.

### *Mechanism of Action*

Doravirine is an antiretroviral drug[see Microbiology (12.4)].

### *Pharmacokinetics*

Doravirine pharmacokinetics are similar in healthy subjects and HIV-1-infected subjects. Doravirine pharmacokinetics are provided in Table 6.
Table 6: Pharmacokinetic Properties of Doravirine

| Parameter | Doravirine |
|---|---|
| General | |
| Steady State ExposureDoravirine 100 mg once daily to HIV-1 infected subjects,Presented as geometric mean (%CV: geometric coefficient of variation) | |

| Parameter | Doravirine |
|---|---|
| AUC0-24<br>(mcg·h/mL) | 16.1 (29) |
| Cmax<br>(mcg/mL) | 0.962 (19) |
| C24<br>(mcg/mL) | 0.396 (63) |
| Time to Steady State (Days) | 2 |
| Accumulation Ratio | 1.2 to 1.4 |
| Absorption | |
| Absolute Bioavailability | 64% |
| Tmax (h) | 2 |
| Effect of FoodGeometric mean ratio [high-fat meal/fasting] and (90% confidence interval) for PK parameters. High fat meal is approximately 1,000 kcal, 50% fat. The effect of food is not clinically relevant. | |
| AUC Ratio | 1.16 (1.06, 1.26) |
| Cmax Ratio | 1.03 (0.89, 1.19) |
| C24 Ratio | 1.36 (1.19, 1.55) |
| Distribution | |
| Vdss (L)Based on IV dose | 60.5 |
| Plasma Protein Binding | 76% |
| Elimination | |
| t1/2 (h) | 15 |
| CL/F (mL/min) | 106 (35.2) |
| CLrenal (mL/min) | 9.3 (18.6) |
| Metabolism | |
| Primary Pathway(s) | CYP3A |
| Excretion | |
| Major Route of Elimination | Metabolism |
| Urine (unchanged) | 6% |
| Biliary/Fecal (unchanged) | Minor |

Specific Populations

No clinically significant difference on the pharmacokinetics of doravirine were observed based on age (18 to 78 years of age), sex, and race/ethnicity, mild to severe renal impairment (creatinine clearance (CLcr) >15 mL/min, estimated by Cockcroft-Gault), or moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of doravirine in patients with end-stage renal disease or undergoing dialysis, severe hepatic impairment (Child-Pugh C), or <18 years of age is unknown.

Patients with Renal Impairment

In a study comparing 8 subjects with severe renal impairment to 8 subjects without renal impairment, the single dose exposure of doravirine was 43% higher in subjects with severe renal impairment. In a population pharmacokinetic analysis, renal function did not have a clinically relevant effect on doravirine pharmacokinetics. Doravirine has not been studied in patients with end-stage renal disease or in patients undergoing dialysis[see Use in Specific Populations (8.6)].

Patients with Hepatic Impairment

No clinically significant difference in the pharmacokinetics of doravirine was observed in subjects with moderate hepatic impairment (Child-Pugh score B) compared to subjects without hepatic impairment. Doravirine has not been studied in subjects with severe hepatic impairment (Child-Pugh score C)[see Use in Specific Populations (8.7)].

Drug Interaction Studies

Doravirine is primarily metabolized by CYP3A, and drugs that induce or inhibit CYP3A may affect the clearance of doravirine. Co-administration of doravirine and drugs that induce CYP3A may result in decreased plasma concentrations of doravirine. Co-administration of doravirine and drugs that inhibit CYP3A may result in increased plasma concentrations of doravirine.

Doravirine is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes. Doravirine did not inhibit major drug metabolizing enzymesin vitro, including CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, and UGT1A1 and is not likely to be an inducer of CYP1A2, 2B6, or 3A4. Based onin vitroassays, doravirine is not likely to be an inhibitor of OATP1B1, OATP1B3, P-glycoprotein, BSEP, OAT1, OAT3, OCT2, MATE1, and MATE2K. Drug interaction studies were performed with doravirine and other drugs likely to be co-administered or commonly used as probes for pharmacokinetic interactions. The effects of co-administration with other drugs on the exposure (Cmax, AUC, and C24) of doravirine are summarized in Table 7. A single doravirine 100 mg dose was administered in these studies unless otherwise noted.

Table 7: Drug Interactions: Changes in Pharmacokinetic Parameter Values of Doravirine in the Presence of Co-administered Drug

| **Co-administered Drug** | **Regimen of Co-administered Drug** | **N** | **Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00)** | | |
|---|---|---|---|---|---|
| | | | **AUCAUC0-∞for single-dose, AUC0-24for once daily.** | **Cmax** | **C24** |
| Azole Antifungal Agents | | | | | |
| ketoconazoleChanges in doravirine pharmacokinetic values are not clinically relevant. | 400 mg QD | 10 | 3.06 (2.85, 3.29) | 1.25 (1.05, 1.49) | 2.75 (2.54, 2.98) |
| Antimycobacterials | | | | | |

| Co-administered Drug | Regimen of Co-administered Drug | N | Geometric Mean Ratio (90% CI) of Doravirine Pharmacokinetics with/without Co-administered Drug (No Effect=1.00) | | |
|---|---|---|---|---|---|
| | | | AUCAUC0-∞for single-dose, AUC0-24for once daily. | Cmax | C24 |
| rifampin | 600 mg QD | 10 | 0.12 (0.10, 0.15) | 0.43 (0.35, 0.52) | 0.03 (0.02, 0.04) |
| rifabutin | 300 mg QD | 12 | 0.50 (0.45, 0.55) | 0.99 (0.85, 1.15) | 0.32 (0.28, 0.35) |
| HIV Antiviral Agents | | | | | |
| ritonavir,A single doravirine 50 mg dose (0.5 times the recommended approved dose) was administered. | 100 mg BID | 8 | 3.54 (3.04, 4.11) | 1.31 (1.17, 1.46) | 2.91 (2.33, 3.62) |
| efavirenz | 600 mg QDThe first day following the cessation of efavirenz therapy and initiation of doravirine 100 mg QD. | 17 | 0.38 (0.33, 0.45) | 0.65 (0.58, 0.73) | 0.15 (0.10, 0.23) |
| | 600 mg QD14 days following the cessation of efavirenz therapy and initiation of doravirine 100 mg QD. | 17 | 0.68 (0.58, 0.80) | 0.86 (0.77, 0.97) | 0.50 (0.39, 0.64) |

Based on drug interaction studies conducted with doravirine, no clinically significant drug interactions have been observed following the co-administration of doravirine and the following drugs: dolutegravir, ritonavir, TDF, lamivudine, elbasvir and grazoprevir, ledipasvir and sofosbuvir, ketoconazole, aluminum hydroxide/magnesium hydroxide/simethicone containing antacid, pantoprazole, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, and midazolam.

## Drug Interactions

7.1 Effect of Other Drugs on PIFELTRO

Co-administration of PIFELTRO with a CYP3A inducer decreases doravirine plasma concentrations, which may reduce PIFELTRO efficacy[see Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]. Co-administration of PIFELTRO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

Table 5 shows significant drug interactions with PIFELTRO.

Table 5: Drug Interactions with PIFELTROThis table is not all inclusive.

| Concomitant Drug Class:<br>Drug Name | Effect on Concentration | Clinical Comment |
|---|---|---|
| Androgen Receptors | | |
| enzalutamide | ↓ doravirine | Co-administration is contraindicated with enzalutamide.<br>At least a 4-week cessation period is recommended prior to initiation of PIFELTRO. |
| Anticonvulsants | | |
| carbamazepine<br>oxcarbazepine<br>phenobarbital<br>phenytoin | ↓ doravirine | Co-administration is contraindicated with these anticonvulsants.<br>At least a 4-week cessation period is recommended prior to initiation of PIFELTRO. |
| Antimycobacterials | | |
| rifampinThe interaction between PIFELTRO and the concomitant drug was evaluated in a clinical study.<br>rifapentine | ↓ doravirine | Co-administration is contraindicated with rifampin or rifapentine.<br>At least a 4-week cessation period is recommended prior to initiation of PIFELTRO. |
| rifabutin | ↓ doravirine | Increase PIFELTRO dosage to one tablet twice daily when co-administered with rifabutin [see Dosage and Administration (2.2)].<br>At least a 4-week cessation period is recommended prior to initiation of PIFELTRO. |
| Cytotoxic Agents | | |
| mitotane | ↓ doravirine | Co-administration is contraindicated with mitotane.<br>At least a 4-week cessation period is recommended prior to initiation of PIFELTRO. |
| HIV Antiviral Agents | | |
| efavirenz<br>etravirine<br>nevirapine | ↓ doravirine | Use with efavirenz, etravirine, or nevirapine is not recommended. |
| Herbal Products | | |
| St. John's wort | ↓ doravirine | Co-administration is contraindicated with St. John's wort.<br>At least a 4-week cessation period is recommended prior to initiation of PIFELTRO. |

No clinically significant changes in concentration were observed for doravirine when co-administered with the following agents: dolutegravir, TDF, lamivudine, elbasvir and grazoprevir, ledipasvir and sofosbuvir, ritonavir, ketoconazole, aluminum hydroxide/magnesium hydroxide/simethicone containing antacid, pantoprazole, and methadone[see Clinical Pharmacology (12.3)].

7.2 Effect of PIFELTRO on Other Drugs

No clinically significant changes in concentration were observed for the following agents when co-administered with doravirine: dolutegravir, lamivudine, TDF, elbasvir and grazoprevir, ledipasvir and sofosbuvir, atorvastatin, an oral contraceptive containing ethinyl estradiol and levonorgestrel, metformin, methadone, and midazolam [see Clinical Pharmacology (12.3)].

## Contraindications

PIFELTRO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of PIFELTRO[see Warnings and Precautions (5.1), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]. These drugs include, but are not limited to, the following:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the androgen receptor inhibitor enzalutamide
- the antimycobacterials rifampin, rifapentine
- the cytotoxic agent mitotane
- St. John's wort (Hypericum perforatum)

## Use in Specific Populations

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to PIFELTRO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

No adequate human data are available to establish whether or not PIFELTRO poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when doravirine was administered at exposures ≥8 times the exposure in humans at the recommended human dose (RHD) of PIFELTRO (see Data).

The background rate of major birth defects is 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates individuals and infants from the limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

Data

Animal Data

Doravirine was administered orally to pregnant rabbits (up to 300 mg/kg/day on gestation days (GD) 7 to 20) and rats (up to 450 mg/kg/day on GD 6 to 20 and separately from GD 6 to lactation/postpartum day 20). No significant toxicological effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at exposures (AUC) approximately 9 times (rats) and 8 times (rabbits) the exposure in humans at the RHD. Doravirine was transferred to the fetus through the placenta in embryo-fetal studies, with fetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on gestation day 20.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking potential transmission of HIV-1 infection.
It is unknown whether doravirine is present in human milk, affects human milk production, or has effects on the breastfed infant. Doravirine is present in the milk of lactating rats (see Data). Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving PIFELTRO.
Data
Doravirine was excreted into the milk of lactating rats following oral administration (450 mg/kg/day) from gestation day 6 to lactation day 14, with milk concentrations approximately 1.5 times that of maternal plasma concentrations observed 2 hours post dose on lactation day 14.
8.4 Pediatric Use
Safety and efficacy of PIFELTRO have not been established in pediatric patients less than 18 years of age.
8.5 Geriatric Use
Clinical trials of PIFELTRO did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of PIFELTRO in elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy[see Clinical Pharmacology (12.3)].
8.6 Renal Impairment
No dosage adjustment of PIFELTRO is required in patients with mild, moderate, or severe renal impairment. PIFELTRO has not been adequately studied in patients with end-stage renal disease and has not been studied in dialysis patients[see Clinical Pharmacology (12.3)].
8.7 Hepatic Impairment
No dosage adjustment of PIFELTRO is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PIFELTRO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C)[see Clinical Pharmacology (12.3)].

## References

Pifeltro Prescribing information. Accessed Feb 23, 2019.