CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209388Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209388
PDUFA Goal Date	June 19, 2020
OSE RCM #	2018-1163
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS Ingrid N. Chapman, PharmD, BCPS
Acting Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	June 3, 2020
Subject	Evaluation of Need for a REMS
Established Name	Metoclopramide nasal spray
Trade Name	Gimoti
Name of Applicant	Evoke Pharma, Inc
Therapeutic Class	Dopamine$_2$-receptor antagonist/Gastrointestinal agent
Formulation(s)	Nasal spray: 15 mg in each spray
Dosing Regimen	15 mg, 30 minutes before each meal and at bedtime (maximum of 60 mg per day) for 2 to (b)(4) weeks

Reference ID: 4618577

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Gimoti (metoclopramide) nasal spray is necessary to ensure the benefits outweigh its risks. Evoke Pharma, Inc previously submitted a New Drug Application (NDA) 209388 under the 505(b)(2) regulatory pathway for Gimoti on June 1, 2018 with the proposed indication: for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis. The risks associated with Gimoti include tardive dyskinesia (TD), other extrapyramidal symptoms (EPS), and neuroleptic malignant syndrome. The submission included a Boxed Warning for tardive dyskinesia and a communication plan REMS to mitigate the potential risk of tardive dyskinesia (TD) and other extrapyramidal symptoms (EPS) associated with the use of Gimoti. The Applicant received a Response (CR) letter on April 1, 2019. The Division of Risk Management (DRM) completed a memorandum which deferred the REMS determination due to the insufficient efficacy data to support approval.

On December 19, 2019, the Applicant submitted a Class 2 resubmission in response to the Complete Response, which is the subject of this review. No REMS was included with this resubmission.

The Division of Risk Management (DRM) and the Division of Gastroenterology (DG) have determined that a REMS is not necessary to ensure the benefits of Gimoti outweigh its risks. The risks of tardive dyskinesia and extrapyramidal symptoms are well documented and healthcare providers who treat gastroparesis should be familiar with these risks. The available safety data for Gimoti does not demonstrate a higher risk of tardive dyskinesia or extrapyramidal symptoms compared to other metoclopramide dosage forms. The risks of Gimoti will be conveyed through labeling with a Boxed Warning for tardive dyskinesia and the need to avoid treatment with all dosage forms of metoclopramide for greater than 12 weeks, which is similar to other approved metoclopramide products. Additionally, patients with a history of TD will be contraindicated for use of Gimoti. A Medication Guide and Instructions for Use will also be part of labeling to inform patients on safe use.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Gimoti (metoclopramide) nasal spray, a 505(b)(2) application, [a] is necessary to ensure the benefits outweigh its risks. Evoke Pharma, Inc (Evoke Pharma) previously submitted a New Drug Application (NDA) 209388 for Gimoti (metoclopramide) nasal spray on June 1, 2018 with the proposed indication: for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.[1] This submission included a Boxed Warning for tardive dyskinesia and a communication plan REMS to mitigate the potential risk of tardive dyskinesia (TD) and other extrapyramidal symptoms (EPS) associated with the use of Gimoti. The Applicant received a Response (CR) letter on April 1, 2019.[3] The Division of Risk Management (DRM) completed a memorandum which deferred the REMS determination due to the insufficient efficacy data

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

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to support approval.[2] On December 19, 2019, the Applicant submitted a Class 2 resubmission in response to the Complete Response, which is the subject of this review. No REMS was included with this resubmission.[4] This application is under review in the Division of Gastroenterology (DG).

2 Background

2.1 PRODUCT INFORMATION[5]

Gimoti (metoclopramide) nasal spray is a dopamine$_2$-receptor antagonist/gastrointestinal agent with the proposed indication: for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis. Gimoti (metoclopramide) nasal spray is proposed as an aqueous solution for nasal administration supplied in a 10 mL amber glass vial fitted with a metered spray pump attachment. Each spray delivers 70 µL which contains 15 mg of metoclopramide. While the Applicant originally proposed Gimoti for adult women, the pivotal comparative bioavailability (BA) study was conducted in both male and female subjects and supported the indication for both males and females.[6] Therefore the Agency plans to approve the product with the indication for all adults.

The recommended dosage (per the Agency) is as follows:

- **Adults Less Than 65 Years of Age**:
  One spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum of four times daily) for 2 to (b) (4) weeks, depending on symptomatic response. [b]

- **Adults 65 Years of Age and Older**:
  Elderly patients may be more sensitive to the adverse effects of metoclopramide and require a lower starting dosage. Gimoti is not recommended in geriatric patients as initial therapy.

  Geriatric patients receiving an alternative metoclopramide product at a stable dosage of 10 mg four times daily can be switched to Gimoti1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum four times daily) for 2 to (b) (4) weeks, depending on symptomatic response. Avoid treatment with metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks.

If approved, Gimoti would offer a new route of administration for patients with swallowing difficulties and may be administered in both the outpatient and inpatient setting. Gimoti is not currently marketed in any jurisdiction. However, the active ingredient, metoclopramide, was first approved in the United States (US) in 1979. The following dosage forms of metoclopramide are currently marketed in the US:[7]

- Oral tablets: 5 mg and 10 mg
- Orally disintegrating tablets: 5 mg and 10 mg
- Oral solution: 5 mg/5 mL and 10 mg/10 mL
- Injectable solution: 5 mg/mL

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

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Central Nervous System (CNS) related extrapyramidal reactions including acute dystonic reactions, parkinsonian-like symptoms, akathisia, and tardive dyskinesia are known adverse events associated with all dosage forms of metoclopramide. The prescribing information for all approved metoclopramide products includes a Boxed Warning for the risk of TD and to avoid treatment with metoclopramide (any dosage forms and routes) for longer than 12 cumulative weeks due to this risk. Additionally, metoclopramide is contraindicated in patients with a history of TD or dystonic reactions.

While Reglan and Reglan ODT (orally disintegrating tablet) were FDA-approved in 1980 and 2005 respectively, both products were approved with a REMS to mitigate the risk of TD on September 4, 2009. The REMS included a Medication Guide and a Timetable for Submission of Assessments. On August 2, 2011, the Agency issued a combined REMS Assessment Acknowledgement Letter and Supplement Approval letter to release the REMS requirement for the approved Reglan (metoclopramide) REMS. The REMS assessment was determined to be complete and maintaining the Medication Guide as part of approved labeling was determined to be adequate to address the serious risk of TD.[9]

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 209388 relevant to this review:

- 08/02/2011: The Reglan (metoclopramide) REMS requirement was released.
- 06/01/2018: A 505(b)(2) application submission was received for Gimoti (metoclopramide) nasal spray, NDA 209388. The submission included a CP REMS proposal.[1]
- 04/01/2019: The FDA issued a Complete Response letter to Evoke Pharma for the clinical pharmacology and product quality/device quality deficiencies.[3] DRM also completed a memorandum on this date to defer the REMS determination.[2]
- 12/19/2019: Evoke Pharma resubmitted NDA 209388 and responded to the CR deficiencies. A REMS was not included as part of this submission.[4]

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Gastroparesis is a chronic disorder that is characterized by delayed gastric emptying in the absence of any mechanical obstruction.[10] The main symptoms include nausea, vomiting, early satiety, bloating, and upper abdominal pain. Gastroparesis is thought to be caused by autonomic nerve dysfunction resulting in gastric motility abnormalities.[11] A large population based study found the age-adjusted prevalence of gastroparesis was 38 per 100,000 for women and 9.6 per 100,000 for men, and the age-adjusted incidence was 9.8 per 100,000 person years for women and 2.4 per 100, 000 person years for men.[12,c] This may be an underestimate of the true prevalence as current data is based only on the patients who

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

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seek treatment for symptoms. There are many conditions and interventions that may cause gastroparesis, however, the most common etiologies include diabetes mellitus (29%), post-surgical (13%), and idiopathic (36%).[10]

Gastroparesis is commonly associated with longstanding diabetes. One community-based study found that over a 10-year period, about 5% of type 1 diabetics and about 1% of type 2 diabetics developed gastroparesis.[13] However, other studies in referral populations have suggested the prevalence may be 25-50%.[14] Symptoms due to gastroparesis are reported by 5-12% of patients with diabetes.[15] Diabetic gastroparesis is associated with significant morbidity, impaired quality of life, poor glycemic control, and increased healthcare costs due to acute exacerbations requiring hospitalizations and emergency department visits. The effect on mortality is less clear with some studies showing no effect and others finding lower survival compared to matched subjects without gastroparesis.[12,16,d]

3.2 Description of Current Treatment Options[10]

The American Journal of Gastroenterology recommends that the initial management of gastroparesis includes dietary modifications (e.g. smaller meals, liquid meals), appropriate hydration, and optimizing glycemic control. Pharmacologic therapy, such as prokinetics or antiemetics, may be considered in patients to improve gastric emptying and symptoms. The guidelines recommend metoclopramide therapy as a first-line option. Due to the risks of TD and EPS, it is recommended to initiate metoclopramide at the lowest possible effective dose and monitor for signs of CNS adverse reactions. Metoclopramide is currently the only FDA-approved medication for the treatment of gastroparesis.

If metoclopramide is not effective or tolerated, other prokinetic agents such as domperidone and erythromycin may be considered. Erythromycin works as a motilin receptor agonist leading to antral contractions that improve gastric emptying and symptoms. The use of erythromycin is limited since tachyphylaxis develops after prolonged (>4 weeks) of therapy; however, intravenous use is beneficial for treatment of acute exacerbations leading to hospitalization. Risks associated with erythromycin include QTc prolongation and arrythmias, ototoxicity, gastrointestinal adverse events, risk of inducing bacterial resistance with prolonged use, and several drug interactions. Domperidone is another dopamine-2 receptor antagonist that may be considered for patients who fail or develop side effects with metoclopramide. It is not currently approved in the United States and may only be prescribed through the FDA Expanded Access program. Domperidone is associated with QTc prolongation and arrhythmias, hyperprolactinemia, and several drug interactions. Antiemetics or tricyclic antidepressants may also be used for symptomatic relief. Other therapies if symptoms persist despite pharmacologic therapy may include pyloric botulinum toxin injection, gastric electrical stimulation, or surgical interventions.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

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4 Benefit Assessment

4.1 Pivotal Comparative Bioavailability (BA) Study with Gimoti

In the original submission, the Applicant conducted a pivotal, open-label, randomized, crossover, bioavailability study (METO-IN-006) to establish a pharmacokinetic bridge between Gimoti and Reglan tablets. This study compared systemic exposure between a single nasal administration of Gimoti 15 mg, 16 mg, and 17 mg and a single oral administration of metoclopramide 10 mg in 98 healthy male and female subjects. Subjects did not self-administer doses in this study, instead they received the nasal spray from dose administrators who received training.

Results showed the area under the curve (AUC) was comparable, however, the mean Cmax for Gimoti was 16-20% lower than the metoclopramide 10 mg tablet dose and did not meet the bioequivalence criteria. There was higher variability in metoclopramide exposure with Gimoti compared to Reglan. There were several subjects with little to no absorption (<5 ng/mL) and it was hypothesized this may indicate inadequate dosing with the nasal spray. These subjects had consistent absorption when given Reglan oral tablets. The clinical pharmacology reviewer concluded that the results did not support the bridging of efficacy between the products.[17,18]

With this resubmission, no new studies were conducted; however, the Applicant submitted a Root Cause Analysis (RCA) report to address the clinical pharmacology deficiency outlined in the CR letter. The RCA was designed to identify and investigate the potential source(s) of the aberrant PK profiles in METO-IN-006. Review of the RCA report, in conjunction with satisfactory resolution of the product quality and device quality issues, support that the aberrant PK profiles resulting in a lower Cmax on average, were likely due to erroneous nasal administration of the study drug by a couple of dose administrators in the comparative BA study METO-IN-006 resulting in little to no systemic exposure in some subjects across all three dose groups.[6]

When the data from subjects who had probable staff administration errors with Gimoti was excluded, Gimoti 15 mg nasal spray showed comparable bioavailability with Reglan 10 mg tablets. The 90% CI associated with the mean ratio for Cmax was within the 80% – 125% bioequivalence bounds. The clinical pharmacology reviewer concluded, the comparative BA data in addition to the information provided in this resubmission sufficiently supports the establishment of a bridge between Gimoti 15 mg and Reglan 10 mg, subsequently relying on the findings of safety and efficacy for the listed drug, Reglan 10 mg, is adequately justified.[6]

4.2 Benefit Conclusion

The Agency is relying upon previous findings of safety and effectiveness for Reglan (metoclopramide) 10 mg oral tablets (NDA 17854) and the relative bioavailability data supported by the application. Findings from the root cause analysis to address the potential source of dosing error, provides sufficient information to conclude that relying on the findings of efficacy for the listed drug (Reglan 10 mg tablet) is reasonable.[6]

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The Agency revised the indication to: [5]

Gimoti is a dopamine-2 (D2) antagonist indicated for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis.

5 Risk Assessment & Safe-Use Conditions

The primary safety data for Gimoti is based on data from the phase 2b clinical trial, METO-IN-002 and the two phase 3 clinical trials METO-IN-003 and METO-IN-004. Of the 543 patients in these three trials, 223 patients received Gimoti 10 mg, 95 received Gimoti 14 mg, and 225 received placebo. The overall mean duration of treatment in the pooled Gimoti studies was about 27 to 28 days. Additional supportive safety data from phase 2 study 25, 512-302R was reviewed, however, this study utilized a different intranasal formulation than Gimoti.

The Clinical Reviewer noted that most of the safety data was from patients receiving the 10 mg dose of Gimoti and that there was no study that evaluated the proposed 15 mg dose. There was also limited data comparing the safety of the proposed nasal spray to the reference listed drug, Reglan.[18]

5.1 Serious Adverse Events[e]

5.1.1 Deaths

There were no deaths in the clinical development program for Gimoti.

5.1.2 Non-fatal Serious Adverse Events (SAEs)

Table 1. Summary of SAEs in Clinical Trials[18,20]

Study	Total Patients with SAE	No. of Patients with SAE by Treatment Group	Description of SAE (No. patients)
METO-IN-002	N=5	Gimoti 10 mg (N=0)	• None
		Gimoti 14 mg (N=2)	• Worsening gastroparesis (N=1) • Acute cholecystitis (N=1)
		Placebo (N=3)	• Diabetic ketoacidosis (N=1) • Kidney infection (N=1) • Chronic obstructive pulmonary disorder exacerbation and non-cardiac chest pain (N=1)
METO-IN-003	N=5	Gimoti 10 mg (N=3)	• Orthostatic hypotension and hypoglycemia (N=1)

[e] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

			• Cellulitis right index finger (N=1) • Chalazion of right eye (N=1)
		Placebo (N=2)	• Worsening of anxiety disorder (N=1) • Non-cardiac chest pain
METO-IN-004	N=2	Gimoti 10 mg (N=0)	• None
		Placebo (N=2)	• Worsening of gastroparesis and inadequate diabetic control (N=1) • Staphylococcal infection of left shin (N=1)

Source: Adapted from Unireview

The clinical reviewer concluded that SAEs were comparable between the treatment groups in the primary safety studies and no SAE appeared related to Gimoti administration.[18]

5.2 ADVERSE EVENT OF SPECIAL INTEREST

5.2.1 Tardive Dyskinesia and Extrapyramidal Reactions

There were no cases of tardive dyskinesia in the clinical development program. However, TD is typically associated with longer treatment durations (>12 weeks) and the trials only provided about 4 weeks of safety data. Four patients in the Gimoti groups in METO-IN-002 reported adverse effects suggestive of EPS symptoms that included tremors (N=2); myoclonus, nystagmus, and tunnel vision (N=1); jitteriness, restlessness, anxiety (N=1), and inability to focus/concentrate (N=1). EPS-like symptoms were also reported in the Gimoti- female only group in study METO-IN-003. Symptoms reported included dystonia (N=2), dysarthria (N=1), tremor (N=1), and restlessness (N=1). The risks of TD and other EPS will be communicated in labeling via a Boxed Warning and in the warning and precautions section of the label, respectively.

The Clinical Reviewer noted: to address the theoretical concern that the intranasal route of administration of Gimoti may allow a direct CNS uptake of metoclopramide and thus potentially resulting in an increased risk of CNS AEs including TD, (b) (4) (b) (4)

6 Expected Postmarket Use

Patients with diabetic gastroparesis are likely to be treated by multiple prescriber types including general practitioners and gastroenterologists. Other dosage forms of metoclopramide are commonly prescribed for diabetic gastroparesis and prescribers are likely familiar with the risks, including the risks of TD and EPS. Gimoti may be prescribed in both outpatient and inpatient settings. Labeling will include Instructions for Use and a Medication Guide will be available to inform patients on the safe use and proper self-administration technique for Gimoti.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Gimoti beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Division of Gastroenterology recommends approval of Gimoti based on the comparative bioavailability data which sufficiently supports the establishment of a bridge between Gimoti (metoclopramide) nasal spray 15 mg and Reglan 10 mg tablets.

Diabetic gastroparesis may occur in patients with longstanding diabetes mellitus. Diabetic gastroparesis is associated with significant morbidity, impaired quality of life, poor glycemic control, and increased healthcare utilization and costs. Pharmacologic treatment options are limited and Gimoti offers an alternative route of administration for patients who have difficulty with the oral or parenteral metoclopramide products.

The risks of TD and other EPS are well documented for metoclopramide products. The available safety data for Gimoti does not demonstrate a higher risk of TD or other EPS compared to other dosage forms. Additionally, Ingrezza (valbenazine) and Austedo (deutetrbenazine) are FDA-approved for the treatment of adults with TD. The risk of TD will be communicated in labeling via a Boxed Warning and Medication Guide; similar to currently approved metoclopramide products. The risk of other EPS is addressed in the Warnings and Precautions section of the proposed label. Also, the maximum recommended treatment duration for this dosage form and for any combination of metoclopramide treatment products will be communicated in labeling. The likely prescribers of Gimoti should be familiar with these risks and the need for a limited treatment duration as the Boxed Warning has been in labeling since 2009 and the Reglan REMS that was released in 2011 included the rationale that labeling (included the Medication Guide) was adequate to communicate the risk of TD. Lastly, the proposed labeling for Gimoti includes Instruction for Use to inform patients on safe use.

At this time, this reviewer is not recommending a REMS for the management of the risks associated with Gimoti.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with Gimoti use are well documented, there are FDA-approved treatments for TD if it occurs, and healthcare providers who treat gastroparesis are familiar with the risk of TD and other EPS and the importance of patient monitoring.

Should the Division of Gastroenterology have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

1. Evoke Pharma. Original submission for Gimoti (metoclopramide nasal spray), NDA 209388. June 1, 2018.
2. Chapman I. Division of Risk Management. REMS Memorandum for Gimoti (metoclopramide nasal spray), NDA 209388. April 1, 2019.
3. Korvick J. Complete Response Letter for Gimoti (metoclopramide nasal spray), NDA 209388. April 1, 2019.
4. Evoke Pharma. Resubmission for Gimoti (metoclopramide nasal spray), NDA 209388. December 19, 2019.
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10. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. *Am J Gastroenterol.* 2013;108(1):18-37; quiz 38.
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16. Chang J, Rayner CK, Jones KL, Horowitz M. Prognosis of diabetic gastroparesis--a 25-year evaluation. *Diabet Med.* 2013;30(5):e185-188.
17. Yi S. Division of Gastroenterology and Inborn Errors Products. Office of Clinical Pharmacology Review for Gimoti (metcolopramide nasal spray), NDA 209388. March 7, 2019.
18. Division of Gastroenterology and Inborn Errors Products. Unireview for Gimoti (metcolopramide nasal spray), NDA 209388. March 29, 2019.
19. Evoke Pharma. Summary of Clinical Efficacy for Gimoti (metoclopramide nasal spray), NDA 209388. December 19, 2019.
20. Evoke Pharma. Summary of Clinical Safety for Gimoti (metoclopramide nasal spray), NDA 209388. December 19, 2019.

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/s/

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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209388
PDUFA Goal Date	April 1, 2019
OSE RCM #	2018-1163
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Director	Jamie Wilkins, Pharm.D.
Review Completion Date	April 1, 2019
Subject	Defer comment on DRISK evaluation of the need for a REMS
Established Name	Metoclopramide nasal spray
Trade Name	Gimoti
Name of Applicant	Evoke Pharma, Inc
Therapeutic Class	Dopamine$_2$-receptor antagonist/Gastrointestinal agent
Formulation(s)	Nasal spray: 15 mg in each spray
Dosing Regimen	15 mg, 30 minutes before each meal and at bedtime (maximum of 60 mg per day) for 2 to (b) (4) weeks

Reference ID: 4412680

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Reference ID: 4412680

1 Introduction

This memo is to defer the Division of Risk Management's (DRISK) review of the need for a risk evaluation and mitigation strategy (REMS) for Gimoti (metoclopramide nasal spray), NDA 209388.

Evoke Pharma, Inc submitted a 505(b)(2) application for metoclopramide nasal spray on June 1, 2018 for the proposed indication: for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.[1] The submission included a Boxed Warning for tardive dyskinesia and a communication plan (CP) REMS to mitigate the potential risk of tardive dyskinesia (TD) and other extrapyramidal symptoms (EPS) associated with the use of Gimoti. This application is under review in the Division of Gastroenterology and Inborn Errors Products (DGIEP).

2 Product Information

2.1 Product Information

Gimoti (metoclopramide nasal spray) is a dopamine$_2$-receptor antagonist/gastrointestinal agent with the proposed indication: for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis. Gimoti is proposed as an aqueous solution for nasal administration supplied in an amber glass vial fitted with a metered spray pump attachment. Gimoti delivers 15 mg of metoclopramide with each spray. See Table 1 for the proposed recommended dosage.

Table 1[1]. Recommended Gimoti (metoclopramide nasal spray) Dosage in Female Patients with Acute and Recurrent Diabetic Gastroparesis

Population	Recommended Dosage	Maximum Recommended Daily Dosage
Adult patients	15 mg 4 times daily (30 minutes before each meal and at bedtime)	60 mg
Mild hepatic impairment (Child-Pugh A)		
Elderly patients	(b) (4)	60 mg
Moderate or severe hepatic impairment (Child-Pugh B or C)	(b) (4)	
CYP2D6 poor metabolizers		
Concomitant use with strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine)		
Moderate or severe renal impairment (creatinine clearance less than 60 mL/minute)		
Patients with end-stage renal disease (ESRD) including those treated with hemodialysis and continuous ambulatory peritoneal dialysis	(b) (4)	

Gimoti is not currently marketed in the United States. However, the active ingredient, metoclopramide, was first approved in the US in 1979. The following dosage forms of metoclopramide are currently marketed in the US:[2]

- Oral tablets: 5 mg and 10 mg
- Orally disintegrating tablets: 5 mg and 10 mg
- Oral solution: 5 mg/5 mL and 10 mg/10 mL
- Injectable solution: 5 mg/mL

2.2 Regulatory History

- 06/01/2018: A 505(b)(2) application (NDA 209388) submission was received for Gimoti (metoclopramide nasal spray). The submission included a CP REMS proposal.

- 02/28/2019: The FDA issued a Discipline Review Letter to Evoke Pharma Inc, to convey the deficiencies identified during review of NDA 209388.[3]

3 Risk Management Activities Proposed by the Applicant

The Applicant proposed risk management activities for Gimoti beyond routine pharmacovigilance and labeling including a CP REMS to mitigate the potential risk of tardive dyskinesia (TD) and other extrapyramidal symptoms (EPS) associated with the use of Gimoti. Evoke Pharma Inc, submitted a complete REMS proposal including a REMS document, REMS supporting document, and REMS materials with their original NDA submission.

REMS Goal

The goal of the REMS for Gimoti is to mitigate the potential risk of tardive dyskinesia (TD) and other extrapyramidal symptoms (EPS) associated with the use of Gimoti by:

1. Informing healthcare providers that the risk of TD and other EPS with use of Gimoti which increases with longer-term use
2. Informing healthcare providers that they should counsel patients about the risks associated with Gimoti

REMS Materials

- Letter for Health Care Providers
- Letter for Professional Societies
- REMS Fact Sheet
- REMS Program Website

Reviewer's Comments: *DRISK defers comments on the Applicant's proposed REMS at this time.*

Reference ID: 4412680

4 Benefit Assessment

Substantial review issues were identified from clinical (as well as clinical pharmacology and product quality) during the review of Gimoti. The review team concluded that the efficacy data provided in NDA 209388 are insufficient to support approval of Gimoti at this time.[4]

4.1 CLINICAL[3]

Four clinical studies support the 505(b)(2) application for Gimoti.[5] These studies provide efficacy and safety data for Gimoti and Reglan 10 mg tablets. The details of these studies are included in Table 2 in the appendix. The efficacy studies were conducted at lower doses than the proposed dose and failed to show efficacy in female and male patients; therefore, the data are not informative to support effectiveness of Gimoti at the proposed dose. In addition, the Applicant alluded to the fact that the lack of observed efficacy in males may be in part attributed to sex-related PK differences. However, the listed drug which is approved for both males and females, also demonstrates sex-specific differences in PK. Therefore, lower systemic exposure in males would not be a valid reason for limiting the use of Gimoti to female patients.

5 Conclusion & Recommendations

Because of the inability of the drug to demonstrate efficacy and therefore benefit, DRISK is currently unable to formulate recommendations for risk management, specifically the need for a REMS. An evaluation of the need for a REMS for metoclopramide nasal spray will be completed after the Sponsor addresses the identified deficiencies. This memo serves to close the existing consult request to DRISK for metoclopramide nasal spray under NDA 209388.

6 Appendices

6.1 REFERENCES

1. Evoke Pharma, Inc. Gimoti (metoclopramide nasal spray). NDA 209388. Prescribing Information, draft. June 1, 2018.
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5. Evoke Pharma, Inc. Gimoti (metoclopramide nasal spray). NDA 209388. Module 2.7.3 - Summary of Clinical Efficacy. June 1, 2018.
6. Nayyar A. Food and Drug Administration, Division of Gastroenterology and Inborn Errors Products (DGIEP). Gimoti (metoclopramide) nasal spray. NDA 209388. Team Meeting, Clincal Slides. January 7, 2019.

Reference ID: 4412680

6.2 TABLE 2: [5,6] CLINICAL STUDIES FOR GIMOTI

Study Number	Study Design	Product and Doses Studied	Patient Population	Results
METO-IN-002 Phase 2b	Randomized, double-blind, placebo-controlled, dose-ranging, efficacy, and safety study	Gimoti 10 mg Gimoti 14 mg Placebo	Males and females with diabetic gastroparesis	Failed primary and secondary endpoints; Post-hoc analysis in females statistically significant but not clinically meaningful
METO-IN-003 Phase 3	Randomized, double-blind, placebo-controlled, efficacy, and safety study with population PK assessment	Gimoti 10 mg Placebo	Females with diabetic gastroparesis	Failed primary and secondary endpoints; Post-hoc analysis in more severely symptomatic patients achieved statistical significance possibly due to chance
METO-IN-004 Phase 3	Randomized, double-blind, placebo-controlled, efficacy, and safety study with population PK assessment	Gimoti 10 mg Placebo	Males with diabetic gastroparesis	Stopped after 26 months due to stalled enrollment; Data is insufficient to conclude that males would not have achieved a clinical benefit
25,512-302R Phase 2a	Active-controlled, randomized, open-label, parallel-design study to compare the PK, safety, and exploratory efficacy of 2 doses of a previous formulation of metoclopramide nasal spray	Reglan Tablets 10 mg *MCP 10 mg *MCP 20 mg	Male and female patients with diabetic gastroparesis	Efficacy of intranasal MCP 10 mg and 20 mg similar to Reglan 10 mg
*MCP = (b) (4) metoclopramide nasal spray formulation				

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