CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209388Orig1s000

<u>OTHER REVIEW(S)</u>

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	June 12, 2020
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 209388
Product Name and Strength:	Gimoti (metoclopramide) nasal spray, 15 mg per spray
Applicant/Sponsor Name:	Evoke Pharma, Inc
OSE RCM #:	2018-1162-3
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 10, 2020 for Gimoti. We review the revised container label and carton labeling for Gimoti (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Vee S. Label and Labeling Review for Gimoti (NDA 209388). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 13. RCM No.: 2018-1162-2.

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/s/

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IDALIA E RYCHLIK
06/15/2020 09:43:34 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 28, 2020
To:	Maureen Dewey Senior Regulatory Project Manager **Division of Regulatory Operations for Immunology and Inflammation (DRO-II)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, PharmD. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	GIMOTI (metoclopramide)
Dosage Form and Route:	nasal spray
Application Type/Number:	NDA 209388
Applicant:	Evoke Pharma, Inc.

1 INTRODUCTION

On January 10, 2020, Evoke Pharma, Inc., submitted for the Agency's review a Class 2 resubmission for New Drug Application (NDA) 209388 for GIMOTI (metoclopramide) nasal spray. The proposed indication for GIMOTI (metoclopramide) nasal spray is for acute and recurrent diabetic gastroparesis in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Regulatory Operations for Immunology and Inflammation (DRO-II) on February 11, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU)] for GIMOTI (metoclopramide) nasal spray.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft GIMOTI (metoclopramide) MG and IFU received on January 10, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 20, 2020.
- Draft GIMOTI (metoclopramide) Prescribing Information (PI) received on January 10, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 20, 2020.
- Approved REGLAN (metoclopramide hydrocholoride) comparator labeling dated August 29, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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MARIA T NGUYEN
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DMPP-OPDP review of metoclopramide (GIMOTI) NDA 209388 MG IFU

MEETA N PATEL
05/28/2020 10:12:55 AM

MARCIA B WILLIAMS
05/28/2020 10:16:19 AM

LASHAWN M GRIFFITHS
05/28/2020 11:02:50 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 22, 2020

To: Maureen Dewey, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for GIMOTI (metoclopramide) nasal spray

NDA: 209388

In response to DGIEP's consult request dated February 10, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), labeling for the original NDA submission for Gimoti.

PI and Medication Guide/IFU: OPDP has no comments on the proposed labeling based on the draft PI received by electronic mail from DGIEP on May 20, 2020.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide/IFU will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
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DEPARTMENT OF HEALTH HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone: 301-796-2200
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PEDIATRIC LABELING REVIEW

From:&	Carolyn L. Yancey, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:&	Shetarra Walker, MD, MSCR, Acting Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director, DPMH
NDA Number:&	209388/Supplement (S)-027
Sponsor:&	Evoke Pharma, Incorporated
Drug:&	Gimoti (metoclopramide nasal spray)
Dosage Form and Route of Administration:	10 mL glass vial with a metered nasal spray pump (delivering a metered spray of 15 mg metoclopramide in each 70-microliter spray).
Dosing Regimen:&	One spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime time [maximum of 4 sprays (60 mg per day)] for 2 to (b)(4) weeks.
Proposed Indication:&	For the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.
Consult Request:&	The Division of Gastroenterology and Inborn Errors of Metabolism [DGIEP renamed in reorganization, the Division of Gastroenterology (DG)] requests DPMH Pediatric Team assistance with review of pediatric labeling in the Class 2 resubmission of new drug application (NDA) 209388/S-027 for Gimoti (metoclopramide nasal spray) by Evoke Pharma. This 505(b)(2) NDA 209833 relies on the listed drug (LD) Reglan [metoclopramide hydrochloride (HCl)] oral tablet (NDA 017854). DG also requests DPMH assistance on preparation for the Pediatric Research Committee (PeRC) meeting. The consult (dated February 10, 2020) is due on June 19, 2020.

Background

A DPMH review of the original NDA Gimoti submission was completed on February 22, 2019. This Class 2 resubmission of 505(b)(2) NDA 209388 for Gimoti (metoclopramide nasal spray) is proposed for the

relief of symptoms in adult women with acute and recurrent diabetic gastroparesis based on findings of safety and efficacy, and comparative bioavailability (BA) to the LD, Reglan (metoclopramide HCl) 10 mg oral tablet (approved December 1980). Reglan is approved for treatment of 4 to 12 weeks of symptomatic, documented gastroesophageal reflux in adults who fail to respond to conventional therapy, and for relief of symptoms in adults (women and men) with diabetic gastroparesis. The applicant is not seeking an indication in gastroesophageal reflux. The NDA resubmission (received on December 19, 2019) is in response to a complete response (CR) dated April 1, 2019 based on the following deficiencies:

- The pharmacokinetic (PK) bridge between Gimoti 15 mg nasal spray dose and Reglan 10 mg tablet fails to justify reliance on findings of safety and efficacy for Reglan to assure comparable safety and efficacy between Gimoti and Reglan. Clinical pharmacology detailed concerns that the Gimoti nasal spray product is not able to deliver metoclopramide in a reliable and consistent manner. The lower mean maximum concentration (C_{max}) was driven by patients who received very little metoclopramide via nasal spray delivery.

- The proposed specification for the drug product is inadequate based on quality control and essential performance characteristics of the combination product.

The proposed therapeutic dose for Gimoti is 15 mg administered four times daily (30 minutes prior to each meal and at bedtime) and the to-be-marketed product is as an intranasal (IN) spray in an (b) (4)[1] metered spray pump. As cited in the attached review, the Pediatric Research Equity Act (PREA) does not apply to Gimoti because diabetic gastroparesis is on the FDA-Automatic Waiver List of adult-related conditions that are rarely or never diagnosed in pediatric patients and, as such, studies would be impossible or highly impracticable in pediatric patients.

Class 2 Resubmission of NDA 209388 Gimoti (metoclopramide nasal spray)

FDA convened a Type A meeting with the applicant on July 25, 2019 to discuss plans to address the deficiencies on the quality of drug substance manufacturing and device quality. Per the Office of Product Quality (OPQ), the applicant has provided adequate drug product data using the commercial formulation (equivalent to 15 mg dose) and the planned commercial device, (b) (4) spray pump. OPQ confirmed that the droplet size distribution and spray patterns are acceptable using the (b) (4) spray pump technology.[2]

Selection of the 15 mg to-be-marketed dose of Gimoti is based on data from the pivotal comparative BA/bioequivalence (BE) Phase 1 study, METO-IN-006, a 4-way crossover study in 98 healthy subjects (males and females) with Gimoti (15 mg, 16 mg, and 17 mg), Reglan 10 mg tablet, and Reglan 5 mg, intravenously. Gimoti 15 mg demonstrated comparable area under the curve (AUC), and a 20% lower mean C_{max} compared to Reglan 10 mg (N=97). Clinical Pharmacology cites that "11 of 293 PK profiles (3.75%) of Gimoti 15 mg to 17 mg showed none to minimal drug exposure whereas no such cases were found after oral administration of Reglan tablets which appeared to contribute to the 20% lower mean C_{max} of Gimoti compared to Reglan."[3] The CR was based on incomplete and inconsistent absorption of Gimoti 15 mg IN spray and therefore, failure to demonstrate adequate bridging to Reglan upon which comparable efficacy (and safety) could not be demonstrated between Gimoti and Reglan.

Resubmission of NDA 209388 included a root cause analysis including re-analysis of the BA/BE study, METO-IN-006. Inconsistencies were reported with the activation force of the IN device used in study METO-

(b) (4)

[2] See NDA 209388 Gimoti (metoclopramide nasal spray), OPQ comments by Caroline Strasinger, Drug Product, and Katherine Duncan, Drug Substance.

[3] See Unireview, NDA 209388 Gimoti (metoclopramide NS), Section 5 Clinical Pharmacology, page 25 - 26.

IN-006 based on subjective differences across 8 dose-administrators, differing training needs, the ability to dose the IN device accurately, and a large number of doses being administered within a short period of time (administering doses to multiple patients at ~4 minute intervals), collectively. Each issue may have contributed to dosing errors and the observed low drug concentration (C_{max}). Per Clinical Pharmacology, when Gimoti 15 mg was compared to Reglan 10 mg tablet, without data from patients for whom a nasal spray administrator error was likely, Gimoti 15 mg showed comparable BA with Reglan 10 mg with a 90% confidence interval (CI) associated with the mean ratio for C_{max} within the 80-120% bioequivalence bounds. Therefore, the BA of metoclopramide from Gimoti nasal spray 15 mg is considered sufficiently comparable to the oral Reglan 10 mg tablet.[3]

Reviewer Comments:
Based on clinical trial patient-use data (METO-IN-003 and METO-IN-004), DG concludes that patient self-administration supported by the revised Instructions for Use (IFU) for the IN spray could reduce dosing errors. DG accepts the Root Cause Analysis and concludes that the IFU section of labeling is adequately revised to more clearly describe the appropriate priming needed to deliver a full-dose of the nasal spray.

Regarding the applicant's claimed differences across females compared to men, the applicant claims that the geometric mean (gMean) for AUC and C_{max} were higher in female than in male subjects, and C_{max} was consistently too low to meet criteria for BE in men. Different primary efficacy endpoints were used in different studies making it challenging to compare results across studies.[4] Per the Statistics Reviewer, subgroup analysis of women in study METO-IN-002[5] and METO-IN-003[6] was multiplicity adjusted and both studies failed to achieve statistical significance on the primary efficacy endpoints. Companion Phase 3 study METO-IN-004[7] employing population PK assessment in only male diabetic gastroparesis patients receiving Gimoti 10 mg or placebo (PBO) for 4 weeks was terminated after 26 months due to difficulty recruiting males with diabetic gastroparesis. Confirmatory trial, METO-IN-006, in women failed to achieve significance for the primary analysis. The applicant's proposed indication for relief of symptoms in only adult women with diabetic gastroparesis is based on a post-hoc subgroup analyses and, therefore, unacceptable per DG Clinical and Clinical Pharmacology.

Reviewer Comments:
DG Clinical Team concludes that Gimoti has been demonstrated to show comparable systemic exposure to oral Reglan 10 mg tablet.

Study METO-IN-006 was not designed to identify PK differences between males and females, and it cannot be ruled out that other factors (aside from body size) may have contributed in part to the observed PK difference between male and female (e.g., CYP2D6 phenotype). See the Clinical Pharmacology Review by Sojeong Yi, Ph.D. and Insook Kim, Ph,D.

Reviewer Comments:
DPMH defers to DG Clinical Pharmacology conclusion that the applicant's observation of a higher mean

[4] Study METO-IN-002 used the primary efficacy endpoint, the modified Gastroparesis Cardinal Symptom Index-Daily Dairy (mGSCI-DD); Study METO-IN-003 used the Gastroparesis Symptom Assessment (GSA); Study MET-IN-004 used the GSA-Eligibility (GSA-E); and the total symptom score (TSS) for Study 25,512-302R.
[5] Study METO-IN-002 was a dose-ranging, efficacy and safety study in female and male diabetic gastroparesis patients receiving Gimoti 10 mg, 14 mg, or PBO for 4 weeks.
[6] Study METO-IN-003 was an efficacy and safety study with population PK assessment in female diabetic gastroparesis patients receiving Gimoti 10 mg or PBO for 4 weeks.
[7] Study METO-IN-004 was an efficacy and safety that used population PK assessment in only male diabetic gastroparesis patients receiving Gimoti 10 mg or PBO for 4 weeks with the primary efficacy endpoint, GSA-Eligibility (GSA-E).

AUC and C_{max} in females is confounded by the effect of body size on drug distribution and clearance because females tend to be lighter and smaller than males.[8] *Per the Statistical Reviewer, the statistical analysis using an analysis of variance (ANOVA) model incorporating covariates of both sex and body weight (supplement PK analysis of META-IN-001 and META-IN-006) suggest that C_{max} and AUC were not significantly different between males and females. Clinical Pharmacology concludes that a covariate effect (e.g., sex, race, or body weight) on PK is more reliably identified by population PK modeling. The applicant's population PK analysis pooling multiple studies of Gimoti indicate that 'lean body mass' significantly affected PK parameters whereas 'sex' does not affect PK parameters. DG Clinical Pharmacology reports that the final PK model only included 'lean body mass' as a covariate. Clinical Pharmacology and Clinical conclude that clinical data supports use of Gimoti (metoclopramide) in women and men.*

The applicant proposes (b) (4) (b) (4)

Reviewer Comments:
DG Clinical Pharmacology and Clinical recommend that the applicant develop a lower strength formulation, (7.5 mg strength nasal spray). As of this review, DG is considering a postmarketing requirement for development of a lower strength formulation of metoclopramide to address specific populations of patients with moderate to severe hepatic impairment, renal impairment including end-stage renal disease, and patients who are CYP2D6 poor metabolizers or have need for concomitant use with CYP2D6 inhibitors.

DPMH Pediatric Labeling Recommendations
As cited in the attached DPMH Labeling Review, Gimoti (metoclopramide nasal spray), like the LD (Reglan), has no indication(s) in pediatric patients of any age. GIMOTI is not recommended for use in pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates. The most recent version of the DG substantially complete proposed GIMOTI labeling (dated May 12, 2020) is in PLR/PLLR format. DPMH's recommended information added to the labeling is underlined. Information to be deleted has a ~~strikethrough~~. Comments and rationale for DPMH's recommendations to the labeling are in *italics*.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Gimoti is indicated for the relief of symptoms in adults (b) (4) -with acute and recurrent diabetic gastroparesis.

Limitations of Use:
GIMOTI is not recommended for use in:

- (b) (4) pediatric patients due to the risk of developing tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates *[see Use in Specific Populations (8.4)]*.
- (b) (4) moderate or severe hepatic impairment (Child-Pugh B or C), (b) (4) moderate or severe renal impairment (creatinine clearance less than 60 mL/minute), (b) (4)

[8] NDA 209388 Gimoti (metoclopramide nasal spray), DG Clinical Pharmacology Reviewer Sojeong Yi, Ph.D. and Kim Insook, Ph.D., comments in substantially complete Gimoti (metoclopramide nasal spray) labeling (dated May 12, 2020).

(b) (4) using strong CYP2D6 inhibitors due to the risk of increased drug exposure and adverse reactions *[see Warnings and Precautions (5.9)]*

Reviewer Comment: DPMH agrees with DG on the revised indication in both adult women and men based on the BA study METO-IN-006 (see Clinical Pharmacology Review by Sojeong Yi, Ph.D. and Insook Kim, Ph.D.) and minor revisions in the Limitations of Use.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Metoclopramide is not recommended for use in pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates. The safety and effectiveness of GIMOTI in pediatric patients have not been established.

Dystonias and other extrapyramidal symptoms associated with metoclopramide are more common in pediatric patients than in adults *[see Indications and Usage (1), Warnings and Precautions (5.1, 5.2)]*. In addition, neonates have reduced levels of NADH-cytochrome b_5 reductase, making them more susceptible to methemoglobinemia, a possible adverse reaction of metoclopramide use in neonates *[see Use in Specific Populations (8.8)]*.

Reviewer Comments:
DPMH recommends cross referencing the risks of dystonias and other extrapyramidal symptoms associated with metoclopramide being more common in pediatric patients than in adults from (8.4) to Indications and Usage (1), specifically to Limitations of Use to inform prescribers on pediatric safety information.

DPMH Actions and Labeling Recommendations
DPMH reviewed the Class 2 resubmission of Evoke Pharma proposed labeling for Gimoti (metoclopramide nasal spray) and participated in meetings with the DG Review Team from March to May 2020. The most recent proposed labeling revisions per DPMH are dated May 12, 2020. DPMH labeling recommendations were provided in track changes for DG consideration to revise the Gimoti nasal spray labeling to align with the listed drug labeling for Reglan and to conform to the Draft Guidance for Industry and Review Staff on Pediatric Labeling.[9]

APPENDIX:
UNIREVIEW, Section 9 Pediatrics
Under the Pediatric Research Equity Act (PREA), (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. GIMOTI (metoclopramide nasal spray) represents a new dosage form and new route of administration for metoclopramide. However, diabetic gastroparesis is on the FDA-Automatic Waiver List of adult-related conditions that are rarely or never diagnosed in pediatric patients and, as such, studies would be impossible or highly impracticable in pediatric patients.

[9] *Draft Guidance for Industry and Review Staff* – Pediatric Information Incorporated into Human Prescription Drug and Biological Products for Labeling, February 2013.

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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PLLR Labeling Memorandum

Date: May 15, 2020 **Date consulted:** February 10, 2020

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Maureen Dewey, Regulatory Project Manager (RPM)
Division of Gastroenterology (DG)

Drug: Gimoti (metoclopramide nasal spray)

NDA: 209388

Applicant: Evoke Pharma

Subject: Pregnancy and Lactation Labeling

Proposed Indication: The relief of symptoms in adult women with acute and recurrent diabetic gastroparesis

Materials Reviewed:

- NDA 209388 resubmission dated December 19, 2019.
- DPMH PLLR review of Gimoti (metoclopramide nasal spray) NDA 209388 by Kristie Baisden, DO, dated January 4, 2019. DARRTs Reference ID: 4371806.

- DPMH PLLR review of Reglan (metoclopramide) Tablets USP (NDA 017854) by Christos Mastroyannis, MD, dated August 22, 2017. DARRTs Reference ID: 4143788.[1]

Consult Question: DG requests "Maternal Health review of the PLLR labeling"

INTRODUCTION

On December 19, 2019, the applicant, Evoke Pharma, resubmitted a new drug application (NDA 209388) for Gimoti (metoclopramide nasal spray) via the 505(b)(2) regulatory pathway. On February 10, 2020, the Division of Gastroenterology (DG) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- The proposed indication for Gimoti (metoclopramide nasal spray) is the relief of symptoms in adult women with acute or chronic diabetic gastroparesis.
- The applicant is relying on the FDA's finding of safety and effectiveness for Reglan (metoclopramide) tablets (NDA 017854) as the listed drug relied upon.
- Metoclopramide received initial U.S. market approval in 1979.
- On June 1, 2018, the original NDA for Gimoti was submitted. On April 1, 2019, a Complete Response Letter (CRL) was issued which cited deficiencies in clinical pharmacology and product quality.
- On December 19, 2019, the applicant resubmitted NDA 209388 for Gimoti.

Drug Characteristics[2]

- *Drug class*: dopamine-2-receptor antagonist
- *Mechanism of action*: stimulates motility of the upper gastrointestinal tract. The exact mechanism of metoclopramide in the treatment of diabetic gastroparesis is unknown; it seems to sensitize tissues to the action of acetylcholine.
- *Dosage and administration*: 15 mg nasal spray administered before each meal and at bedtime for 2 to (b)(4) weeks, depending on symptomatic response.
- *Molecular weight*: 354.3 Daltons
- *Bioavailability*: 47.4%. Bioavailability of the nasal administration of Gimoti 15 mg is comparable to the oral administration of the metoclopramide 10 mg tablet.
- *Protein binding*: 30%
- *Half-life*: 8 hours
- *Adverse reactions*: dysgeusia, headache, fatigue, restlessness, drowsiness, and lassitude.

[1] The cross-reference to the Reglan consult is included to avoid duplicating background information relevant to this class of products. DPMH's recommendations for the Gimoti labeling discussed below are based solely on information from literature that is not specific to a particular metoclopramide product.
[2] Gimoti (NDA 209388) proposed package insert

Current State of the Labeling[3]

Reglan (metoclopramide) tablets (NDA 017854), the listed drug relied upon, currently approved labeling is in the Physician Labeling Rule (PLR) format and was converted to PLLR format in 2017.

- *8.1 Pregnancy*:
  - Published studies, including retrospective cohort studies, national registry studies, and meta-analyses, do not report an increased risk of adverse pregnancy-outcomes with use of metoclopramide during pregnancy.
  - No adverse developmental effects were observed with oral administration of metoclopramide to pregnant rats and rabbits at exposures about 6 and 12 times the maximum recommended human dose.
  - A Clinical Consideration for Fetal/Neonatal Adverse Reactions is included which notes metoclopramide crosses the placental barrier and may cause extrapyramidal signs and methemoglobinemia in neonates with maternal administration during delivery. Monitor neonates for extrapyramidal signs.
- *8.2 Lactation*
  - Limited published data report the presence of metoclopramide in human milk in various amounts. Breastfed infants exposed to metoclopramide have experienced gastrointestinal adverse reactions, including intestinal discomfort and increased intestinal gas formation. Metoclopramide elevates prolactin levels; however, the published data are not adequate to support drug effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Reglan and any potential adverse effects on the breastfed child from Reglan or from the underlying maternal condition."
  - A Clinical Consideration is included to monitor neonates because metoclopramide may cause extrapyramidal signs and methemoglobinemia.

DATA REVIEW

PREGNANCY

Nonclinical Experience

Animal reproduction studies have not been performed with Gimoti.

Clinical Experience

Clinical Trials

Pregnant women were excluded from clinical trials with Gimoti. The applicant stated 1 pregnancy was reported (subject (b) (6) in phase 1 Study METO-IN-006) as follows: A healthy 36-year-old female who received Gimoti 15mg and was discontinued from the study because of a positive serum pregnancy test on Day 16. The outcome was an uncomplicated term livebirth.

Applicant's Review of the Published Literature

The applicant did not specify the search criteria, but resubmitted the following relevant articles which were previously reviewed by DPMH[4,5]:

[3] Reglan currently approved labeling from 8/27/19. Drugs@FDA

- Among 28,486 women exposed to metoclopramide in the first trimester in a large register-based cohort study, there was no increased risk of major congenital malformations (MCM) overall, for any of the 20 individual malformation categories assessed, spontaneous abortion, or stillbirth (Pasternak 2013 et al).[6]
- In a large cohort of infants exposed to metoclopramide in the first trimester (n=3,458), exposure was not associated with significantly increased risk of any of several adverse outcomes, including congenital malformations, low birth weight, and preterm delivery (Matok et al 2009).[7]

DPMH's Review of the Published Literature
Clinical experience data on metoclopramide use in pregnancy was previously reviewed by DPMH in 2017 and 2018.[4,5] DPMH concluded the following:

> The available data from published retrospective cohort studies, national registry studies, and meta-analyses (reflecting over 20 years of use in thousands of pregnant women) failed to demonstrate an association of adverse developmental outcomes with metoclopramide use during pregnancy. There were adverse reactions reported, however, these are not dissimilar to those expected and already described in the Warnings and Precautions section of metoclopramide labeling.

This Reviewer performed a focused literature search in PubMed, Embase, Micromedex[8], TERIS[9], Reprotox[10], and Briggs[11] to find any relevant articles published since the most recent DPMH PLLR Review of metoclopramide in 2018. Search terms included: "metoclopramide" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." One relevant article was identified as described below.

- A 2019 retrospective cohort study using the Quebec Pregnancy Cohort (1998-2015) to assess first trimester metoclopramide exposures (n=958) for their association with MCM. Metoclopramide use was associated with an increased risk of overall MCM (aOR 1.27, 95% CI:1.03-1.57; 105 exposed cases) and with an increased risk of genital organ defects (aOR 2.26, 95% CI: 1.14-4.48; 10 exposed cases).[12]

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[4] DPMH PLLR review of Gimoti (metoclopramide nasal spray) NDA 209388 by Kristie Baisden, DO, dated January 4, 2019. DARRTs Reference ID: 4371806.
[5] DPMH review of Reglan (metoclopramide) Tablets USP (NDA 017854) by Christos Mastroyannis, MD, dated August 22, 2017. DARRTs Reference ID: 4143788.
[6] Pasternak B, Svanstrom H, Molgaard-Nielsen D, Melbye M, Hviid A. Metoclopramide in pregnancy and risk of major congenital malformations and fetal death. JAMA. 2013;310(15):1601-11.
[7] Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med. 2009;360(24):2528-35.
[8]Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 5/5/20
[9]TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 5/5/20.
[10]Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 5/5/20.
[11] Briggs GG, et al. Drugs in Pregnancy and Lactation: A Reference Guide , 9th Ed. 2011.
[12] Berard A, et al. New Evidence for concern over the risk of birth defects from medications for nausea and vomiting of pregnancy. Journal of Clinical Epidemiology 116 (2019) 30-48.

Reviewer's Comment
The increased risk of MCM with metoclopramide exposure reported in the above retrospective cohort study (Berard et al 2019)[12] is inconsistent with several other published studies previously reviewed by DPMH that do not report an increased risk of MCM (including retrospective cohort studies, case-control studies, meta-analyses, and national registry studies).[6,7,13,14,15,16,17,18] Therefore, DPMH requested DG consult OSE's Division of Epidemiology (DEPI) and Division of Pharmacovigilance (DPV), and the Division of Biostatistics 7 (DB7) for assistance in evaluating this new conflicting data on MCM risk with metoclopramide use in pregnancy.

DB7 reviewed the Berard et al 2019 publication and shared multiple statistical comments with DPMH regarding limitations of the study.[19] DB7 noted the authors did not define primary or secondary outcomes nor provide a formal power assessment based on the primary outcome, which makes interpreting hypothesis testing difficult. Further, DB7 noted the effect of metoclopramide may have been confounded by the effect of concomitant exposure to other antiemetics. In addition, it is likely that uncontrolled confounding still remains due to the lack of information on over-the-counter folic acid use, smoking, and alcohol consumption. Overall, DB7 concluded "because of the limitations and the implicit exploratory nature of the study, we do not recommend DPMH include the findings of this paper in the labeling of metoclopramide."

DEPI reviewed the Berard et al 2019 retrospective cohort study, as well as the two large retrospective cohort studies submitted by the applicant above (Pasternak et al 2013, Matok et al 2009) which in contrast do not indicate an increased risk of MCM with first trimester metoclopramide exposure.[20] DEPI concluded,

> *[M]issing controls for geographic location and calendar time might explain the anomalous association observed by Berard 2019 between in utero first trimester exposure to metoclopramide and MCM in singleton liveborn infants. Statistical variability without adjustments for multiple testing might explain the strong association reported by Berard 2019 between in utero first trimester exposure to metoclopramide and genital organ MCM in singleton liveborn infants. Pasternak 2013 used methods for covariate control superior to Berard.*

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[13] Pinder, RM et al. Metoclopramide, a review of its pharmacological properties. Drugs. 12:81-131, 1976.
[14] Anderka, M et al. National Birth Defects Prevention Study. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defects Res. A Clin. Mol. Teratol. 94(1):22-30, 2012.
[15] Nageotte MP et al. Droperidol and diphenhydramine in the management of hyperemesis gravidarum. Am J Obstet Gynecol 174:1801-1805, 1996.
[16] Berkovitch M et al. Metoclopramide for nausea and vomiting of pregnancy: a prospective multicenter international study. Am J Perinatol 2002;19:311-6.
[17] Sorensen HT, et al. Birth outcomes following maternal use of metoclopramide. Br J Clin Pharmacol 49(3):264-268, 2000
[18] Yost NP, et al. A randomized, placebo-controlled trial of corticosteroids for hyperemesis due to pregnancy. Obstet Gynecol 102(6):1250-1254, 2003.
[19] Division of Biometrics VII Statistical Review and Evaluation, Gimoti NDA 209388, by Joo-Yeon Lee, PhD, dated 4/29/20, DARRTs Reference ID: 4600465.
[20] Office of Pharmacovigilance and Epidemiology Integrated Review, Gimoti (metoclopramide) NDA 209388, by Joel L. Weissfeld, MD, MPH and Michelle Hines, PharmD. DARRTs Reference ID: 4603369.

Overall, DEPI's recommendations state "any presentation of possible metoclopramide-associated MCM risk should balance questionable results from Quebec (Berard et al 2019) against perhaps more credible results from Denmark (Pasternak 2013)."

Finally, DPV searched the FDA Adverse Event Reporting System (FAERs) for all reports of MCM associated with metoclopramide during pregnancy through March 8, 2020.[20] A total of 35 MCM cases were identified including: circulatory (n=12; 7 atrial septal defects and 4 ventricular septal defects); musculoskeletal (n=9); urinary (n=5); eye, ear, face, or neck (n=2); lip/palate (n=2); respiratory (n=2); genital (n=2); integumentary (n=2); nervous (n=1); and other (n=1). DPV stated their assessment of risk factors and trends among cases was largely limited by a lack of information. DPV concluded "the most frequently described MCMs in this case series mirror those commonly reported in birth defect surveillance programs; we were unable to identify a pattern specific to fetuses with transplacental metoclopramide exposure."

LACTATION

Nonclinical Experience

Animal lactation studies have not been performed with Gimoti.

Clinical Experience

Clinical Trials

Lactating women were excluded from clinical trials with Gimoti. No lactation cases have been reported.

Applicant's Review of the Published Literature

The applicant did not perform a published literature search related to metoclopramide use in lactating women.

DPMH's Review of the Published Literature

Clinical experience data on metoclopramide use during lactation was previously reviewed by DPMH in 2017 and 2018.[4,5] DPMH concluded the following:

> Metoclopramide is present in the breastmilk. Metoclopramide has been used off-label to induce lactation and improve milk production in women who wish to breastfeed; however, the data are insufficient to support that the drug increases milk production. No adverse reactions have been observed in breastfed infants of mothers who were taking metoclopramide while breastfeeding except for intestinal discomfort (n=2). Metoclopramide may cause extrapyramidal signs (dystonia) and methemoglobinemia in breastfeeding neonates (neonates have reduced levels of NADH-cytochrome b5 reductase, making them more susceptible to methemoglobinemia). Therefore, these neonates should be closely monitored.

This Reviewer performed a focused search in *Medications and Mother's Milk*[21], Micromedex[8], Reprotox[10], PubMed, and Embase to find any relevant articles published

[21] Hale, Thomas (2017) Medications and Mother's Milk. Amarillo, Texas. Hale Publishing.

since the most recent DPMH PLLR review of metoclopramide in 2018. Search terms included: "metoclopramide" AND "lactation" OR "breastfeeding." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal fertility studies have not been performed with Gimoti.

Clinical Experience

Applicant's Review of the Published Literature

The applicant did not perform a published literature search related to metoclopramide use and effects on fertility.

DPMH's Review of the Published Literature

Clinical experience data on metoclopramide use and potential effects on fertility was previously reviewed by DPMH in 2017 and 2018.[4,5] DPMH concluded the following:

> Publications identified during this review report on metoclopramide use in fertility, but do not report any specific fertility-related adverse reactions. Theoretically, metoclopramide elevates prolactin levels and this in turn suppresses hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. Suppressed hypothalamic GnRH can inhibit reproductive function by impairing gonadal steroidogenesis in both females and males of reproductive potential. Serum prolactin levels typically return to normal in 1 week and adverse effects typically resolve within a few weeks to months following metoclopramide administration. Metoclopramide does not cause an increase to major congenital malformations and miscarriage in humans; therefore, there are no recommendations for contraception and need for pregnancy testing. Labeling subsection 8.3, Females and Males of Reproductive Potential, will not be included in metoclopramide labeling.

This Reviewer performed a focused search in PubMed, Embase, and Reprotox[10] to find any relevant articles published since the most recent DPMH PLLR review of metoclopramide in 2018. Search terms included: "metoclopramide" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

DISCUSSION/CONCLUSIONS

Pregnancy

Pregnant women were excluded from Gimoti clinical trials. One pregnancy exposure was reported during the development program, for which Gimoti was immediately discontinued, with the outcome of a normal livebirth. This single pregnancy case is insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes with Gimoti use during pregnancy.

As discussed above, in 2017 and 2018 DPMH reviewed several large epidemiological studies (including retrospective cohorts, case-control, meta-analyses, and registry based studies) that do not report an association with metoclopramide use and major congenital malformations.[4,5] However, in the course of the current PLLR published literature search for Gimoti, DPMH identified a single retrospective cohort study (Berard 2019)[12] that found a possible association between metoclopramide exposure in the first trimester and an increased risk of major congenital malformations, including genital malformations. The DEPI/DB7 reviews of this study noted several methodological limitations that might explain the anomalous findings, including uncontrolled confounding and statistical variability without adjustments for multiple testing. Further, DPV's cumulative FAER's search for reports of major congenital malformations in fetuses with metoclopramide exposure identified 35 cases with no specific pattern of malformations.

DPMH, DEPI, and DG clinical discussed the above considerations at the May 4, 2020 labeling meeting for Gimoti. DPMH concludes that overall the available data based on published observational studies and several decades of postmarketing experience with metoclopramide use in pregnant women do not suggest a drug-associated increased risk in major congenital malformations, miscarriage, or adverse maternal or fetal outcomes. The additional study by Berard suggests a possible association, however, considering the methodological limitations and the lack of similar findings among available clinical data (both literature and FAERS pharmacovigilance reports), DPMH recommends maintaining the language in Gimoti labeling subsection 8.1 Pregnancy consistent with other metoclopramide product labelings. If additional clinical data becomes available that demonstrates similar findings as the Berard study, consideration should be given to the addition of a human data section to metoclopramide product labeling that describes the large published epidemiology studies along with their limitations in a balanced manner.

DPMH also recommends including the following Clinical Consideration, which is consistent with PLLR labeling for Reglan: "metoclopramide crosses the placental barrier and may cause extrapyramidal signs and methemoglobinemia in neonates with maternal administration during delivery. Monitor neonates for extrapyramidal signs."

Lactation

Clinical lactation studies have not been performed with Gimoti and lactating women were excluded from clinical trials during the development program. There are no available data on the presence of metoclopramide in human milk following nasal administration. However, pharmacokinetic studies indicate the bioavailability of the nasal administration of Gimoti 15 mg is comparable to the oral administration of the metoclopramide 10 mg tablet. Therefore, DPMH recommends Gimoti subsection 8.2 labeling that is consistent with currently approved PLLR labeling for Reglan, the listed drug relied upon.

Fertility

DPMH recommends omitting subsection 8.3 of Gimoti labeling. DPMH did not identify any data to suggest metoclopramide use has an adverse effect on fertility. Pregnancy testing and contraception headings will not be included because the available human data

over decades of use of metoclopramide overall do not suggest an increased risk of major congenital malformations or miscarriage.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 in Gimoti labeling for compliance with the PLLR (see below). DPMH discussed the labeling recommendations below with DG on May 4, 2020. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Gimoti Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Published studies, including retrospective cohort studies, national registry studies, and meta-analyses, do not report a consistent pattern or consistently increased risk of adverse pregnancy-related outcomes with oral use of metoclopramide during pregnancy. However, available data from case reports of Gimoti use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are potential risks to the neonate following exposure *in utero* to metoclopramide during delivery *(see Clinical Considerations).* In animal reproduction studies, no adverse developmental effects were observed with oral administration of metoclopramide to pregnant rats and rabbits at exposures about 6 and 12 times the maximum recommended human dose (MRHD) *(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 to 4% and 15 to 20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Metoclopramide crosses the placental barrier and may cause extrapyramidal signs and methemoglobinemia in neonates with maternal administration during delivery. Monitor neonates for extrapyramidal signs *[see Warnings and Precautions (5.1, 5.2), Use in Specific Populations (8.4)]*.

Data
Animal Data
Reproduction studies have been performed following administration of oral metoclopramide during organogenesis in pregnant rats at about 6 times the MRHD calculated on body surface area and in pregnant rabbits at about 12 times the MRHD calculated on body surface area. No evidence of adverse developmental effects due to metoclopramide were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of metoclopramide in human milk following nasal administration. Systemic exposure following nasal administration is expected to be similar to oral administration. Limited published data report the presence of metoclopramide in human milk in variable amounts following oral administration *(see Data)*. Breastfed infants exposed to metoclopramide have experienced gastrointestinal adverse reactions, including intestinal discomfort and increased intestinal gas formation. Metoclopramide elevates prolactin levels *[see Warnings and Precautions (5.7)]*; however, the published data are not adequate to support drug effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Gimoti and any potential adverse effects on the breastfed child from Gimoti or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding neonates because metoclopramide may cause extrapyramidal signs (dystonias) and methemoglobinemia *[see Warnings and Precautions (5.1, 5.2), Use in Specific Populations (8.4)]*.

Data

In published clinical studies, the estimated amount of metoclopramide received by the breastfed infant was less than 10 percent of the maternal weight-adjusted dose. In one study, the estimated daily amount of metoclopramide received by infants from breast milk ranged from 6 to 24 mcg/kg/day in early puerperium (3 to 9 days postpartum) and from 1 to 13 mcg/kg/day at 8 to 12 weeks postpartum.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KRISTIE W BAISDEN
05/15/2020 05:00:50 PM

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LYNNE P YAO
05/19/2020 03:31:08 PM

U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum
Version: 2018-01-24

Date:	May 14, 2020
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Team Leader:	Catherine L. Callahan, PhD MA Division of Epidemiology I
Deputy Division Director:	CAPT. Sukhminder K. Sandhu, PhD MPH MS, Title Division of Epidemiology I
Subject:	ARIA Sufficiency Assessment
Drug Name(s):	metoclopramide nasal spray (Gimoti™)
Application Type/Number:	NDA 209388
Submission Number:	Resubmission/Class 2 (eCTD 0027; December 19, 2019)
Applicant/sponsor:	Evoke Pharma
OSE RCM #:	2020-192

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	X
-No	
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 209388 seeks FDA approval for Gimoti™ (metoclopramide nasal spray), a new formulation for a drug initially approved by FDA in 1979. This Memorandum addresses DA Active Risk Identification and Analysis (ARIA) System capabilities with respect to post-market assessment of certain neurologic adverse reactions in patients using metoclopramide nasal spray for diabetic gastroparesis.

Metoclopramide (a dopamine-2 receptor antagonist) relieves diabetic gastroparesis by promoting gastric motility.[1] However, inhibition by metoclopramide of dopamine-2 receptors in the central nervous system (CNS) also causes adverse neurologic reactions that include drowsiness, fatigue, lethargy, and extrapyramidal symptoms, such as acute dystonic reactions, akathisia, neuroleptic malignant syndrome (fever, muscle rigidity, confusion, and autonomic instability), and parkinsonism (bradykinesia, tremor, and rigidity).[2] In common with other inhibitors of dopamine-2 action (*e.g.*, first and second generation antipsychotic drugs), metoclopramide (when used chronically) can lead to tardive dyskinesia (TD).[3] In ebruary 2009, DA required a Boxed Warning for TD in metoclopramide labels and a Medication uide discussing TD risk.[4] The Boxed Warning advises prescribers to "avoid treatment with metoclopramide for longer than 12 weeks because of the risk of developing TD with longer-term use."[5] TD risk factors in addition of long duration use of dopamine-2 receptor antagonists include older age and female sex.

1.2. Describe the Safety Concern

actors generating concern about the CNS safety of metoclopramide nasal spray include:

- Substantial limitations to the imoti ™ safety database (characterized by small and uncontrolled studies of short duration), which precludes meaningful assessment of possible TD risk from metoclopramide when administered by nasal route.

- Theoretical potential for increased CNS risk possibly mediated through "direct [drug]

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[1] Diabetic gastroparesis – a clinical syndrome defined by specific symptoms (*e.g.*, nausea, vomiting, upper abdominal pain, early satiety, abdominal fullness, and bloating) and objective evidence of delayed gastric emptying in diabetic patients without evidence for mechanical obstruction to the gastric outlet.

[2] Lee A, Kuo B. Metoclopramide in the treatment of diabetic gastroparesis. Expert Rev Endocrinol Metab 2010;5:653-62.

[3] Tardive dyskinesia – a disabling and usually irreversible neurologic syndrome characterized by repetitive movements of the limbs, lip smacking, grimacing, tongue protrusion, rapid movement or blinking of the eyes, puckering or pursing of the lips, and impaired dexterity of the fingers.

[4] FDA, February 26, 2009, FDA Requires Boxed Warning and Risk Mitigation Strategy for Metoclopramide-Containing Drugs, accessed at https://wayback.archive-it.org/7993/20170112033201/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149533.htm on March 25, 2020.

[5] Prescribing Information for GIMOTI™ (metoclopramide nasal spray), submitted to NDA 209388 (eCTD 0027) on December 19, 2019.

access to the CNS via cribriform plate transfer/nerve pathways."[6]

After assessing the evidence currently available, the OND Division of Gastroenterology (DG) affirmed a "weak index of suspicion" for causal association between intranasal metoclopramide and increased risk (relative to oral metoclopramide) for serious adverse CNS reactions.[7]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

1.4. Statement of Purpose

FDA's Boxed Warning identifies metoclopramide-associated TD as a known serious risk. However, available evidence identifies only a theoretical potential for increased TD risk specifically related to administration by intranasal route. This theoretical concern justifies post-market monitoring (simple monitoring for signal detection) for TD and related serious adverse CNS reactions in diabetic adults treated with metoclopramide nasal spray for symptoms typically associated with gastroparesis.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Limited data exist about TD incidence in patients treated with metoclopramide for diabetic gastroparesis.[8] (Using data provided by a health insurance company serving employees of the Church of Jesus Christ of Latter-day Saints, Merrill, *et al.*, estimated cumulative risk at <1% in patients prescribed metoclopramide for any reason.[9]) TD risk might approach 15% in high-risk groups.[10]

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Monitoring for incident TD and related serious adverse CNS reactions requires an adult diabetic population without (1) exposure to antipsychotic drugs or (2) pre-existing evidence for TD, neuroleptic malignant syndrome, parkinsonism, or Parkinson's disease (medical encounter for ICD-10 G20 or pharmacy dispensing for an anti-Parkinson drug, ATC N04).

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[6] Division of Gastroenterology and Inborn Errors Products, January 11, 2018, Briefing Memorandum for Gimoti (metoclopramide) Intranasal Spray, distributed to Members of the Safety Outcome Trial (SOT) Subcommittee.

[7] Meeting preliminary to a Signal Assessment Meeting (SAM), February 21, 2020, participants included Jacqueline Puigbo (Acting Team Leader, DEPI-I), Joel Weissfeld (Medical Officer, DEPI-I), Juli Tomaino (Team Leader, DG), and Sandhya Apparaju (Safety Analyst, DG).

[8] Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther 2010;31:11-9.

[9] Merrill RM, Lyon JL, Matiaco PM. Tardive and spontaneous dyskinesia incidence in the general population. BMC Psychiatry 2013;13:152.

[10] Lee, *op. cit.*

2.2 Is ARIA sufficient to assess the intended population?

Yes. Diagnosis codes in the Sentinel Distributed Database (SDD) permit identification of diabetics (with or without gastroparesis). Published validation studies demonstrate the usefulness of diagnosis codes for diabetes surveillance in electronic healthcare databases.[11] Table 1 shows ICD-9 codes (along with ICD-10 translations) previously used in the Division of Epidemiology (DEPI) to identify diabetic patients for a metoclopramide drug-use analysis in SDD.[12] This DEPI drug-use analysis identified gastroparesis with ICD-9 536.3 (ICD-10 K31.84). Drug dispensing codes in SDD permit identification of patients with concomitant exposure to antipsychotic drugs (a dominant cause for TD).

Table 1: Candidate diagnosis codes for diabetes.

ICD-9	ICD-9 Description	ICD-10	ICD-10 Description
250.00	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled	E119	Type 2 diabetes mellitus without complications
250.10	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled	E1110	Type 2 diabetes mellitus with ketoacidosis without coma
250.20	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled	E1100	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
250.30	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled	E1111	Type 2 diabetes mellitus with ketoacidosis with coma
250.40	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled	E1129	Type 2 diabetes mellitus with other diabetic kidney complication
250.50	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled	E11311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
250.60	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled	E1140	Type 2 diabetes mellitus with diabetic neuropathy, unspecified

[11] Khokhar B, Jette N, Metcalfe A, et al. Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations. BMJ Open 2016;6:e009952.

Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. Diabetes Res Clin Pract 2010;89:189-95.

de Burgos-Lunar C, Salinero-Fort MA, Cardenas-Valladolid J, et al. Validation of diabetes mellitus and hypertension diagnosis in computerized medical records in primary health care. BMC Med Res Methodol 2011;11:146.

[12] Bright, PL, and W Hua, Metoclopramide Utilization in the Sentinel Distributed Database, filed under NDA 209388 on March 7, 2019 (DARRTS Reference ID: 4400491).

ICD-9	ICD-9 Description	ICD-10	ICD-10 Description
250.70	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled	E1151	Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene
250.80	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled	E11618	Type 2 diabetes mellitus with other diabetic arthropathy
250.90	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled	E118	Type 2 diabetes mellitus with unspecified complications
250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled	E1165	Type 2 diabetes mellitus with hyperglycemia
250.12	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled	E1110	Type 2 diabetes mellitus with ketoacidosis without coma
250.22	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled	E1100	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
250.32	Diabetes with other coma, type II or unspecified type, uncontrolled	E1101	Type 2 diabetes mellitus with hyperosmolarity with coma
250.42	Diabetes with renal manifestations, type II or unspecified type, uncontrolled	E1121	Type 2 diabetes mellitus with diabetic nephropathy
250.52	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled	E11311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
250.62	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled	E1140	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
250.72	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled	E1151	Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene
250.82	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled	E1165	Type 2 diabetes mellitus with hyperglycemia
250.92	Diabetes with unspecified complication, type II or unspecified type, uncontrolled	E1165	Type 2 diabetes mellitus with hyperglycemia

3 EXPOSURES

3.1 Exposures of Interest

The unexpected serious risk pertains to metoclopramide-associated TD and related adverse CNS reactions specifically due to imoti ™ (metoclopramide intranasal spray).

3.2 Is ARIA sufficient to identify the exposure of interest?

Yes. Outpatient drug dispensing codes (National Drug Codes, NDCs) in SDD provide specific information about routes of administration. Appendix 3 in DEPI's drug-use analysis presents NDCs available for oral metoclopramide formulations (tablet, solution, and disintegrating tablet).[13] DEPI expects assignment of new NDCs for Gimoti™ upon FDA approval for the U.S. market.

An earlier drug-use analysis provides partial information about the size of the metoclopramide-exposed population in SDD.[14] This analysis (conducted over a 10-year timeframe) identified 839,609 episodes of metoclopramide treatment in N=502,877 ≥40-year-old non-pregnant women with diabetes (Table 2).

Table 2: Episodes of metoclopramide treatment for ≥40-year-old non-pregnantG women in the Sentinel Distributed Database (January 2008 through DecemberG 2015; [1]).G

Episodes of Treatment with Metoclopramide [2]	All Patients (N=1,436,794)	Diabetes (N=502,877)	Diabetes and astroparesi s (N=52,937)
Episodes, Total	2,163,033	839,609	116,829
Episodes ≥84 daysG	150,356 (7.0%)	80,742 (9.6%)	17,701 (15.2%)

SOURCE: Tables 3a-3c and Tables 11a-11c in Sentinel Report for Metoclopramide Use amongG Diabetic Gastroparesis and Diabetic Patients (QF-1366), accessed at Sentinel Query PortalG asG Final_Sentinel_Report_cder_mpl1r_wp089_nsdp_v01_ND_SCCsuppression_Final.xlsx on April 3, 2020.G

FOOTNOTES:G

1. Requiring continuous pre-treatment 365-day medical and drug enrollment with 45-dayG gaps in allowed.
2. Treatment episodes defined by dispensing or procedure codes for oral or injectableG metoclopramide, 365-day exposure washout (new-user criterion), and treatment gapsG bridged by 50% of days supplied by preceding dispensing.G

4 OUTCOME(S)

4.1 Outcomes of Interest

Serious and often severe outcomes of interest include (1) tardive dyskinesia, (2) drug-induced dystonia, (3) malignant neuroleptic syndrome, and (4) drug-induced parkinsonism.

4.2 Is ARIA sufficient to assess the outcome of interest?

Yes. For monitoring (signal detection) purposes, diagnosis codes in SDD provide sufficient means for identifying TD and related serious adverse CNS reactions. Table 3 shows candidate ICD-10 diagnosis codes (specific and non-specific) for the outcomes of interest. An appendix to this Memorandum lists all ICD-10 diagnosis codes available for extrapyramidal and movement disorders (Appendix Table 1) and abnormal involuntary movements (Appendix Table 2).

DEPI conducted a rapid literature search that identified no reports about the validity of diagnosis codes for TD. However, investigators have used ICD-9 or ICD-10 diagnosis codes to

[13] Bright, *op. cit.*, Appendix 3, pp. 19-25.

[14] Bright, *op. cit.*

study TD and related conditions in electronic healthcare databases. or example,

- Merrill, *et al.*, defined (in a general patient population) TD, spontaneous dyskinesia, and dystonia by ICD-9 333.81 (Blepharospasm), 333.82 (Orofacial dyskinesia), 333.83 (Spasmodic torticollis), 333.84 (Organic writers' cramp), 333.85 (Subacute dyskinesia due to drugs), and 333.89 (Other fragments of torsion dystonia).[15]

- Patterson-Lomba, *et al.*, defined TD (in Medicaid patients with psychotic disorders) by ICD-9 333.81 (Blepharospasm), 333.82 (Orofacial dyskinesia), and 333.85 (Subacute dyskinesia due to drugs or ICD-10 24.01 (Drug induced subacute dyskinesia), 24. 4 (Idiopathic orofacial dystonia), and 24.5 (Blepharospasm).[16]

- Patel, *et al.*, defined TD (psychiatric inpatients in the Healthcare Cost and Utilization Project Nationwide Inpatient Sample) by specific ICD-9 diagnosis code 333.85 (Subacute dyskinesia due to drugs) and non-specific ICD-9 diagnosis codes 333.81 (Blepharospasm), 333.82 (Orofacial dyskinesia), 333.99 (Other extrapyramidal disease and abnormal movement disorder), 307.3 (Stereotypic movement disorder), 307.20 (Tic disorder, unspecified), 333.71 (Athetoid cerebral palsy), 351.8 (Other facial nerve disorders), and 781.0 (Abnormal involuntary movements).[17]

As suggested in Table 3, post-market monitoring in SDD might bound risk estimates for TD and related conditions by conducting separately (1) analysis with specific diagnosis codes and (2) analysis with combinations of specific and non-specific diagnosis codes. Controlled (comparative) analyses (if necessary) might infer confidence in the accuracy (positive predictive value) of TD outcome definitions by requiring (post metoclopramide exposure) (1) ≥2 medical encounters on different dates with TD-related codes or (2) ≥1 medical encounter with TD-related code and ≥1 pharmacy dispensing for a TD-specific drug treatment (*i.e.*, deutetrabenazine or valbenazine).

Table 3: Candidate ICD-10 diagnosis codes for outcomes of interest.

ICD-10	ICD-10 Description
Specific codes for tardive dyskinesia and drug-induced dystonia	
24.01	Drug induced subacute dyskinesia
24.02	Drug induced acute dystonia
24.09	Other drug induced dystonia
Specific code for malignant neuroleptic syndrome	
21.0	Malignant neuroleptic syndrome
Specific codes for drug-induced parkinsonism	
21.11	Neuroleptic induced parkinsonism
21.19	Other drug induced secondary parkinsonism
Possible non-specific codes for outcomes of interest	
21.9	Secondary parkinsonism, unspecified

[15] Merrill, *op. cit.*, p. 2.

[16] Patterson-Lomba O, Ayyagari R, Carroll B. Risk assessment and prediction of TD incidence in psychiatric patients taking concomitant antipsychotics: a retrospective data analysis. BMC Neurol 2019;19:174, p. 2.

[17] Patel RS, Mansuri Z, Chopra A. Analysis of risk factors and outcomes in psychiatric inpatients with tardive dyskinesia: A nationwide case-control study. Heliyon 2019;5:e01745, p. 2.

ICD-10	ICD-10 Description
24.3	Spasmodic torticollis
24.4	Idiopathic orofacial dystonia
G24.5	Blepharospasm
24.9	Dystonia, unspecified
25.70	Drug induced movement disorder, unspecified
25.71	Drug induced akathisia
25.79	Other drug induced movement disorders
25.9	Extrapyramidal and movement disorder, unspecified

5 COVARIATES

5.1 Covariates of Interest

Critical covariates include SDD Data Partner (DP), sex, age, index year, psychiatric comorbidity, and possibly pre-index use of a different metoclopramide formulation.

5.2 Is ARIA sufficient to assess the covariates of interest?

Yes. ARIA provides highly reliable means for defining DP, sex, age and index year in SDD. To adjust for psychiatric comorbidity, ARIA permits stratified analysis by presence or absence of baseline evidence for psychiatric comorbidity (as indicated by pre-index medical encounters for mental illness or pharmacy dispensings for ATC N05 psycholeptics or ATC N06 psychoanaleptics). As indicated in Section 2.2, above, ARIA permits exclusion of patients with baseline (pre-index) evidence for antipsychotic exposure (ATC N05A). Likewise, ARIA permits follow-up truncated by first post-index antipsychotic exposure.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

Post-market monitoring (signal detection) might take two forms, (1) descriptive analysis in one patient cohort (adult diabetic patients identified by index pharmacy dispensing for metoclopramide nasal spray) or (2) sequential analysis comparing two patient cohorts (adult diabetic patients identified by index pharmacy dispensing for metoclopramide nasal spray *vs.* diabetic patients identified by index pharmacy dispensing for oral metoclopramide). The choice between these two approaches might depend on results from preliminary SDD analyses directed at the (1) magnitude of metoclopramide-nasal-spray use (drug update), (2) frequency of long-duration metoclopramide-nasal-spray use, and (3) frequency of TD-related outcomes during defined time periods after index exposures to metoclopramide nasal spray.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. or descriptive analysis, ARIA analytic tools permit multifactor covariate-stratified tabulation of patient counts, outcomes (patients with ≥1 event), and cumulative follow-up durations (patient-years) in flexibly defined patient cohorts. These tabulations permit calculations of cumulative risk and incidence. ARIA analytic tools also permit comparisons between propensity-score-matched cohorts with an option for analysis repeated sequentially over calendar time.

Appendix i gure 1 offers a graphical depiction of ARIA parameter settings for an SDD cohort analysis designed to estimate TD incidence after initiation of metoclopramide nasal spray.

Appendix igure 2 offers a graphical depiction of ARIA parameter settings for an SDD cohort analysis designed to estimate TD incidence after sustained use (at least 12 full weeks) of metoclopramide nasal spray.

Monitoring in SDD might begin with descriptive analyses of i moti™ use and proceed toG crudely or finely stratified risk analyses depending on Gimoti™ uptake (frequency and patternsG of use) and number of outcome events available. In addition to sex and age, factors for covariate control might include index year, SDD Data Partner, or pre-index use of a differentG metoclopramide formulation.

7 NEXT STEPS

OSE held a Signal Assessment Meeting (SAM) on May 8, 2020, to discuss safety concerns regarding Gimoti™ (metoclopramide nasal spray) and current capabilities for Active Risk Identification and Analysis (ARIA) in the Sentinel Distributed Database (SDD). The SAM reached agreement on the safety concern, regulatory need, and ARIA capabilities, as presented above and summarized below.

- A novel route of administration introduces the potential for excess TD risk from imoti™ (relative to other marketed metoclopramide products).

- This safety concern requires active post-market monitoring (signal detection) for TD and other related serious adverse CNS reactions in adults treated with metoclopramide nasal spray.

- ARIA provides sufficient capabilities for monitoring TD and other related serious adverse CNS reactions to metoclopramide in diabetic patients with or without gastroparesis.

Consequently, the SAM recommended post-market monitoring for metoclopramide-related TD and other related serious adverse CNS reactions by ARIA in SDD *in lieu* of a corresponding Section 505(o)(3) Post-Marketing Requirement (PMR) for Gimoti™ NDA 209388.

8 APPENDIX: ICD-10 DIAGNOSIS CODES

Appendix Table 1: Extrapyramidal and movement disorders.

ICD-10	ICD-10 Description
20	Parkinson's disease
21	Secondary parkinsonism
G21.0	Malignant neuroleptic syndrome
21.1	Other drug-induced secondary parkinsonism
21.11	Neuroleptic induced parkinsonism
21.19	Other drug induced secondary parkinsonism
21.2	Secondary parkinsonism due to other external agents
21.3	Postencephalitic parkinsonism
21.4	Vascular parkinsonism
21.8	Other secondary parkinsonism
21.9	Secondary parkinsonism, unspecified
23	Other degenerative diseases of basal ganglia
23.0	Hallervorden-Spatz disease
23.1	Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]
23.2	Striatonigral degeneration
23.8	Other specified degenerative diseases of basal ganglia
23.9	Degenerative disease of basal ganglia, unspecified
24	Dystonia
24.0	Drug induced dystonia
24.01	Drug induced subacute dyskinesia
24.02	Drug induced acute dystonia
24.09	Other drug induced dystonia
24.1	enetic torsion dystonia
24.2	Idiopathic nonfamilial dystonia
24.3	Spasmodic torticollis
24.4	Idiopathic orofacial dystonia
24.5	Blepharospasm
24.8	Other dystonia
24.9	Dystonia, unspecified
25	Other extrapyramidal and movement disorders
25.0	Essential tremor
25.1	Drug-induced tremor
25.2	Other specified forms of tremor
25.3	Myoclonus
25.4	Drug-induced chorea
25.5	Other chorea
25.6	Drug induced tics and other tics of organic origin
25.61	Drug induced tics
25.69	Other tics of organic origin
25.7	Other and unspecified drug induced movement disorders
25.70	Drug induced movement disorder, unspecified
25.71	Drug induced akathisia
25.79	Other drug induced movement disorders
25.8	Other specified extrapyramidal and movement disorders

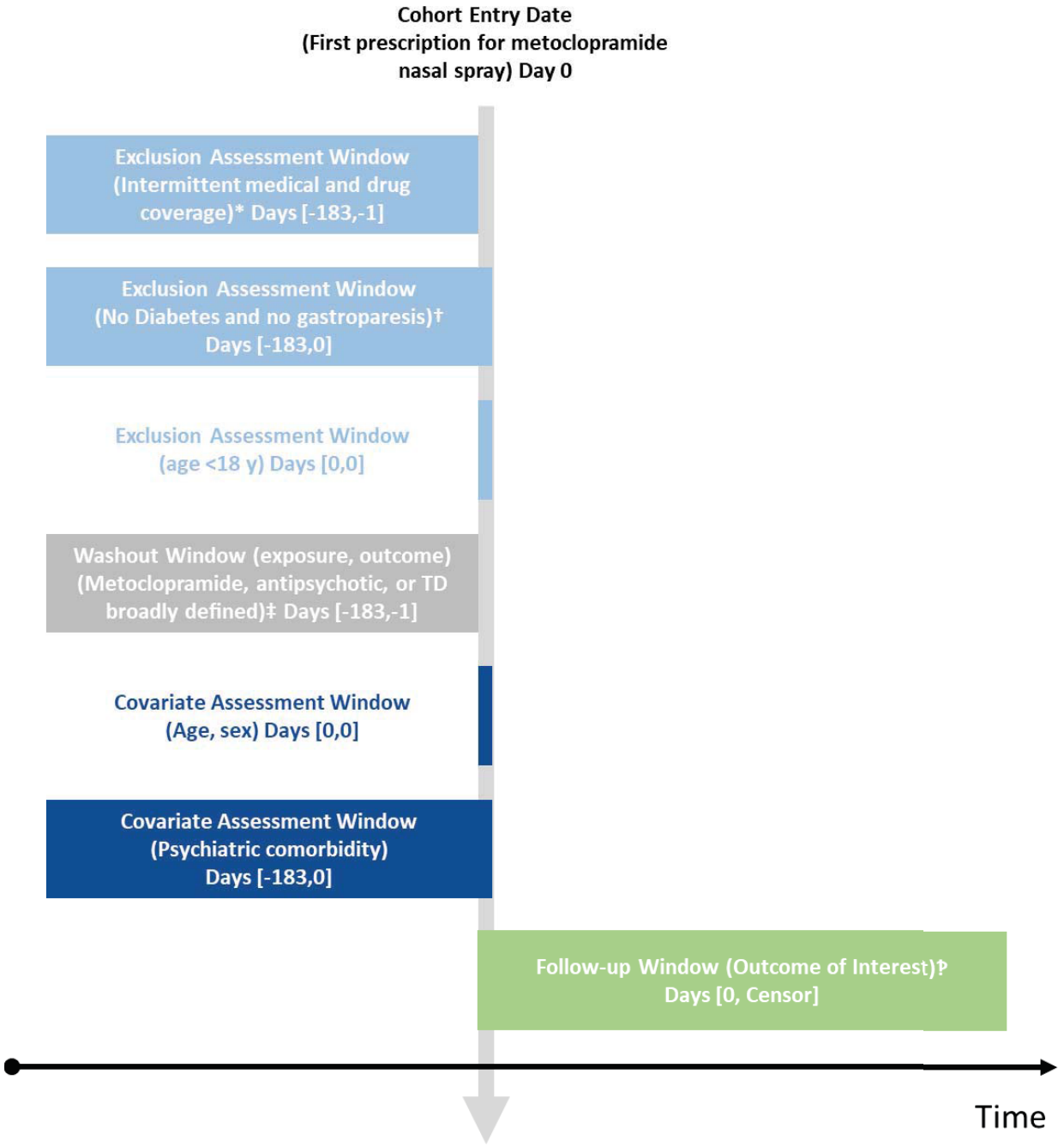
ICD-10	ICD-10 Description
25.81	Restless legs syndrome
25.82	Stiff-man syndrome
25.83	Benign shuddering attacks
25.89	Other specified extrapyramidal and movement disorders
G25.9	Extrapyramidal and movement disorder, unspecified
26	Extrapyramidal and movement disorders in diseases classified elsewhere

Appendix Table 2: Abnormal involuntary movements.

ICD-10	ICD-10 Description
R25	Abnormal involuntary movements
R25.0	Abnormal head movements
R25.1	Tremor, unspecified
R25.2	Cramp and spasm
R25.3	asciculation
R25.8	Other abnormal involuntary movements
R25.9	Unspecified abnormal involuntary movements

9 DESIGN DIAGRAMS

Appendix i gure 1: Graphical depiction of ARIA parameter settings for an SDD cohort analysis designed to estimate TD incidence after initiation of metoclopramide nasal spray.



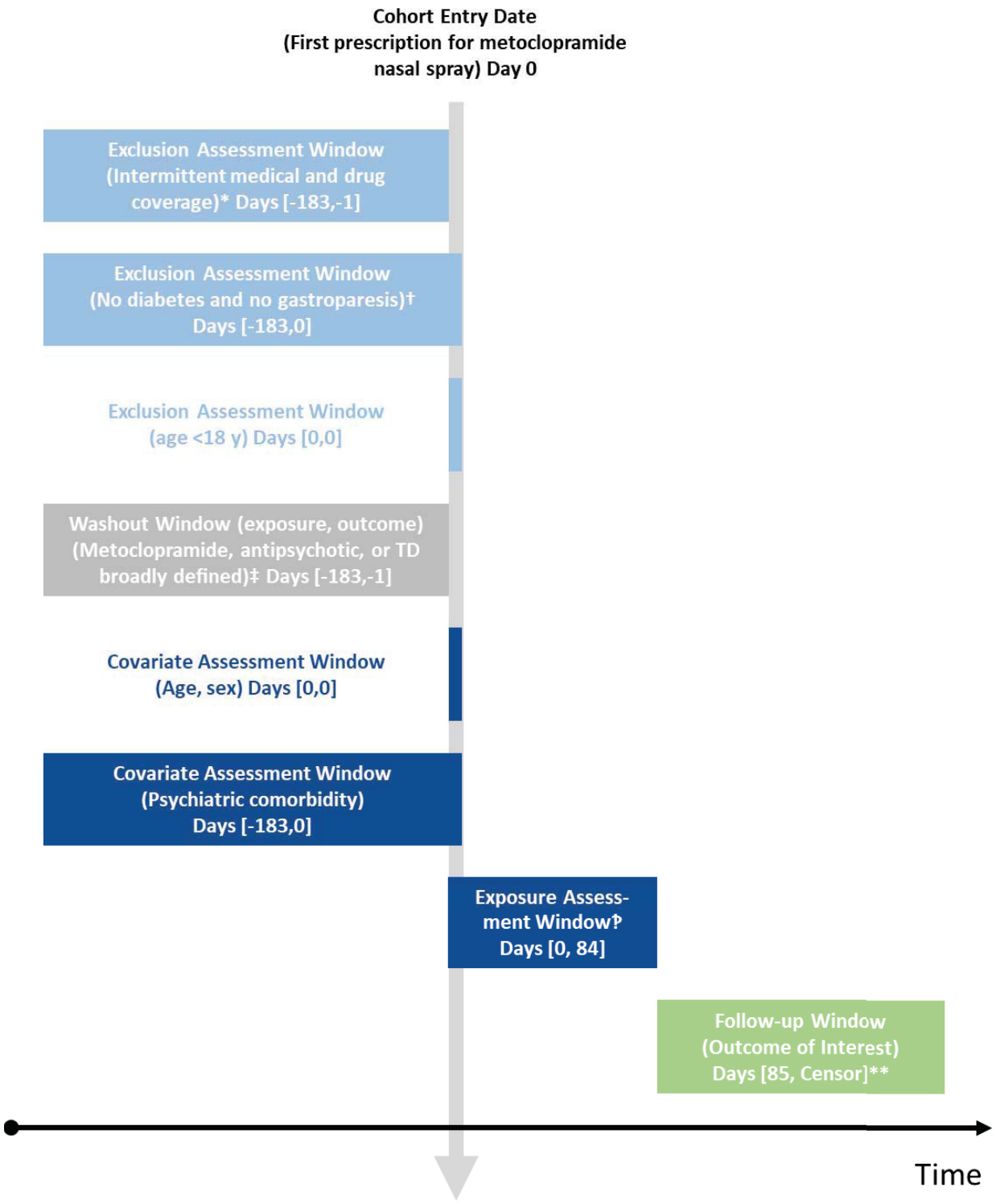
* 45-day gaps in medical harmacy enrollment allowed.

† Less restrictive analysis might include all diabetic patients (with or without gastroparesis).

‡ Pharmacy dispensing for metoclopramide nasal spray, pharmacy dispensing for an antipsychotic (ATC N05A), Parkinson's disease (medical encounter for Parkinson's disease, ICD-10 G20, or pharmacy dispensing for an anti-Parkinson drug, ATC N04), or tardive dyskinesia (TD) as defined by specific and non-specific diagnosis codes for the outcome of interest (Table 3). Supplementary analyses might defineG exposure washout by pharmacy dispensing for intranasal or oral metoclopramide formulation.G

? Follow-up truncated on occurrence of the outcome of interest (Table 3), pharmacy dispensing for an antipsychotic (ATC N05A), death, disenrollment, day 365, or end of study period. Supplementary analyses might truncate follow-up on prescription dispensing for oral metoclopramide.

Appendix i gure 2: Graphical depiction of ARIA parameter settings for an SDD cohort analysis designed to estimate TD incidence after sustained use (at least 12 full weeks) of metoclopramide nasal spray.



* 45-day gaps in medical harmacy enrollment allowed.
† Less restrictive analysis might include all diabetic patients (with or without gastroparesis).

‡ Pharmacy dispensing for metoclopramide nasal spray, pharmacy dispensing for an antipsychotic (ATC N05A), Parkinson's disease (medical encounter for Parkinson's disease, ICD-10 G20, or pharmacy dispensing for an anti-Parkinson drug, ATC N04), or tardive dyskinesia (TD) as defined by specific and non-specific diagnosis codes for the outcome of interest (Table 3). Supplementary analyses might define exposure washout by pharmacy dispensing for intranasal or oral metoclopramide formulation.

? Pharmacy dispensings on days 0 through 84 that provide 84 total days of treatment with metoclopramide nasal spray.

** Follow-up truncated on occurrence of the outcome of interest (Table 3), pharmacy dispensing for an antipsychotic (ATC N05A), death, disenrollment, day 365, or end of study period. Supplementary analyses might truncate follow-up on prescription dispensing for oral metoclopramide.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOEL L WEISSFELD
05/14/2020 11:04:23 AM

CATHERINE L CALLAHAN
05/14/2020 11:08:24 AM

SUKHMINDER K SANDHU
05/14/2020 11:10:30 AM

JUDITH W ZANDER
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MICHAEL D NGUYEN
05/14/2020 11:50:11 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	May 13, 2020
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 209388
Product Name and Strength:	Gimoti (metoclopramide) nasal spray, 15 mg per spray
Applicant/Sponsor Name:	Evoke Pharma, Inc
OSE RCM #:	2018-1162-2
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 11, 2020 for Gimoti. We review the revised container label and carton labeling for Gimoti (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective.

3 RECOMMENDATIONS FOR EVOKE PHARMA, INC

We recommend the following be implemented prior to approval of this NDA:

A. Container Label
   a. The "Rx only" statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. Add the "Rx only" statement.
B. Carton Labeling

[a] Vee S. Label and Labeling Review for Gimoti (NDA 209388). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 07. RCM No.: 2018-1162-1.

a. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)" to read "Recommended Dosage: See prescribing information.".
b. For clarity, revise the abbreviation "mcL" on the side panel to "microliter".

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
05/13/2020 12:43:36 PM

ASHLEIGH V LOWERY
05/13/2020 02:58:05 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Office of Pharmacovigilance and Epidemiology Integrated Review

Date:	May 5, 2020
Reviewers:	Joel L. Weissfeld, MD, MPH Medical Officer Division of Epidemiology I
	Michelle Hines, PharmD Safety Evaluator Division of Pharmacovigilance I
	Ivone Kim, MD Medical Officer Division of Pharmacovigilance I
Team Leaders:	Carmen Cheng, PharmD Team Leader Division of Pharmacovigilance I
	Jacqueline Puigbo, PhD Epidemiologist Division of Epidemiology I
Division Directors:	CAPT. Sukhminder K. Sandhu, PhD, MPH, MS Deputy Division Director Division of Epidemiology I
	CDR Monica Muñoz, PharmD, PhD Deputy Division Director Division of Pharmacovigilance I
Subject:	Major Congenital Malformations
Drug Name:	Metoclopramide (Gimoti®)
Application Type/Number:	NDA 209388
Applicant:	Evoke Pharma, Inc.
OSE RCM #:	2020-448

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Responding to a request from the Division of Pediatric and Maternal Health (DPMH), the Office of Pharmacovigilance and Epidemiology (OPE) assessed medical literature and adverse event reports for evidence of major congenital malformation (MCM) as a consequence of prenatal exposure to metoclopramide.

Metoclopramide is a dopamine-2 receptor antagonist currently approved by FDA for gastro-esophageal reflux and diabetic gastroparesis. Physicians sometimes prescribe metoclopramide (off-label) for nausea and vomiting of pregnancy.

During review of NDA 209388 for metoclopramide nasal spray (Gimoti®), DPMH identified a recently published article (**Bérard 2019**) presenting evidence for possible association between metoclopramide use during pregnancy and occurrence of MCM in liveborn offspring.

Consequently, DPMH requested,

- An OPE Division of Epidemiology I (DEPI) assessment of **Bérard 2019** and two other published reports from observational studies of pregnancy and infant outcomes after exposure to metoclopramide during pregnancy (**Matok 2009** and **Pasternak 2013**).
- An OPE Division of Pharmacovigilance I (DPV) search in the FDA Adverse Event Reporting System (FAERS) for cases of MCM associated with exposure to metoclopramide during pregnancy.

DPV identified FAERS cases of MCM with maternal metoclopramide exposure during pregnancy; however, we cannot exclude the role of other factors such as genetics or concomitant substance exposures in the development of malformations. DPV's assessment of risk factors and trend among cases in the FAERS database of MCM with maternal metoclopramide exposure during pregnancy was largely limited by lack of information included in the cases.

Bérard 2019 reported statistically significant association between *in utero* first-trimester exposure to metoclopramide and MCM in singleton liveborn infants (adjusted Odds Ratio, OR, 1.27, 95% Confidence Interval, CI, 1.03-1.57). By comparison, the other investigators reported statistically non-significant associations between metoclopramide and MCM (**Matok 2009**: OR 1.04, 95% CI 0.89-1.21; **Pasternak 2013**: OR 0.93, 95% CI 0.86-1.02).

OPE noted an ongoing effort directed by DPMH to obtain more information about **Bérard 2019** through direct communication with the study investigators.

DEPI determined that confounding occurring as a consequence of missing design and statistical controls for geographic location and calendar time might explain the anomalous association reported by **Bérard 2019**. DEPI determined that **Pasternak 2013** used superior methods for covariate control.

OPE recommended that DPMH balance questionable results from **Bérard 2019** against perhaps more credible results from **Pasternak 2013**.

1 INTRODUCTION

Responding to a request from the Division of Pediatric and Maternal Health (DPMH), the Office of Pharmacovigilance and Epidemiology (OPE) assessed medical literature and adverse event reports for evidence of major congenital malformation (MCM) as a consequence of prenatal exposure to metoclopramide.

MCMs are structural changes present at birth that have significant medical, social, or cosmetic consequences for the affected individual and typically require medical intervention; in contrast, minor congenital malformations pose no significant health problem in the neonatal period [1]. Consequently, congenital malformation surveillance efforts focus largely on MCM. Most congenital malformations occur during the first trimester of pregnancy; however, some occur later [2]. Congenital malformations can be caused by genetic, behavioral, or environmental factors or exposures, including certain prescription drugs.

Metoclopramide is a dopamine-2 receptor antagonist currently approved by FDA for gastroesophageal reflux and diabetic gastroparesis. Despite limited evidence for efficacy [3], physicians sometimes prescribe metoclopramide (off-label) for nausea and vomiting of pregnancy. FDA prescribing information for metoclopramide (Reglan®) indicates that "published studies, including retrospective cohort studies, national registry studies, and meta-analyses, do not report an increased risk of adverse pregnancy-related outcomes with use of metoclopramide during pregnancy."[a]

During review of NDA 209388 for metoclopramide nasal spray (Gimoti®), DPMH identified a recently published article presenting "new evidence over the risk of birth defects" from medications (including metoclopramide) for nausea and vomiting of pregnancy (**Bérard 2019** [4]).

Consequently, DMPH requested,

- An OPE Division of Epidemiology I (DEPI) assessment of **Bérard 2019** [4] and two other published reports from observational studies of pregnancy and infant outcomes after exposure to metoclopramide during pregnancy (**Matok 2009** [5] and **Pasternak 2013** [6]).
- An OPE Division of Pharmacovigilance I (DPV) search in the FDA Adverse Event Reporting System (FAERS) for cases of MCM associated with exposure to metoclopramide during pregnancy.

[a] Prescribing Information for REGLAN® (metoclopramide) tablets, accessed at Drugs@FDA on April 23, 2020.

2 METHODS AND MATERIALS

2.1 FAERS

2.1.1 Case Selection Criteria

Because the signal of MCM with maternal metoclopramide exposure during pregnancy was identified in the **Bérard 2019** [4] study, DPV aimed to provide a high-level overview of all postmarketing reports of MCM that had maternal metoclopramide exposure during pregnancy. We did not adjudicate reports for causal association with metoclopramide.

2.1.2 FAERS Search Strategy

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*

	Search 1	**Search 2**
Date of search	March 9, 2020	
Time period of search	All reports through March 8, 2020	
Search type	Quick Query	
Product Active Ingredients	Metoclopramide Metoclopramide hydrochloride Metoclopramide hydrochloride anhydrous	
MedDRA search terms (Version 22.0)	All terms included	System Organ Class: Congenital, familial and genetic disorders
Serious outcome	Congenital anomaly	All outcomes included

* See **Appendix A** for a description of the FAERS database.
MedDRA-Medical Dictionary for Regulatory Activities

2.2 LITERATURE REVIEW

DPMH asked DEPI to review three articles:

- Bérard A, Sheehy O, Gorgui J, Zhao JP, Soares de Moura C, Bernatsky S. New evidence for concern over the risk of birth defects from medications for nausea and vomitting of pregnancy. J Clin Epidemiol. 2019 Dec;116:39-48.
- Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med. 2009 Jun 11;360(24):2528-35.
- Pasternak B, Svanstrom H, Molgaard-Nielsen D, Melbye M, Hviid A. Metoclopramide in pregnancy and risk of major congenital malformations and fetal death. JAMA. 2013 Oct 16;310(15):1601-11.

DPMH identified **Bérard 2019** [4] as the evidence source of primary interest and concern. Consequently, DEPI used special formats (narrative and tabular) to present results from **Bérard 2019** [4]. DEPI used an alternative narrative format to present results from the two secondary evidence sources, **Matok 2009** [5] and **Pasternak 2013** [6]**.**

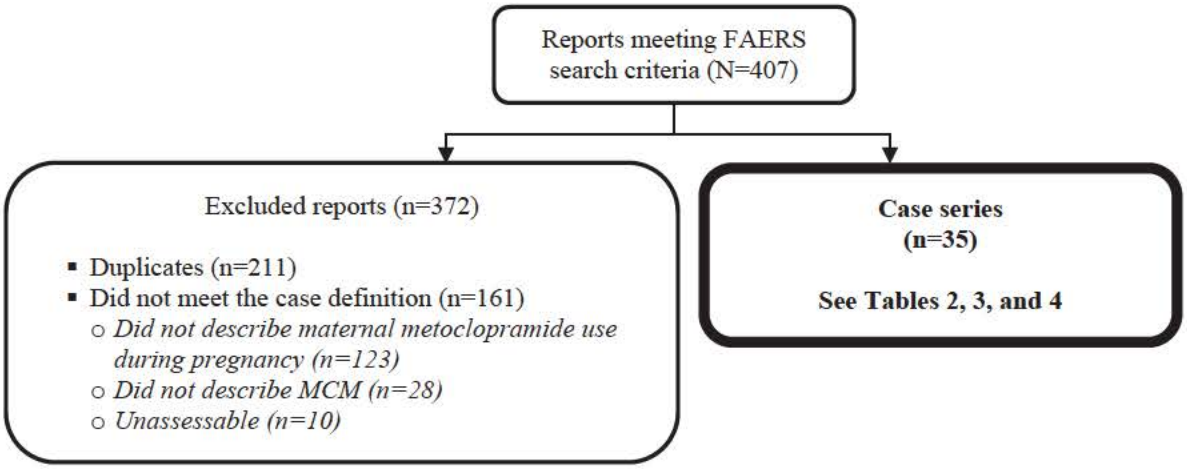
3 RESULTS

3.1 FAERS DATABASE RESULTS

3.1.1 FAERS Case Selection

DPV retrieved 407 reports from the FAERS searches described in **Table 1** (Search 1, n=151 reports; Search 2, n=256 reports). After accounting for duplicate reports and applying the case selection criteria in Section 2.1.1, we included 35 cases in the case series of MCM with maternal metoclopramide exposure during pregnancy (see **Figure 1**).

Figure 1. FAERS Case Selection



3.1.2 Summary of FAERS Cases

Appendix B contains line listings for FAERS cases included in the case series of MCM with maternal metoclopramide exposure during pregnancy. **Table 2** displays descriptive characteristics for cases included in the case series, including information about metoclopramide dose, week/trimester of pregnancy of metoclopramide initiation, and duration of use.

Table 2. Descriptive Characteristics of Cases of Major Congenital Malformation With Maternal Metoclopramide Exposure During Pregnancy, Received by FDA Through March 8, 2020 (N=35)	
Country	Foreign (22) United States (13)
Serious outcome(s)*	Congenital anomaly (32) Other serious outcome (13) Hospitalization (9) Life-threatening (4) Death (3) Disability (3)
Metoclopramide indication	Nausea or vomiting of pregnancy (7) Hyperemesis gravidarum (4)

Table 2. Descriptive Characteristics of Cases of Major Congenital Malformation With Maternal Metoclopramide Exposure During Pregnancy, Received by FDA Through March 8, 2020 (N=35)	
	Gastroenteritis (1) Indigestion (1) Migraine (1) Paralytic ileus (1) Not reported (20)
Metoclopramide total daily dose†	5 milligrams (mg) (1) 10 mg (4) 15 mg (1) 20 mg (1) 30 mg (2) 40 mg (1) Not reported (25)
Metoclopramide taken as needed or scheduled†	Scheduled (7) As needed (3) Not reported (25)
Gestational age at metoclopramide initiation	5 weeks (1) 6 weeks (2) 7 weeks (2) 8 weeks (2) 9 weeks (1) Not reported (27)
Pregnancy trimester at metoclopramide initiation	1st trimester (13) 2nd trimester (3) Not reported (19)
Duration of metoclopramide exposure during pregnancy	1st trimester only (9) 2nd trimester only (2) 1st and 2nd trimesters (1) 2nd and 3rd trimesters (1) Not reported (22)

* A serious adverse drug experience per regulatory definition (CFR 314.80) includes outcomes of: death, life-threatening, hospitalization, disability, congenital anomaly, or other serious important medical events. A case can have one or more outcomes.
† As prescribed, or as taken by patient if provided in case

Table 3 below displays the maternal and other family characteristics for cases included in the case series; including maternal demographic information, substance use, and maternal or other family history of congenital or chromosomal defects. Of note, cases contained limited information to assess the quantity and duration of maternal use for prenatal vitamins, concomitant prescription drugs, or other substances during pregnancy.

Table 3. Maternal and Family Characteristics of Cases of Major Congenital Malformation With Maternal Metoclopramide Exposure During Pregnancy, Received by FDA Through March 8, 2020 (N=35)	
Maternal age (years), median [range]	30 [24 – 38]

Table 3. Maternal and Family Characteristics of Cases of Major Congenital Malformation With Maternal Metoclopramide Exposure During Pregnancy, Received by FDA Through March 8, 2020 (N=35)	
	Not reported (16)
Maternal ethnicity	White (3) Not reported (32)
Maternal infection during pregnancy	Yes (4) *Human immunodeficiency virus (2)* *Urinary tract infection (2)* Not reported (31)
Maternal prenatal vitamin or folic acid supplementation during pregnancy	Yes (11) Not reported (24)
Maternal concomitant prescription drug use during pregnancy	Yes (30)* *Ondansetron (10)* *Antidepressant (9)* *Antiepileptic (4)* *Angiotensin II receptor blocker (2)* *Antiretroviral (2)* *Nonsteroidal anti-inflammatory drug (2)* *Angiotensin-converting enzyme inhibitor (1)* *Chemotherapy (1)* *Statin (1)* Not reported (5)
Maternal substance use during pregnancy†	Yes / No / Not reported
Alcohol	1 / 7 / 27
Tobacco	3 / 6 / 26
Other substances	0 / 7 / 28
Maternal history of prior pregnancy	Yes (9) *Prior miscarriage (4)*‡ *No prior malformation or miscarriage (3)*§ *Prior malformation (0)* *Prior pregnancy outcome not reported (2)*‖ No (2) Not reported (24)
Maternal or paternal history of congenital or chromosomal defect	No (2) Not reported (33)

* Concomitant prescription drug classes of potential interest per reviewer are listed below. Of 30 cases that had concomitant prescription drugs, 21 listed one or more concomitant prescription drugs of potential interest.
† Some mothers used multiple substances during pregnancy.
‡ One mother had a history of miscarriage and healthy children.
§ Includes one mother who had a healthy child and one terminated pregnancy.
‖ Includes one terminated pregnancy.

Table 4 below displays pregnancy outcomes and MCM characteristics for cases included in the case series.

Table 4. Pregnancy Outcomes and Malformation Characteristics for Cases of Major Congenital Malformation With Maternal Metoclopramide Exposure During Pregnancy, Received by FDA Through March 8, 2020 (N=35)	
Pregnancy outcome	Live birth (27) Baby died "shortly after" or within 7 days of birth (2) Terminated (2) Not reported (4)
Gestational age at birth (n=29)*	Full term (12)† 36 weeks (2)‡ 35 weeks (2) 34 weeks (3)§ 33 weeks (1) 30 weeks (1) Not reported (8)
Sex of baby	Male (18) Female (6) Not reported (11)
Chromosomal defect identified in baby	No (5) Yes (1) Not reported (29)
Malformed organ system(s)‖,¶ *(malformations with 2 or more cases are listed)*	Circulatory (12) *Atrial septal defect (7)* *Ventricular septal defect (4)* Musculoskeletal (9) Urinary (5) *Congenital hydronephrosis (2)* Eye, ear, face, or neck (2) Lip/palate (2) *Cleft palate (2)* Respiratory (2) Genital (2) *Hypospadias (2)* Integumentary (1) Nervous (1) Other (1)

* Includes 29 fetuses that had pregnancy outcome of live birth (n=27), died "shortly after" birth (n=1), or died within 7 days of birth (n=1)
† A gestational age ≥37 weeks is considered full term.
‡ One was delivered at 36 weeks by C-section for intrauterine growth restriction.
§ One was delivered at 34 weeks by C-section for anhydramnios.
‖ Categorized per the International Classification of Diseases – XVII Congenital Malformations (available at https://embryology med.unsw.edu.au/embryology/index.php/International_Classification_of_Diseases_-_XVII_Congenital_Malformations, accessed on April 27, 2020)
¶ Some cases listed more than one malformed organ system.

3.2 LITERATURE REVIEW

3.2.1 Bérard 2019

3.2.1.1 Study Overview

Bérard 2019 [4] used the Quebec Pregnancy Cohort (QPC) to estimate associations between *in utero* first-trimester exposures to antiemetics and occurrence of MCM in singleton live births. See **Appendix C** for tabular summary of **Bérard 2019** [4].

3.2.1.2 Study Objective

Bérard 2019 [4] aimed "to quantify the risk of overall MCMs and organ system-specific MCMs associated with first-trimester exposure to doxylamine-pyridoxine, metoclopramide, and ondansetron" (p. 40).

3.2.1.3 Study Methods

3.2.1.3.1 Study Setting

QPC organizes information about pregnancies in women with prescription drug coverage through the Quebec Prescription Drug Insurance Plan. All permanent residents of Quebec must carry prescription drug insurance through either the Quebec Prescription Drug Insurance Plan (public option administered through RAMQ, Régie de l'assurance maladie du Québec) or a private plan (group insurance or employee benefit plan).[b] (QPC captured "19.4% of all deliveries occurring in the Province of Quebec between 1998-2009" [7].)

Bérard 2019 [4] constructed QPC by linking three databases [7].

- RAMQ provided data from a Demographic file (age, sex, and enrollment dates), Medical Services file (encounter dates, physician diagnoses, and procedures), and Prescription Drug file (drug names and dates dispensed).
- MedEcho provided data about acute care hospitalizations.
- ISQ (l'Institut de la Statistique du Québec) provided data from birth and death certificates.

Hospital delivery records in MedEcho provided gestational age estimated by prenatal ultrasound. QPC used "dates of birth, first names, and family names" to link maternal to infant records in RAMQ and ISQ [7]. (QPC successfully linked at least one infant to 156,696 of 167,398 (93.6%) mothers with QPC delivery dates in 2006 through 2010 [7].)

3.2.1.3.2 Eligibility Criteria

Bérard 2019 [4] selected 1998 through 2015 singleton live-birth deliveries in women with:

- ≥12 months continuous prescription drug coverage before first day of pregnancy (first

[b] Régie de l'assurance maladie du Québec, Prescription drug insurance obligation, accessed at https://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/Pages/obligation.aspx on April 6, 2020.

day of last menstrual period).

- Continuous prescription drug coverage throughout pregnancy.
- No fetotoxic medications during first trimester.[c]
- Newborn without diagnosis of chromosomal abnormality.[d]
- Newborn with only minor congenital malformations (**Appendix D**).

Bérard 2019 [4] identified liveborn infants by using ISQ to confirm mother-child links provided by RAMQ.

3.2.1.3.3 Exposure Variables

Bérard 2019 [4] defined antiemetic exposure by ≥1 prescription dispensed during 1st trimester (1st to 98th day of pregnancy) for doxylamine-pyridoxine, metoclopramide, or ondansetron.

3.2.1.3.4 Outcome Variables

Bérard 2019 [4] defined the singleton live-birth pregnancy outcome of MCM by ICD-9 740-759 (Chromosomal anomalies, ICD-9 758, excluded by cohort selection) or ICD-10 Q00-Q89 (excluding ICD-9 and ICD-10 codes for minor congenital malformation; **Appendix D**) in RAMQ or MedEcho encounters for a linked infant during the first six months of life. **Bérard 2019** [4] defined eight MCM categories aligning with code groupings in ICD-9 and ICD-10 (**Table 5**).

Table 5: Code definitions for eight categories of Major Congenital Malformation (MCM).

Category of Major Congenital Malformation	Coding System	
	ICD-9	ICD-10
Nervous system	740-742	Q00-Q07
Eye, ear, face and neck	743-744	Q10-Q18
Circulatory system	745-747	Q20-Q28
Respiratory system	748	Q30-Q34
Digestive system	749-751	Q35-Q45
Genital organ system	752	Q50-Q56
Urinary system	753	Q60-Q64
Musculoskeletal system	754-756	Q65-Q79

SOURCE: **Bérard 2019** [4] Table S2.
FOOTNOTE: Excluding minor congenital malformation codes in **Appendix D**.

[c] Fetotoxic medications include retinoids, antiepileptics, anti-thyroid drugs, anti-coagulants (warfarin), tetracyclines, angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, androgens, antineoplastic agents, and statins. See Table S1 in **Bérard 2019** [4] for a complete list.

[d] Possibly identified by ICD-9 758 (Chromosomal anomalies) or ICD-10 Q90–Q99 (Chromosomal abnormalities, not elsewhere classified) in RAMQ or MedEcho encounters for a linked infant during the first six months of life [4].

3.2.1.3.5 Other Variables

Covariates (assessed during a 1-year pre-index period except where indicated) included:

- Sociodemographic status on 1st day of pregnancy – maternal age, social assistance, and urban residence.
- Maternal comorbidity variables – obesity, diabetes, hypertension, asthma, psychiatric illness (depression, anxiety, or bipolar disorder), epilepsy, tobacco use disorder, and alcohol dependence.[e]
- Indices of health service use – hospitalization or emergency room visit, number of visits to a general practitioner, number of visits to specialist physicians, and number of other prescribed medications (excepting antiemetics and medications used to define other covariates).
- Pregnancy-related variables – previous pregnancy and obstetric care for index pregnancy.
- Severity-of-illness variables (nausea or vomiting diagnosis) – ≥1 outpatient visit during pregnancy with diagnosis code for nausea or vomiting and ≥1 hospitalization during pregnancy with diagnosis code for nausea or vomiting.[f]
- Prescription folate – periconceptional (6 months before pregnancy through first trimester) prescription dispensed for high-dose folate (>5 mg/d).

3.2.1.3.6 Sample Size and Power

Cohort selection criteria in Section 3.2.1.3.2 (above) identified 224,876 singleton live births.

3.2.1.3.7 Statistical Analysis

To account for women with more than one pregnancy ending in singleton live birth, **Bérard 2019** [4] used generalized estimating equations (GEEs) with exchangeable correlation structure (intra-patient correlation expressed by one parameter) to obtain covariate-adjusted odds ratios (ORs). ORs estimated the odds of MCM in singleton live births with *in utero* first-trimester antiemetic exposure divided by the odds of MCM in singleton live births without *in utero* first-trimester antiemetic exposure. GEE models included separate terms for first-trimester exposure to doxylamine-pyridoxine, metoclopramide, and ondansetron.

3.2.1.3.8 Governance and Reporting

Bérard 2019 [4] conducted analyses to respond to a "query from Health Canada and the Drug Safety and Effectiveness Network" (p. 40). The published manuscript contains no mention of a study protocol or statistical analysis plan.

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[e] See Table S3 in **Bérard 2019** [4] for diagnosis and prescription codes defining diabetes, hypertension, psychiatric illness, asthma, and epilepsy.

[f] ICD-9 643 (Excessive vomiting in pregnancy), 536.2 (Persistent vomiting), 787.0 (Nausea and vomiting), ICD-10 O21 (Excessive vomiting in pregnancy), R11 (Nausea and vomiting).

3.2.1.4 Study Results

3.2.1.4.1 Prevalence of first-trimester antiemetic exposure

Bérard 2019 [4] identified 224,876 study-eligible singleton live-birth pregnancies, including 45,770 (20.4%) with first-trimester exposure to an antiemetic (doxylamine-pyridoxine, metoclopramide, or ondansetron). **Bérard 2019** [4] documented first-trimester exposure to doxylamine-pyridoxine in 45,623 (20.3%), metoclopramide in 958 (0.4%), and ondansetron in 31 (0.01%). The index antiemetic dispensing occurred on mean week 8.2. 9.4, and 10.2 of gestation for doxylamine-pyridoxine, metoclopramide, and ondansetron, respectively. A plot by calendar year of first day of pregnancy (1998-2015) showed ≈60% (≈17.5% to ≈27.5%) and ≈1100% (≈0.1% to ≈1.1%) increases over an 18-year timeframe with respect to prevalence of first-trimester exposure to doxylamine-pyridoxine and metoclopramide, respectively.

3.2.1.4.2 First-trimester antiemetic exposure

Bérard 2019 [4] presented (as manuscript Table 1) frequency distributions for all covariates by first-trimester antiemetic exposure. Covariates with possibly meaningful imbalance (standardized difference ≥0.10) by exposure (any antiemetic *vs.* no antiemetic) included social assistance (28.2% *vs.* 21.9%), psychiatric illness (12.0% *vs.* 9.0%), and ≥3 other prescribed medications (29.3% *vs.* 22.3%; **Table 6**).

Table 6: Singleton live-birth pregnancies in Quebec Pregnancy Cohort (1998-2015; N=224,876), selected covariates by first-trimester antiemetic exposure.

Covariate	1st trimester antiemetic (%)		StdDiff
	None (N=179,106)	Any (N=45,770)	
Demographic			
age >35 years	15.6	13.4	0.06
social assistance	21.9	28.2	0.14
Maternal comorbidity			
psychiatric illness	9.0	12.0	0.10
Health service use			
≥3 other prescribed medications	22.3	29.3	0.16

SOURCE: **Bérard 2019** [4], Table 1.
ABBREVIATION: StdDiff – standardized difference calculated by DEPI according to Austin 2011 [8], p. 412.

3.2.1.4.3 MCM and other outcomes

Bérard 2019 [4] identified one or more MCMs in 3,962 of 45,770 (8.7%) and 14,402 of 179,106 (8.0%) singleton live births with and without *in utero* first-trimester exposure to any antiemetic (doxylamine-pyridoxine, metoclopramide, or ondansetron), respectively. **Bérard 2019** [4] identified one or more MCMs in 3,945 of 45,623 (8.7%), 105 of 958 (11.0%) and 2 of 31 (6.5%) singleton live births with *in utero* first-trimester exposure to doxylamine-pyridoxine, metoclopramide, or ondansetron, respectively. A main GEE model estimated covariate-adjusted association with MCM at OR 1.07 (95% confidence interval, CI, 1.03-1.11) and OR 1.27 (95% CI 1.03-1.57) for *in utero* first-trimester doxylamine-pyridoxine and metoclopramide,

respectively. Other covariates with moderately strong association (adjusted OR ≥1.20) with MCM included prescription folate (OR 1.68, 95% 1.19-2.37), diabetes (OR 1.38, 95% CI 1.22-1.57), epilepsy (OR 1.42, 95% CI 1.16-1.74), tobacco use disorder (OR 1.29, 95% CI 1.16-1.51), and obstetric care for index pregnancy (OR 1.21, 95% CI 1.17-1.25).

Except for frequency of prematurity (gestational age <37 weeks, 7.0% *vs.* 6.7% for any antiemetic *vs.* no antiemetics), results appeared similar for other non-MCM outcomes in singleton live-birth pregnancies with and without first-trimester antiemetic exposure (overall, mean gestational age 38.9 weeks, mean birth weight 3,350 g, 5.1% with birth weight <2,500 g, and newborn sex 51.3% male).

3.2.1.4.4 MCM by organ system

Bérard 2019 [4] presented (as manuscript Table 3) results for MCM overall and nine categories of MCM (**Table 7**). Notable associations included spina bifida with doxylamine-pyridoxine (covariate-adjusted OR 1.87, 95% CI 1.11-3.14) and genital organ system MCM with metoclopramide (covariate-adjusted OR 2.26, 95% CI 1.14-4.48).

Table 7: Major Congenital Malformation (MCM, any and organ-specific) in singleton live births from Quebec Pregnancy Cohort (1998-2015, N=224,845), by *in utero* first-trimester antiemetic exposure.

	First-trimester antiemetic						**Covariate-adjusted association with MCM**	
	none (N=179,106)		**doxylamine-pyridoxine (N=45,598)**		**metoclo-pramide (N=939)**		**doxylamine-pyridoxine**	**metoclopra-mide**
MCM Category	**n**	**%**	**n**	**%**	**n**	**%**	**OR (95% CI)**	**OR (95% CI)**
Any MCM	14,402	8.04	3,945	8.65	103	10.97	1.07 (1.03-1.11)	1.26 (1.02-1.56)
Nervous system	665	0.37	225	0.49	7	0.75	1.25 (1.06-1.47)	1.26 (0.56-2.87)
Spina bifida	45	0.03	23	0.05	1	0.11	1.87 (1.11-3.14)	2.05 (0.23-17.9)
Eye, ear, face and neck	578	0.32	147	0.32	3	0.32	1.02 (0.84-1.22)	0.98 (0.31-3.16)
Circulatory system	3,552	1.98	972	2.13	30	3.19	1.02 (0.95-1.11)	1.39 (0.96-2.02)
Respiratory system	755	0.42	219	0.48	7	0.75	1.07 (0.91-1.25)	1.29 (0.57-2.91)
Digestive system	1,210	0.68	369	0.81	11	1.17	1.12 (0.99-1.26)	1.36 (0.71-2.59)
Genital organ system	930	0.52	232	0.51	10	1.06	0.98 (0.84-1.14)	2.26 (1.14-4.48)
Urinary system	1,719	0.96	433	0.95	8	0.85	1.02 (0.92-1.14)	0.95 (0.47-1.92)
Musculoskeletal system	6,393	3.57	1,735	3.80	39	4.15	1.08 (1.02-1.14)	1.09 (0.78-1.52)

SOURCE: **Bérard 2019** [4], Table 3.
FOOTNOTE: Analyses summarized in this table excluded 31 singleton live births with *in utero* first-trimester exposure to ondansetron. **Bérard 2019** [4] presumably determined each organ-system-specific odds ratio by separate GEE models with an organ-specific MCM response of present *vs.* absent. Table 5 shows ICD codes for organ-system-specific MCMs (spina bifida codes not available in **Bérard 2019** [4]).

3.2.1.4.5 Conclusions

Conducting a study in Quebec, **Bérard 2019** [4] concluded by finding statistically significant MCM associations with first-trimester exposure to doxylamine-pyridoxine and metoclopramide. **Bérard 2019** [4] indicated that these results, though "consistent with other published studies," required "replications in further investigations" (p. 47).

3.2.2 Matok 2009

Matok 2009 [5] conducted a retrospective cohort study by linking electronic healthcare data for Clalit Health Services (a Health Maintenance Organization, HMO, serving southern Israel) and Soroka Medical Center (a major hospital in Beer-Sheva, Israel). The HMO data source provided information about drug use during pregnancy. Two hospital databases provided information about maternal health and MCM in liveborn and stillborn infants. One hospital database (Demog-ICD9) aggregated diagnosis codes from hospitalization records (maternal delivery records and linked hospital records for newborns). A second hospital database (serving the Department of Obstetrics and Gynecology) provided data about ethnicity (Jewish or Bedouin), smoking status during pregnancy, pregnancy history (parity), maternal health during pregnancy, gestational age at delivery (the number of days since last menstrual period), perinatal death, and infant birth weight.

Matok 2009 [5] restricted analysis to 81,703 singleton liveborn or stillborn infants delivered between January 1998 and March 2007 at the Soroka Medical Center to 15-49-year-old mothers living in the Beer-Sheva district and enrolled in Clalit Health Services. With exposure defined by prescriptions dispensed to mothers during the 13th week of gestation or earlier in pregnancy, **Matok 2009** [5] identified 3,458 (4.2% of 81,703) infants with *in utero* exposure to metoclopramide. With MCM defined by ICD-9 diagnosis codes in infant hospital discharge records,[g] **Matok 2009** [5] identified MCM in 182 (5.3% of 3,458) and 3,834 (4.9% of 78,245) infants with and without *in utero* first-trimester exposure to metoclopramide, respectively (adjusted OR 1.04, 95% CI 0.89-1.21).[h]

Matok 2009 [5] identified MCM of genital organs in 12 and 321 infants with and without *in utero* first-trimester exposure to metoclopramide, respectively (adjusted OR 0.83, 95% CI 0.47-1.48; Table 8).

Table 8: Singleton liveborn or stillborn infants from Beer-Sheva district of Israel, number (n) with Major Congenital Malformation (MCM) and MCM birth prevalence (P, per 1000 births; January 1998 – March 2007, N=81,703), by MCM category and *in utero* first-trimester exposure to metoclopramide.

Major Congenital Malformation (MCM) Category	**ICD-9**	**Exposure to Metoclopramide**			
		Yes N=3,458		**No N=78,245**	
		n	**P**	**n**	**P**
Anencephaly	740	3	0.9	8	0.1
Spina bifida	741	2	0.6	46	0.6
Other anomaly of the nervous system	742	24	6.9	439	5.6

[g] Definition for MCM as "developed by the Metropolitan Atlanta Congenital Defects Program of the Centers for Disease Control and Prevention" with "chromosomal diseases" (ICD-9 758) excluded. **Matok 2009** [5], p. 2530.

[h] Adjusted by logistic regression for maternal age, ethnic group, maternal diabetes, maternal smoking, and parity.

Major Congenital Malformation (MCM) Category	ICD-9	Exposure to Metoclopramide			
		Yes N=3,458		No N=78,245	
		n	P	n	P
Anomalies of the eye	743	5	1.4	72	0.9
Anomalies of the ear, face, and neck	744	0	0.0	5	0.1
Bulbus cordis anomalies and anomalies of cardiac septal closure	745	47	13.6	909	11.6
Other anomalies of the heart	746	19	5.5	530	6.8
Other anomalies of the circulatory system	747	12	3.5	213	2.7
Anomalies of the respiratory system	748	13	3.8	223	2.9
Cleft palate and lip	749	4	1.2	104	1.3
Other anomalies of the upper alimentary tract	750	3	0.9	94	1.2
Other anomalies of the digestive system	751	8	2.3	214	2.7
Genital anomalies	752	12	3.5	321	4.1
Anomalies of the urinary system	753	10	2.9	272	3.5
Musculoskeletal deformities	754	35	10.1	604	7.7
Other anomalies of the limbs	755	4	1.2	107	1.4
Other musculoskeletal anomalies	756	17	4.9	468	6.0
Anomaly of the integument	757	0	0.0	6	0.1

SOURCE: **Matok 2009** [5], Web Table 1.

3.2.3 Pasternak 2013

Pasternak 2013 [6] conducted a retrospective cohort study in linked population-based registers for Denmark (Central Person Register, Statistics Denmark, National Prescription Registry, Medical Birth Register, and National Patient Register). After excluding infants with birth defects attributable to chromosomal aberrations or other possible etiology,[i] **Pasternak 2013** [6]

[i] Diagnoses (ICD-10) excluding infants from MCM analysis: chromosomal aberrations (D82.1, Q90-99), genetic syndromes (Q44.7B, Q61.9A, Q75.1, Q75.4, Q77.1, Q77.2, Q78.0, Q79.6, Q85, Q87), malformation syndromes (Q86), or certain congenital virus infections (P35.0, P35.1, P35.2, P37.1).

identified 879,235 singleton live-birth infants (with plausible information for gestational age) delivered between January 1997 and March 2011 by mothers without pre-pregnancy (6-month-lookback) history of cancer or pre-pregnancy (1-month-lookback) exposure to metoclopramide. With metoclopramide exposure defined by prescriptions dispensed to mothers during the 12th week of gestation or earlier in pregnancy, **Pasternak 2013** [6] identified 28,505 (3.2% of 879,235) infants with *in utero* exposure to metoclopramide. **Pasternak 2013** [6] identified MCM by ICD-10 diagnosis codes in National Patient Register records for infants up to one year of age.[j]

Analyses for MCM included 28,486 of 28,505 (99.93%) singleton liveborn infants from pregnancies with first-trimester exposure to metoclopramide and 113,698 (4:1 matched) singleton liveborn infants from pregnancies without first-trimester exposure to metoclopramide. Baseline factors used for matching included maternal age (5-year strata) on pregnancy start date (first day of last menstrual period), calendar year on pregnancy start date, and propensity score (nearest-neighbor match within 0.2 standard deviation units on logit scale). The propensity score model used logistic regression to estimate the probability of first-trimester metoclopramide exposure in the base population of 879,235 infants eligible for MCM analysis. The propensity score model included (1) maternal demographic factors (age at pregnancy onset, place of birth, county of residence, marital status, education level, calendar year of delivery, and gross household income), (2) pregnancy history variables (parity, previous pregnancy with congenital malformation, and smoking status during current pregnancy), (3) baseline medical history of diabetes mellitus (identified by pre-pregnancy diagnosis and pharmacy codes), (4) baseline drug use (pre-pregnancy use with 3-month lookback for proton-pump inhibitor/histamine-2 receptor blocker, nonsteroidal anti-inflammatory drug, antimigraine drug, and drugs possibly used to prepare for *in vitro* fertilization), (5) health care utilization variables (number of hospitalizations in the year before pregnancy, number of outpatient hospital contacts in the year before pregnancy, and number of prescription drugs used in the six months before pregnancy, and (6) fifteen 2-way interactions involving the six maternal demographic factors.[k]

Pasternak 2013 [6] used logistic regression in matched cohort to estimate the prevalence odds of MCM in infants exposed *vs.* infants not exposed prenatally to metoclopramide in the first trimester. This final logistic regression included statistical controls for (1) maternal first-trimester hospitalization with hyperemesis gravidarum, nausea, or vomiting (ICD-10 O21, R11) and (2) maternal first-trimester use of non-metoclopramide antiemetic (antihistamine, ondansetron, scopolamine, or domperidone).

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[j] ICD-10 code algorithm for MCM (European Surveillance of Congenital Anomalies classification system modified by excluding codes for minor congenital anomalies): Nervous system (Q00-Q07), Eye (Q10-Q15, excluding Q10.1-Q10.3, Q10.5, Q13.5), Ear, face and neck (Q16-Q18, excluding Q17.0-Q17.5, Q17.9, Q18.0-Q18.2, Q18.4-Q18.7, Q18.9), Congenital heart defects (Q20-Q26, excluding Q21.1C, Q25.0), Respiratory (Q30-34, excluding Q31.4, Q31.5, Q32.0, Q33.1), Orofacial clefts (Q35-3), Digestive system (Q38-45, Q79.0, excluding Q38.1, Q38.2, Q38.5, Q40.0, Q40.1, Q43.0), Abdominal wall defects (Q79.2, Q79.3, Q79.5), Urinary (Q60-64, Q79.4, excluding Q61.0, Q62.7, Q63.3), Genital (Q50-52, Q54-56, excluding Q52.3, Q52.5, Q55.2F), Limb (Q66-74, excluding Q66.2-Q66.9, Q67.0-Q67.8, Q68.0, Q68.2A, Q68.3-Q68.5, Q74.0G), Other (Q75.0, Q77, Q78.0, Q78.2-Q78.8, Q79.8, Q80-82, Q89.3, Q89.4, excluding Q82.5, Q82.80).

[k] For codes used to specify variables for propensity score models, see **Pasternak 2013** [6], eTable 3.

Matched cohorts appeared well balanced (standardized difference <0.10) on propensity-score variables used for MCM analysis (**Pasternak 2013** [6], eFigure). **Pasternak 2013** [6] estimated maternal first-trimester exposure to a non-metoclopramide antiemetic at 3.2% and 0.3% in matched metoclopramide exposed and unexposed cohorts, respectively. Age-, calendar-year-, and propensity-score-matched analysis identified MCM in 721 of 28,486 (2.53%) and 3,024 of 113,698 (2.66%) singleton liveborn infants from first-trimester metoclopramide exposed and unexposed pregnancy, respectively (adjusted OR 0.93, 95% CI 0.86-1.02).[l]

Pasternak 2013 [6] separately assessed metoclopramide-associated risks for 20 pre-specified MCM categories. Two MCM categories showed possibly elevated metoclopramide-associated risk (adjusted OR ≥1.20), (1) coarctation of aorta (adjusted OR 1.28, 95% CI 0.70-2.35) and (2) congenital skin disorders (adjusted OR 1.32, 95% CI 0.68-2.54). **Pasternak 2013** [6] assessed risk for one specific genital organ defect, hypospadias in boys (adjusted OR 0.84, 95% CI 0.63-1.12).

4 DISCUSSION

Responding to a request from DPMH, OPE assessed medical literature and adverse event reports for evidence of MCM as a consequence of prenatal exposure to metoclopramide. DEPI assessed three published reports from observational studies of pregnancy and infant outcomes after pregnancy exposure to metoclopramide [4, 5, 6]. DEPI restricted attention to the infant outcome of MCM after *in utero* first-trimester exposure to metoclopramide with focus on **Bérard 2019** [4], the only study reporting statistically significant association between metoclopramide and MCM. DPV restricted attention to postmarketing cases of MCM in the FAERS database with maternal metoclopramide exposure during pregnancy.

4.1 DEPI DISCUSSION OF LITERATURE

Table 9 summarizes the three observational studies selected by DPMH for DEPI review. Each study used electronic healthcare data to identify pregnancy cohorts, metoclopramide exposure, and MCM. One study (**Matok 2009** [5]) assessed MCM in singleton liveborn or stillborn infants, whereas the other two studies assessed MCM in singleton liveborn infants.[m] Each study used data sources covering well defined source populations, (1) Quebec residents with publicly available prescription drug coverage (**Bérard 2019** [4]), (2) residents of Beer-Sheva (Israel) with health coverage through Clalit Health Services (**Matok 2009** [5]), and (3) residents of Denmark (**Pasternak 2013** [6]).

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[l] Adjusted for (1) maternal first-trimester hospitalization with hyperemesis gravidarum, nausea, or vomiting (ICD-10 (ICD-10 O21, R11) and (2) maternal first-trimester use of non-metoclopramide antiemetic (antihistamine, ondansetron, scopolamine, or domperidone).

[m] **Pasternak 2013** [6] presented results from a sensitivity analysis that assessed MCM in induced abortions and stillbirths in addition to singleton live births.

Table 9: Three observational studies of first-trimester pregnancy exposure to metoclopramide and Major Congenital Malformation (MCM).

	Matok 2009 [5]	**Pasternak 2013** [6]	**Bérard 2019** [4]
Location	Israel	Denmark	Quebec
Time Period	1998-2007	1997-2011	1998-2015
Metoclopramide exposed, N	3,458	28,486	958
MCM in exposed, n (%)	182 (5.3%)	721 (2.5%)	105 (11.0%)
Adjusted OR (95% CI)	1.04 (0.89-1.21)	0.93 (0.86-1.02)	1.27 (1.03-1.57)

ABBREVIATION: OR – odds ratio; CI – confidence interval

Each study used diagnosis codes in electronic healthcare databases to identify infants with MCM, though studies ascertained MCM over different time periods after birth, (1) up to six months after birth (**Bérard 2019** [4]), (2) hospital birth record only (**Matok 2009** [5]), and (3) up to one year after birth (**Pasternak 2013** [6]). Timeframes for ascertaining MCM might impact study power or estimates of MCM incidence (particularly for less severe MCMs that become clinically more apparent months after birth), but not necessarily study-specific estimates of MCM relative risk.

Blais 2013 [9] assessed the accuracy of congenital malformation codes in the RAMQ and MedEcho databases for Quebec. **Blais 2013** [9] oversampled infants delivered to mothers with asthma and infants with codes for facial cleft, cardiac, or limb malformation. Medical archivists and research nurses at 18 hospitals abstracted information from medical charts for 289 infants delivered alive between 1990 and 2002 with one or more MCM codes in RAMQ or MedEcho. Blinded to RAMQ/MedEcho data, a teratologist assessed these medical chart abstracts to find one or more MCMs in 214 infants (positive predictive value, PPV, 74.0%, 95% CI 68.7% – 78.8%).[n]

As shown in Table 9, estimates for MCM birth prevalence in metoclopramide-exposed infants varied widely, 2.5%, 5.3%, and 11.0% for Denmark (**Pasternak 2013** [6]), Israel (**Matok 2009** [5]), and Quebec (**Bérard 2019** [4]), respectively. Explanations for this variability might include (1) variable MCM risk in the source (background) population and (2) MCM ascertainment by methods with dissimilar PPV. However, the high MCM risk estimated in Quebec by **Bérard 2019** [4] differs substantially from the 2 to 4% estimate typically presented in FDA labels for the prevalence of major birth defects in "clinically recognized pregnancies" for the U.S. general population.[o] The distinctly high MCM live birth prevalence estimated by **Bérard 2019** [4] might indicate MCM physician practice or coding standards peculiar to Quebec.

Of concern, MCM physician practice or coding standards for Quebec might vary by geographic region. **Zhao 2015** [10] used 1998-2008 QPC data to estimate MCM live birth prevalence in each of 17 administrative regions for Quebec. **Zhao 2015** [10] assessed codes in RAMQ and MedEcho infant records up to one year of age and defined MCM by requiring ≥2 diagnosis codes

[n] PPV and 95% CI (pooling infants of mothers with and without asthma) calculated by DEPI using OpenEpi (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed 2020/04/23.)

[o] Prescribing Information for REGLAN®, *op. cit.*

in the same MCM category. MCM live birth prevalence (3.7% for Quebec overall) varied from 1.3% in Outaouais to 4.8% in Lanaudière. Results reported by **Zhao 2015** [10] suggest that geographic differences might confound associations observed between metoclopramide and MCM in Quebec overall. Of note, **Bérard 2019** [4] presented results from analyses with no apparent design or statistical control for geographic region.

Bérard 2019 [4] describes metoclopramide as second-line treatment (after doxylamine-pyridoxine) in Quebec for nausea and vomiting in early pregnancy. **Bérard 2019** [4] estimated the prevalence of first-trimester metoclopramide use at only 0.4% (for pregnancy ending in live birth between 1998 and 2015). By comparison, **Matok 2009** [5] estimated the prevalence of first-trimester metoclopramide use in Israel at 4.2% (for pregnancy ending in stillbirth or live birth between 1998-2007). **Pasternak 2013** [6] estimated the prevalence of first-trimester metoclopramide use in Demark at 3.2% (for pregnancy ending in live birth between 1997 and 2011). Of concern, first-trimester metoclopramide use increased 11-fold in Quebec between 1998 and 2015. Therefore, temporal differences might confound associations observed in Quebec between metoclopramide and MCM overall. Of note, **Bérard 2019** [4] presented results from analyses with no apparent design or statistical control for calendar time.

Bérard 2019 [4] used a convenient statistical method (potential confounders entered as covariates in GEE models) to control for non-metoclopramide antiemetics (doxylamine-pyridoxine and ondansetron) during early pregnancy and other covariates listed in Section 3.2.1.3.5 (above). **Pasternak 2013** [6] used an arguably preferred, if not superior method for covariate control (propensity-score matched design). Of note, **Pasternak 2013** [6] implemented design controls for both calendar time (direct matching on calendar year at beginning of pregnancy) and geographic location (matching on country of residence through a propensity score). As mentioned above, **Bérard 2019** [4] presented results from analyses with no apparent control for calendar time or geographic location.

Each study estimated association between first-trimester metoclopramide and MCM with statistical uncertainty. Testing without correcting for multiplicity might explain the statistically significant association reported by **Bérard 2019** [4] between first-trimester metoclopramide and genital organ MCM (adjusted OR 2.26, 95% CI 1.14-4.48). By comparison, **Matok 2009** [5] estimated association between first-trimester metoclopramide and genital organ MCM with adjusted OR 0.83, 95% CI 0.47-1.48. **Pasternak 2013** [6] assessed hypospadias in boys as the only genital organ MCM frequent enough for reliable analysis. **Pasternak 2013** [6] estimated association between first-trimester metoclopramide and hypospadias with adjusted OR 0.84, 95% CI 0.63-1.12.

OPE is aware of an effort directed by DPMH to obtain more information about **Bérard 2019** [4] through direct communication with the study investigators. If the investigators respond to these efforts, OPE might subsequently amend conclusions and recommendations shown below.

4.2 DPV Discussion of Postmarketing Cases in the FAERS Database

To complement DEPI's analysis of the literature, DPV assembled a high-level overview of 35 postmarketing cases of MCM in the FAERS database with maternal metoclopramide exposure during pregnancy. Because the signal of MCM was identified in the **Bérard 2019** [4] study and

the limited nature of spontaneous adverse event reports, we did not adjudicate reports for causal association with metoclopramide.

DPV's assessment of risk factors and trends among cases in the FAERS database of MCM with maternal metoclopramide exposure during pregnancy was largely limited by lack of information included in the cases. Most cases did not consistently report the information needed to assess for patterns, such as gestational age at metoclopramide initiation (77 percent not reported), prescribed metoclopramide dose (71 percent not reported) or prescribing instructions (71 percent not reported), maternal substance or prenatal vitamin use (69 percent not reported), or family history of congenital malformation or chromosomal defect (94 percent not reported). Maternal alcohol or tobacco use during pregnancy is associated with congenital malformations; however, most cases in the FAERS database did not report whether there was maternal alcohol or tobacco use. Of the 35 cases, 30 reported concomitant prescription drug use during pregnancy; 21 of these reported use of prescription drug classes that have been associated with congenital malformations. Therefore, it is possible that some cases had an alternate etiology for the malformation. The most frequently described MCMs in the case series mirror those commonly reported in birth defect surveillance programs; we were unable to identify a pattern specific to fetuses with transplacental metoclopramide exposure.

5 CONCLUSIONS

Missing controls for geographic location and calendar time might explain the anomalous association observed by **Bérard 2019** [4] between *in utero* first-trimester exposure to metoclopramide and MCM in singleton liveborn infants. Statistical variability without adjustments for multiple testing might explain the strong association reported by **Bérard 2019** [4] between *in utero* first-trimester exposure to metoclopramide and genital organ MCM in singleton liveborn infants. **Pasternak 2013** [6] used methods for covariate control superior to **Bérard 2019** [4].

We identified FAERS cases of MCM with maternal metoclopramide exposure during pregnancy; however, we cannot exclude the role of other factors such as genetics or concomitant substance exposures in the development of malformations. DPV's assessment of risk factors and trend among cases in the FAERS database of MCM with maternal metoclopramide exposure during pregnancy was largely limited by lack of information included in the cases.

6 RECOMMENDATIONS

Any presentation of possible metoclopramide-associated MCM risk should balance questionable results from Quebec (**Bérard 2019** [4]) against perhaps more credible results from Denmark (**Pasternak 2013** [6]). FDA might ask the **Bérard 2019** [4] investigators about (1) Health Canada's reason for requesting a study of MCM and antiemetics during pregnancy and (2) the availability of a study protocol or statistical analysis plan for **Bérard 2019** [4].

DPV recommends no additional labeling from postmarketing cases in the FAERS database.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING FOR MAJOR CONGENITAL MALFORMATION WITH MATERNAL METOCLOPRAMIDE EXPOSURE DURING PREGNANCY CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Report Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	2/19/2002	3765642	5	HQ0633311FEB2002	Expedited (15-Day)	-.56	NULL	USA	CA,OT
2	5/4/2010	7376433	1	US-WATSON-2010-05634	Expedited (15-Day)	-.03	MALE	USA	CA
3	8/22/2014	10402757	1	NL-ASTRAZENECA-2014SE59990	Expedited (15-Day)	0	MALE	NLD	CA
4	12/31/2019	17218036	1	DE-TEVA-2019-DE-1159785	Expedited (15-Day)	0	FEMALE	DEU	OT
5	5/29/2018	14948464	2	FR-TEVA-2018-FR-898862	Expedited (15-Day)	0	MALE	FRA	CA,DE,OT
6	3/19/2010	7325707	2	FR-ASTRAZENECA-2010SE11134	Expedited (15-Day)	0	FEMALE	FRA	CA,HO,OT
7	11/20/2014	10595374	4	DE-JNJFOC-20141105075	Expedited (15-Day)	.00274	MALE	DEU	CA
8	10/30/2014	10555454	1	DE-TEVA-517197GER	Expedited (15-Day)	.00274	MALE	DEU	CA,OT
9	7/8/2017	13733969	1	FR-009507513-1706FRA009602	Expedited (15-Day)	.00274	FEMALE	FRA	CA
10	4/30/2010	7371492	2	US-TEVA-232004USA	Expedited (15-Day)	.05	MALE	USA	CA
11	3/23/2012	8474981	2	CA-FRI-1000029281	Expedited (15-Day)	24	NULL	CAN	CA,OT
12	12/6/2004	5691915	1		Direct	31	FEMALE	USA	CA,HO,LT
13	2/3/2003	3900446	3	200214592FR	Expedited (15-Day)	34	FEMALE	FRA	CA,DS
14	5/19/2011	7952389	2	NO-TEVA-281555ISR	Expedited (15-Day)	35	NULL	NOR	CA
15	2/13/2001	3609445	1	A102418	Expedited (15-Day)		UNKNOWN	BEL	CA,DE,DS,HO,OT
16	5/7/2013	9275764	6	US-JNJFOC-20130502650	Expedited (15-Day)		MALE	USA	CA
17	1/6/2016	11890902	1	BR-BRISTOL-MYERS SQUIBB COMPANY-15212319	Expedited (15-Day)		FEMALE	BRA	CA
18	1/13/2016	11912794	1	BR-BRISTOL-MYERS SQUIBB COMPANY-15212228	Expedited (15-Day)		MALE	BRA	CA
19	3/20/2013	9173341	4	US-JNJFOC-20130310413	Expedited (15-Day)		MALE	USA	HO
20	2/28/2013	9129045	3	US-JNJFOC-20130215752	Expedited (15-Day)		FEMALE	USA	CA
21	3/19/2013	9170541	5	US-JNJFOC-20130310451	Expedited (15-Day)		MALE	USA	CA,HO
22	9/2/2014	10425387	1	FR-ASTRAZENECA-2014SE64789	Expedited (15-Day)		MALE	FRA	CA
23	2/14/2020	17417256	1	US-009507513-2002USA004977	Expedited (15-Day)		MALE	USA	CA

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Report Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
24	4/5/2012	8496187	1	CA-GLAXOSMITHKLINE-A0972058A	Expedited (15-Day)		NULL	CAN	CA,DS,HO, LT,RI,OT
25	6/20/2013	9357274	1	DE-JNJFOC-20130601905	Expedited (15-Day)		MALE	DEU	CA,HO
26	6/21/2018	15041765	1	DE-IPCA LABORATORIES LIMITED-IPC-2018-DE-001301	Expedited (15-Day)		NULL	DEU	CA,LT
27	6/21/2018	15041774	1	DE-IPCA LABORATORIES LIMITED-IPC-2018-DE-001302	Expedited (15-Day)		NULL	DEU	CA,HO
28	6/21/2018	15041798	1	DE-IPCA LABORATORIES LIMITED-IPC-2018-DE-001303	Expedited (15-Day)		NULL	DEU	CA,HO,LT
29	9/3/2019	16766846	3	DE-IBIGEN-2019.07171	Expedited (15-Day)		MALE	DEU	CA,OT
30	4/25/2008	6877334	1	100#03#2008-02154	Expedited (15-Day)		NULL	GBR	CA,DE,OT
31	3/11/2011	7852256	1	PHHY2011IT18839	Expedited (15-Day)		NULL	ITA	CA,OT
32	5/2/2018	14838405	1	PHEH2018US015995	Expedited (15-Day)		NULL	USA	CA
33	10/25/1996	5466200	1	896281012S	Expedited (15-Day)		UNKNOWN	USA	OT
34	10/30/2015	11687080	1	PHHY2015US140814	Expedited (15-Day)		FEMALE	USA	CA
35	3/30/2004	4121352	1	B0326031A	Expedited (15-Day)		MALE	USA	CA,OT

Abbreviations: CA, congenital anomaly; DE, death; DS, disability; HO, hospitalization; LT, life-threatening; OT, other medically significant; RI, required intervention
*As per 21 CFR 314.80, the regulatory definition of serious is 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, and other serious important medical events. A case can have more than one serious outcome.

8.3 APPENDIX C. TABULAR SUMMARY OF BÉRARD 2019

Design Feature	Description
1.1 Objectives/Aims/Scope	Quantify association between first-trimester pregnancy use of antiemetics and live birth with major congenital malformation (MCM)
1.2.1 Design for the Primary Analysis	
1.2.1.1 Type	Cohort
1.2.1.2 Data Source	Quebec Pregnancy Cohort
1.2.1.3 Time Period	1998-2015
1.2.1.4 Criterion (Selection) Standards	Criteria for selection included: • ≥12 months continuous prescription drug coverage before first day of pregnancy (1DG) • Continuous prescription drug coverage throughout pregnancy • Pregnancy with singleton live birth • No fetotoxic medications during first trimester • No newborn diagnoses of chromosomal abnormality • No isolated minor malformations (in absence of MCM)
1.2.1.5 Protected Health Information	Study approved by the Sainte-Justine's Hospital Ethics Committee
1.2.2 Setting	Permanent residents of Quebec with drug coverage through Quebec Prescription Drug Insurance Plan
1.2.3 Exposure/Intervention	≥1 prescription dispensed during 1st trimester (LMP to 98th day of pregnancy) for an antiemetic (doxylamine-pyridoxine, metoclopramide, or ondansetron)
1.2.4 Outcome(s)	MCM identified "in the first 6 months of life" by ICD-9 or ICD-10 code in insurance (RAMQ) or hospital (MedEcho) database
1.2.5 Covariates	Covariates included in statistical models: • Sociodemographic – maternal age, social assistance, and urban residence

<table>
<tr><td></td><td>• Maternal comorbidity – obesity, diabetes, hypertension, asthma, psychiatric illness (depression, anxiety, or bipolar disorder), epilepsy, tobacco use disorder, and alcohol dependence
• Use of health services – hospitalization or ER visit, number of visits to a general practitioner, number of visits to specialist physicians, and number of other prescribed medications
• Pregnancy-related variables – previous pregnancy, obstetric care for index pregnancy
• Nausea or vomiting – ≥1 outpatient visit with diagnosis code for nausea or vomiting and ≥1 hospitalization with diagnosis code for nausea or vomiting
• Folate – periconceptional (6 months before pregnancy through first trimester) prescription dispensed for high-dose folate (>5 mg/d)</td></tr>
<tr><td>1.2.6 Sample Size</td><td>N=224,876 singleton live births</td></tr>
<tr><td>1.2.7 Statistical Analyses</td><td>Odds ratios (ORs) estimated by generalized estimating equation (GEE)</td></tr>
<tr><td>1.2.8 Study Results</td><td>Singleton live birth MCM prevalence, by first-trimester antiemetic exposure
<table>
<tr><td></td><td>None</td><td>Any</td><td>D-P</td><td>MTP</td><td>OND</td></tr>
<tr><td>Live births, N</td><td>179,106</td><td>45,770</td><td>45,623</td><td>958</td><td>31</td></tr>
<tr><td>MCM, N</td><td>14,402</td><td>3,962</td><td>3,945</td><td>105</td><td>2</td></tr>
<tr><td>MCM, %</td><td>8.04</td><td>8.66</td><td>8.65</td><td>10.96</td><td>6.45</td></tr>
<tr><td>Ratio</td><td>REF</td><td>1.08</td><td>1.08</td><td>1.36</td><td>0.80</td></tr>
</table>
ABBREVIATIONS: D-P – doxylamine-pyridoxine; MTP – metoclopramide; OND – ondansetron</td></tr>
</table>

ABBREVIATIONS: ER – emergency room; RAMQ – Régie de l’assurance maladie du Québec

8.4 APPENDIX D. DIAGNOSIS CODES FOR MINOR CONGENITAL MALFORMATION

ICD-9	Description
743.6	Congenital anomalies of eyelids, lacrimal system, and orbit
744.1	Congenital anomalies of accessory auricle
744.2	Other specified congenital anomalies of ear
744.4	Congenital branchial cleft cyst or fistula; preauricular sinus
744.8	Other specified congenital anomalies of face and neck
744.9	Unspecified congenital anomaly of face and neck
747.0	Patent ductus arteriosus
747.5	Congenital absence or hypoplasia of umbilical artery
750.0	Tongue tie
752.4	Congenital anomalies of cervix, vagina, and external female genitalia
752.5	Undescended and retractile testicle
754.6	Congenital valgus deformities of feet
755.0	Polydactyly
755.1	Syndactyly
757.2	Dermatoglyphic anomalies
757.3	Other specified congenital anomalies of skin
757.4	Specified congenital anomalies of hair
757.5	Specified congenital anomalies of nails
757.6	Specified congenital anomalies of breast
757.8	Other specified congenital anomalies of the integument
757.9	Unspecified congenital anomaly of the integument

ICD-10	Description
Q10	Congenital malformations of eyelid, lacrimal apparatus and orbit
Q16.2	Absence of eustachian tube
Q17	Other congenital malformations of ear
Q18.0	Sinus, fistula and cyst of branchial cleft
Q18.1	Preauricular sinus and cyst
Q18.2	Other branchial cleft malformations
Q18.4	Macrostomia
Q18.5	Microstomia
Q18.6	Macrocheilia
Q18.7	Microcheilia
Q18.8	Other specified congenital malformations of face and neck
Q18.9	Congenital malformation of face and neck, unspecified
Q25.0	Patent ductus arteriosus
Q27.0	Congenital absence and hypoplasia of umbilical artery
Q38.1	Ankyloglossia
Q51.5	Agenesis and aplasia of cervix
Q51.6	Embryonic cyst of cervix
Q52.0	Congenital absence of vagina
Q52.1	Doubling of vagina
Q52.2	Congenital rectovaginal fistula
Q52.3	Imperforate hymen
Q52.4	Other congenital malformations of vagina

ICD-10	Description
Q52.5	Fusion of labia
Q52.6	Congenital malformation of clitoris
Q52.7	Other and unspecified congenital malformations of vulva
Q53	Undescended and ectopic testicle
Q66.4	Congenital talipes calcaneovalgus
Q66.5	Congenital pes planus
Q66.6	Other congenital valgus deformities of feet
Q69	Polydactyly
Q70	Syndactyly
Q81	Epidermolysis bullosa
Q82	Other congenital malformations of skin
Q83	Congenital malformations of breast
Q84	Other congenital malformations of integument
Q95.0	Balanced translocation and insertion in normal individual
Q95.1	Chromosome inversion in normal individual
Q95.2	Balanced autosomal rearrangement in abnormal individual
Q95.5	Individual with autosomal fragile site
Q95.9	Balanced rearrangement and structural marker, unspecified

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 11, 2019

To: Maureen Dewey, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Gimoti (metoclopramide) nasal spray

NDA: 209388

This memo is in response to DGIEP labeling consult request dated June 19, 2018. Reference is made to a Complete Response letter that was issued on April 1, 2019. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DGIEP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
04/11/2019 09:05:12 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 7, 2020
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	NDA 209388
Product Name, Dosage Form, and Strength:	Gimoti (metoclopramide) nasal spray, 15 mg per spray
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Evoke Pharma, Inc.
FDA Received Date:	December 19, 2019
OSE RCM #:	2018-1162-1
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Gimoti (metoclopramide) nasal spray, the Division of Gastroenterology (DG) requested that we review the proposed Gimoti prescribing information (PI), instructions for use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 209388 for metoclopramide nasal spray previously received a complete response on April 1, 2019 due to clinical pharmacology and product quality/device quality issues.[a]

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Evoke Pharma submitted an NDA for Gimoti (metoclopramide) nasal spray. We reviewed the PI, IFU, carton labeling, and container label. We identified areas in the Gimoti PI, IFU, container label, and carton labeling that can be improved to increase readability and prominence of important information

5 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We provide the recommendations in section 5.1 and 5.2 below and recommend that they are implemented prior to approval.

[a] Dewey, M. FDA Communication: Complete Response for Gimoti (NDA 209388). Silver Spring (MD): FDA, CDER, OND, DGIEP, (US): 2019 APR 01.

5.1 RECOMMENDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

A. Highlights of Prescribing Information
   1. Dosage and Administration Section
      a. The recommended dosing instructions should be expressed in number of sprays and indicate which nostril(s) (e.g. 1 spray in one nostril only or per nostril).

B. Full Prescribing Information
   1. Dosage and Administration Section
      a. The recommended dosing instructions should be expressed in number of sprays and indicate which nostril(s) (e.g. 1 spray in one nostril only or per nostril).
   2. How Supplied/Storage and Handling Section
      a. This section should be revised to include total # of sprays per bottle.

C. Instructions for Use
   1. The statement "[redacted] (b) (4)" in the Important Information section should be deleted. We note that an affirmative statement with respect to the correct route of the administration already exists in this section. Additionally, we are aware of post-marketing reports that negative statements (e.g. do not) may have the opposite intended meaning because the word "not" can be overlooked, and the warning may be misinterpreted as an affirmative statement.[b]

5.2 RECOMMENDATIONS FOR EVOKE PHARMA, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Labels & Carton Labeling)
   1. The place holder NDC number in all locations should be updated to reflect the actual numerical NDC number.
   2. Revise the statement "[redacted] (b) (4) [redacted]" to read: "Date of first opening _/_/_. Discard unused portion 4 weeks after first use" in bold font under storage information. Additionally, the "__/__/__" statement will alert the users to write a complete date (month, day, and year) on the container label and carton labeling.

B. Container Label
   1. If space allows, add the net quantity statement.

C. Carton Labeling
   1. The statement "[redacted] (b) (4)" located on the side panel should be deleted. We note that an affirmative statement with respect to the correct route of the administration already exists on the principle display panel.

---

[b] Institute for Safe Medication Practices. Affirmative statements (do this) may be better understood that negative warnings (do not d0 that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3

Additionally, we are aware of post-marketing reports that negative statements (e.g.do not) may have the opposite intended meaning because the word "not" can be overlooked, and the warning may be misinterpreted as an affirmative statement.[c]

2. In accordance with 21 CFR 201.55 the "Usual Dose" statement should be added to the side panel (i.e., "Recommended Dosage: See prescribing information.").
3. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier.

   NDC: [insert NDC]
   SERIAL: [insert serial number]
   LOT: [insert lot number]
   EXP: [insert expiration date]

   We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

[c] Institute for Safe Medication Practices. Affirmative statements (do this) may be better understood that negative warnings (do not d0 that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gimoti received on December 19, 2019 from Evoke Pharma, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Gimoti and the Listed Drug

Product Name	**Gimoti**	**Reglan**
Initial Approval Date	N/A	1979
Active Ingredient	metoclopramide	metoclopramide
Indication	For the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis	Treatment of documented gastroesophageal reflux in adults who fail to respond to conventional therapy. Releif of symptoms in adults with acute and recurrent diabetic gastroparesis.
Route of Administration	Intranasal	Oral
Dosage Form	Nasal spray	Tablet
Strength	15 mg per spray	5 mg and 10 mg
Dose and Frequency	Administer 15 mg (1 spray), 30 minutes before each meal and at bedtime (maximum of 60 mg per day) for 2 to (b) (4) weeks	10 mg to 15 mg four times daily for 4 to 12 weeks. Maximum recommended daily dosage is 60 mg.
How Supplied	Supplied as a (b) (4) mg/mL solution of metoclopramide in 10 mL Type 1 amber glass bottle fitted with a metered spray pump attachment, a protective cap, and a safety clip	Bottle of 100 tablets
Storage	(b) (4)	Store at controlled room temperature, between 20°C and 25°C (68°F and 77°F)
Container Closure	Type 1 amber glass bottle fitted with a metered spray pump attachment, a protective cap, and a safety clip	N/A

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 4, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Gimoti. Our search identified one previous review[d] , and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Gimoti labels and labeling submitted by Evoke Pharma, Inc..

- Container label received on December 19, 2019
- Carton labeling received on December 19, 2019
- Instructions for Use received on December 19, 2019, available from \\CDSESUB1\evsprod\NDA209388\0027
- Medication Guide received on December 19, 2019, available from \\CDSESUB1\evsprod\NDA209388\0027
- Prescribing Information (Image not shown) received on December 19, 2019, available from \\CDSESUB1\evsprod\NDA209388\0027

G.2 Label and Labeling Images

(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[d] Griffis (Fanari), M. Label and Labeling Review for Gimoti (NDA 209388). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 15. RCM No.: 2018-1162.

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH K VEE
04/07/2020 11:52:51 AM

ASHLEIGH V LOWERY
04/07/2020 02:36:41 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	April 1, 2019
To:	Dragos Roman, MD Acting Director **Division of Gastroenterology and Inborn Error Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG) anfd Instructions for Use (IFU)
Drug Name (established name):	GIMOTI (metoclopramide)
Dosage Form and Route:	nasal spray
Application Type/Number:	NDA 209388
Applicant:	Evoke Pharma, Inc.

1 INTRODUCTION

On May 30, 2018, Evoke Pharma, Inc. submitted for the Agency's review an original New Drug Application (NDA) for GIMOTI (metoclopramide) nasal spray indicated for acute and recurrent diabetic gastroparesis in adult women. On June 19, 2018, the Division of Gastroenterology and Inborn Error Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU)] for GIMOTI (metoclopramide).

This memorandum documents the DMPP review deferral of the Applicant's proposed MG and IFU for GIMOTI (metoclopramide).

2 CONCLUSIONS

Due to outstanding clinical pharmacology deficiencies, DGIEP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D JACKSON
04/01/2019 02:45:26 PM

MARCIA B WILLIAMS
04/01/2019 02:51:45 PM

COA Tracking ID: C2018185
NDA: 209388

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

Sponsor/Applicant:	Evoke Pharma Inc.
Established Name/Trade Name:	metoclopramide nasal spray/Gimoti
Indication:	relief of symptoms in adult women with acute and recurrent diabetic gastroparesis
Meeting Type/Deliverable:	NDA review
Review Division:	DGIEP
Clinical Reviewer/ Team Leader (TL)	Anil Nayyar, MD/Juli Tomaino, MD
Review Division Project Manager:	Maureen Dewey
COA Reviewer:	Julia Ju, PharmD, PhD
COA TL:	Sarrit Kovacs, PhD
COA Associate Director:	Elektra Papadopoulos, MD, MPH
Date Consult Request Received:	6/20/2018
Date COA Review Completed:	2/26/2019

Please check all that apply: ☐Rare Disease/Orphan Designation
☐Pediatric

A. EXECUTIVE SUMMARY

This clinical outcome assessment (COA) consult review is related to NDA 209388 for metoclopramide nasal spray. The proposed indication is relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.

The Applicant used the following patient-reported outcome (PRO) assessment in their randomized, double-blind, placebo-controlled phase 3 clinical trial (METO-IN-003) in adult women with acute and recurrent diabetic gastroparesis.

Table 1. COA Included in Study METO-IN-003

COA Name (COA Type)	Concept(s)	Endpoint Position[1]	Copy of COA
GSA_Gastroparesis Symptom Assessment (PRO)	Severity of gastroparesis symptoms (nausea, upper abdominal pain, prolonged fullness, bloating, and early satiety)	Primary and Secondary	Appendix A

This submission included a PRO evidence dossier and study synopsis. The Division consulted COA Staff for input on the appropriateness of the GSA used in the pivotal trial METO-IN-003.

[1] Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

Table 2. Fit-for-purpose assessment

COA Attribute	Attribute sufficiently established[2]	Supported by:
Fit-for-purpose (based on available evidence)	☒ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☐ No	☒ Face validity (concepts/items are relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☒ Content validity ☒ COA well-defined and concept able to be accurately communicated ☐ COA is sensitive to change ☐ COA is culturally adapted and adequately translated, if appropriate

The review concludes that the evidence submitted by the applicant is sufficient to demonstrate that the GSA is fit-for-purpose[3] to measure severity of gastroparesis symptoms in the context of use (see Table 2). However, it is unknown what is the threshold of clinical meaningful within patient change in GSA scores due to the limitations of the anchor scales included by the sponsor and it is unknown whether the improvement shown in the post hoc analysis of a subgroup of patients with GSA score >2.7 is clinically meaningful.

B. Comments to Review Division

No COA-related questions were submitted by the applicant. In completion of our COA review, we have the following comments:

- Qualitative development of the GSA appears reasonable and supportive of each of the five symptoms included (nausea, upper abdominal pain, postprandial fullness, early satiety, and bloating).
- The assessment of GSA's ability to detect change was not anchor-based (i.e., using a patient-reported global impression scale) and are not interpretable.
- It is unknown whether the improvement shown in the post hoc analysis of a subgroup of patients with GSA score >2.7 is clinically meaningful.
    - The submitted empirical cumulative distribution function (eCDF) curves were not interpretable because neither anchor scales - Global Severity of Gastroparesis Symptoms (GSGS; see Appendix B) and Change in Gastroparesis Symptom Severity (CGSS; see Appendix C) - included in the sponsor's clinical trial were informative. Some items of the GSGS, which is an investigator assessment, may not be reliable as these gastroparesis symptoms may only be known to patients. The CGSS is a PRO scale, however, the question asked of patients was to report the

[2] See Sections 5 and 6 of this COA review for more detailed information.
[3] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/)

change in severity of their symptoms compared to the week before, instead of comparing to the baseline. Therefore, it is not informative in determining a threshold for meaningful change in GSA scores.

- The sponsor's cut-off in defining a "moderate and severe patients" subgroup to be used for a post hoc analysis is not justified. Based on cut points of the Rasch analysis locations, patients with a GSA-5 average raw score above 2.7 appear to be rated as at least 'severe' as the sponsor stated on page 18 of the Psychometric Analysis of GSA report version 3. There is a concern of the potential for lack of generalizability since they are selecting a threshold based on data in the current study.
- For future studies, we recommend selecting a population of patients that is sufficiently symptomatic at baseline so that a treatment effect can be assessed. In addition, qualitative research studies conducted in development and validation of an instrument should include patients who are sufficiently symptomatic.
- It would be important for future studies to include appropriate global anchor scales that have been agreed upon by FDA before initiation of the clinical trial.

C. BACKGROUND

Previous COA Reviews:

- AT 2011-070_Miskala dated November 15, 2011 (DARRTS Reference ID: 3042751)
- AT 2016-237_IND 025512_Daniels (DARRTS Reference ID: 4034017)

Background:
Gastroparesis is a disorder of the stomach characterized by delayed gastric emptying of solid food in the absence of mechanical obstruction of the stomach; the core signs and symptoms are nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety. These symptoms can be debilitating and negatively impact patients' daily functioning. Symptoms are chronic, with episodic symptom exacerbations. The prevalence of diabetic gastroparesis appears to be higher in women than in men, for unknown reasons.

Other materials reviewed:

- PRO evidence dossier for GSA, final version dated 09/05/2017
- Psychometric Analysis of the Gastroparesis Symptom Assessment: Rasch Measurement Theory analysis on final METO-IN-003 data Report – Version 3
- Sponsor's IR responses dated 11/27/2018 and 12/19/2018

D. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

The target population that was eligible to participate in Study METO-IN-003 included non-pregnant, non-lactating female subjects between the ages of 18 and 75 years (inclusive) with Type 1 or Type 2 diabetes and a diagnosis of diabetic gastroparesis with confirmation of delayed gastric emptying by GES test. In addition, subjects had to have a mean daily GSA total score of ≥ 1.4 and ≤ 3.5 during the Qualification Period and the Baseline Period prior to randomization.

Reviewer's comment(s): *None.*

1.2 Clinical Trial Design

Study METO-IN-003 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of Gimoti 10 mg compared with placebo in adult female subjects with diabetic gastroparesis. A total of 205 women with clinical symptoms attributed to diabetic gastroparesis and delayed gastric emptying who met the protocol-specified entry criteria (mean daily Gastroparesis Symptom Assessment [GSA] total score ≥ 1.4 to ≤ 3.5 during the Qualification and Baseline Periods) were randomized to Gimoti 10 mg or placebo (ratio 1:1) self-administered as a single nasal spray four times per day (approximately 30 minutes before meals and at bedtime) for 4 weeks.

Subjects were trained on the use of an interactive voice response system (IVRS) to record the severity of their gastroparesis symptoms on a daily basis, using the GSA, beginning with the Qualification Period and continuing every day until their last full day on study prior to their final visit.

Table 3 describes the clinical trial design of Study METO-IN-003.

Table 3. Clinical Trial Design for Study METO-IN-003

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☐ Cross-over ☐ Multinational ☐ Non-inferiority	4 weeks	Yes

Refer to the sponsor's submitted clinical study synopsis for more details on the clinical trial design.

Reviewer's comment(s): *None*

1.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule.

Table 4. Endpoint Position, Definition, and Assessment Schedule

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Primary	GSA (PRO)	Symptom severity	Change from the Baseline Period to Week 4 of the Treatment Period in the mean daily 5-item GSA total score (nausea, upper abdominal pain, prolonged fullness, bloating, and early satiety)	☒ Daily ☐ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation
Secondary	GSA (PRO)	Symptom severity	Changes from the Baseline Period to Week 4 of the Treatment Period for the mean daily score of each of the 7 individual IVRS daily diary item scores Changes in vomiting and retching frequencies during the Treatment Period	☒ Daily ☐ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation

Reviewer's comment(s): *Although the GSA total score includes "vomiting" (see Section 2 [Concept(s) of Interest and Conceptual Framework]), the review division noted that the sponsor altered the components of the GSA total score for the primary endpoint from the final protocol (version 2.0; December 23, 2015) to version 1.1 of the SAP (June 18, 2016). More specifically, the vomiting item was replaced by prolonged fullness based on psychometric evaluation of the GSA. The review division noted that the sponsor justified the removal of vomiting by stating that there were few episodes of vomiting during the trials, patients often experience nausea that does not result in vomiting, and that reduction of nausea also reduces vomiting.*

1.4 (b) (4) COA

The sponsor has proposed (b) (4)

(b) (4)

Reviewer's comment(s): (b) (4) (b) (4) (b) (4) *Please see Appendix D and Appendix E for eCDF curves of the treatment vs. placebo arm in ITT population and the subgroup of subjects whose baseline GSA score>2.7, respectively.*

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the GSA are summarized in Table 5.

Table 5. Concepts of Interest for GSA Included in Study METO-IN-003

COA name	Concept(s)
Gastroparesis symptom assessment (GSA) (PRO)	*Severity of Gastroparesis Symptoms (nausea, fullness, bloating, abdominal pain, vomiting)*

The conceptual framework for the GSA is shown in Figure 1 below:

Figure 1. Conceptual framework for the GSA

Concepts: Core Signs / Symptoms	Operationalization of concepts (item wording and response options)	Included in 5-item GSA score	Single item
Nausea	Nausea (feeling sick to your stomach as if you were going to vomit or throw up) (Severity: none to very severe)	X	
Fullness early satiety and post-prandial fullness	Feel full soon after beginning to eat (Severity: none to very severe)	X	
	Prolonged fullness (feeling of food sitting in stomach long after you finish eating a meal) (Severity: none to very severe)	X	
Bloating (physical sensation, visible distension)	Bloating (seeing your belly get large and firm or feeling like you need to loosen your clothes (Severity: none to very severe)	X	
Abdominal Pain	Upper abdominal pain (above the navel) (Severity: none to very severe)	X	
Vomiting	How many times did you vomit (throwing up with food or liquid coming out) in the past 24 hours? (Number of times _____)		X
	How many times did you try to vomit, but nothing came out (dry heave or retching) in the past 24 hours? (Number of times ____)		X

Reviewer's comment(s): *See reviewer's comments under Section 1.3 (Endpoint Position, Definition, and Assessment Schedule) above regarding the sponsor's change in components included in the GSA total score for the primary endpoint (i.e., replacing "vomiting" with "prolonged fullness." The final primary GSA total score endpoint included five symptoms: nausea, upper abdominal pain, prolonged fullness, bloating, and early satiety.*

Including the four symptoms of nausea, upper abdominal pain, prolonged fullness, and early satiety in the GSA total score appears to be consistent with the published draft gastroparesis guidance. The guidance mentions the importance of vomiting to be included as part of a primary endpoint; however, the applicant stated their rationale for its exclusion. We defer to the review division regarding whether vomiting should be taken into account to inform regulatory decision-making.

The fifth GSA concept, bloating, is not mentioned as a core symptom of gastroparesis in the gastroparesis guidance; however, we have had other sponsors provide rationale for its inclusion among the symptoms that gastroparesis patients have reported to be relevant and important for treatment (even when excluding comorbid irritable bowel syndrome [IBS] patients).

3 CLINICAL OUTCOME ASSESSMENT(S)

The GSA is a 5-item scale. The 5 items cover all five core symptoms of gastroparesis identified in the FDA draft gastroparesis guidance document: nausea, fullness soon after beginning to eat (early satiety), postprandial fullness, upper abdominal pain, and vomiting. The GSA also includes an additional symptom, bloating, which were identified as important from patient interviews. The recall period is the past 24 hours.

Reviewer's comment(s): *See reviewer's comments in Sections 1.3 and 2 above regarding the applicant's change in the GSA total score, replacing "vomiting" with "prolonged fullness."*

4 SCORING ALGORITHM

The daily GSA score was computed as the average of 5 individual symptom scores of nausea, early satiety, prolonged fullness, bloating, and upper abdominal pain. The GSA symptom summary score is composed of five symptom items: GSA item 1 Nausea; GSA item 2 Feel full soon after beginning to eat; GSA item 3 Prolonged fullness; GSA item 4 Bloating; and GSA item 5 Upper abdominal pain. Responses to GSA items 1 to 5 (none, mild, moderate, severe, very severe) are scored 0, 1, 2, 3, 4 to represent categories of increasing severity.

A total daily score is derived by summing patients' responses to these five items only if at least four of the five items are completed. The GSA weekly ensemble score is created by averaging the total daily score over seven days for a more accurate (i.e., lower standard error) score. This weekly ensemble score can be calculated only if daily assessments are available for five days of the period or more.

Reviewer's comment(s): *The scoring algorithm appears reasonable.*

5 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

☒ Literature review and/or publications
☒ Documentation of expert input
☒ Qualitative study protocols and interview guides for focus group or patient interviews
☒ Chronology of events for item generation, modification, and finalization (item tracking matrix)
☒ Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
☐ Quantitative study summary with evidence to support item retention and scoring
☐ Transcripts (if available)

Table 6 documents the adequacy of the content of the COAs.

Table 6. Review of Content Validity for GSA

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☒ Literature ☒ Clinical input e.g. discussion with clinical reviewer	
Content validity	☒ Yes ☐ Potentially – insufficient evidence	☒ The item concepts are relevant/important to target patient population and appropriate to the	*Section IV of GSA PRO evidence dossier, previous COA review*

	available; additional information is needed ☐ No	study design and objectives ☒ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☒ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☒ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☒ Descriptive statistics (if available) support content relevance ☐ Other (see Reviewer's comments)	

Reviewer's comment(s): *Qualitative development of the GSA appears reasonable and supportive of the content validity of each of the 5 symptoms included (nausea, upper abdominal pain, postprandial fullness, early satiety, and bloating) in the GSA total score.*

See the following previous COA reviews, during the IND phase, with extensive review of the applicant's research supporting the GSA's content validity, psychometric properties and performance:

- *AT 2011-070_Miskala dated November 15, 2011 (DARRTS Reference ID: 3042751)*
- *AT 2016-237_IND 025512_Daniels (DARRTS Reference ID: 4034017)*

6 OTHER MEASUREMENT PROPERTIES

To date, the following information has been submitted (check all that apply):

☐ Literature review and/or publications
☐ Quantitative analysis synopsis
☐ Full quantitative analysis plan
☒ Quantitative study summary with evidence to support reliability, construct validity, ability to detect change and scoring

Table 7 documents the adequacy of the other measurement properties of the COAs.

Table 7. Review of Other Measurement Properties for GSA

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Internal consistency reliability estimates in acceptable range (e.g., Cronbach's α > 0.70) ☒ Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC ≥0.70) ☐ Inter-rater reliability estimates in acceptable range ☐ Other (see Reviewer's comments)	Section F of GSA evidence dossier
Construct validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Relationship to other assessments with similar concepts is as expected ☐ Relationship to other assessments with dissimilar concepts is as expected ☒ COA differentiates between clinically distinct groups (i.e., known groups validity) ☐ COA scores are related to a known gold standard assessment of the same concept ☐ Other (see Reviewer's comments)	Section F of GSA evidence dossier
Ability to detect change	☐ Yes ☒ Potentially – insufficient evidence available; additional information is needed ☐ No	☐ COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept ☒ Other (see Reviewer's comments)	Section F of GSA evidence dossier

Reviewer's comment(s): *The assessment of GSA's ability to detect change was not anchor-based (e.g., using a patient-reported global) and are not interpretable. The sponsor did not use groups of patients who have changed in severity status of gastroparesis symptoms to examine whether GSA can identify differences in scores in those patients. Instead, the sponsor only examined the GSA score changes among screening, baseline, week 1 through week 4 and those score changes are not informative with regard to the GSA's ability to detect change.*

7 INTERPRETATION OF SCORES

To date, the following information has been submitted:

☒ Anchor-based analyses

☒ Anchor-based empirical cumulative distribution function (eCDF) curves
☒ eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
☒ Anchor-based probability density function (PDF) curves
☒ PDF study arm curves (Treatment vs. Placebo/Active Comparator)
☐ Qualitative support for meaningful change (e.g., patient input)

Table 8 documents the adequacy of the score interpretability of the COAs.

Table 8. Review of Score Interpretability for GSA

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	☐ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☒ No	☐ Appropriate global anchor scales were included for anchor-based analyses ☐ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☐ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☐ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☒ Other (see Reviewer's comments)	*Sponsor's IR response dated 12/19/2018*

Reviewer's comments: *No statistically significant difference was found for the primary efficacy endpoint (change from the Baseline Period to Week 4 of the Treatment Period in the mean daily GSA total score: 0.894 vs. 0.926; p=0.881). In a post hoc analysis performed by Evoke, Gimoti treatment arm showed statistically significant improvement in Phase 3 patients with moderate to severe symptoms at baseline, which included 105 of the 205 patients (51%) enrolled in the study. In the post hoc analysis, patients receiving Gimoti also had statistically significant improvements in nausea and upper abdominal pain, reported to be two of the most debilitating symptoms of gastroparesis, at all four weeks. Note that no evidence on the measurement properties of the GSA single items was generated.*

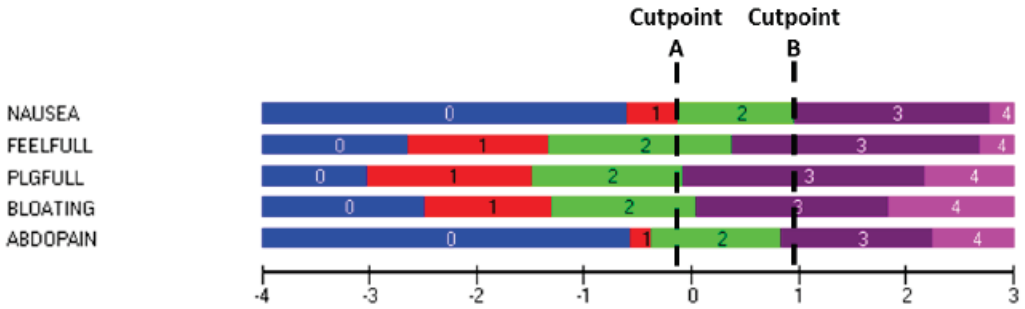
To examine whether improvement in the post hoc analysis of patients with a GSA score of >2.7 was clinically meaningful, we sent the sponsor two information request (IR) letters to request anchor-based empirical cumulative distribution function (eCDF) and probability distribution function (PDF) curves of the change in GSA-5 total score from baseline to week 4 plotted for the categories defined using the GSGS and the CGSS as anchors, in the ITT population and in the subgroup of subjects with baseline GSA-5 total score of >2.7 for the phase 3 trial, METO-IN-003. However, the sponsor's submission of eCDF curves was not interpretable because neither anchor scale (GSGS or CGSS) used is informative. Some items of the GSGS which is an investigator assessment may not be reliable as gastroparesis symptoms may be known only to patients. The CGSS is a PRO scale; however, the question asked patients to report the change in

severity of symptoms compared to the week before, instead of comparing to the baseline. Therefore, it is not informative with regard to determining the threshold of meaningful change in GSA total score from baseline.

Additionally, based on cut points of the Rasch locations (See Figure 2 below), patients with a GSA-5 average raw score above 2.7 are the most probably rated as at least 'Severe.' On page 18 of the Psychometric Analysis of GSA report version 3, the sponsor stated that "Patients with a GSA-5 average raw score above 2.7 are those for whom all GSA-5 symptoms are the most probably rated as at least 'Severe'". Therefore, the sponsor's description of the subgroup of patients with a GSA-5 score >2.7 included in the post hoc analysis as moderate and severe patients is not justified. There is a concern of the potential for lack of generalizability since they are selecting a threshold based on data in the current study. Furthermore, patients who were rated as severe by their clinicians represented only 4% and 7% of participants included in the concept elicitation interview study and cognitive interview study, respectively; these studies were conducted by the applicant in development and validation of the GSA.

In summary, based on the discussion above, it is unknown whether the improvement in the post hoc analysis of subgroup of patients with GSA score >2.7 is clinically meaningful.

Figure 2. Cut points on the Rasch location (in logits) corresponding to cut point A and cut point B



Cutpoint A: 2 on the GSA-5 score to delineate these patients between mild and moderate symptoms
Cutpoint B: 2.7 on the GSA-5 score to delineate patients between moderate and severe symptoms

D. APPENDICES

Appendix A: Gastroparesis Symptom Assessment (GSA)
Appendix B: Global Severity of Gastroparesis Symptoms (GSGS)
Appendix C: Change in Gastroparesis Symptom Severity (CGSS)
Appendix D. eCDF curves by treatment arms in the ITT population
Appendix E. eCDF curves by treatment arms in subjects with baseline GSA score>2.7

Appendix A: Gastroparesis Symptom Assessment (GSA)

Gastroparesis Symptom Assessment

These questions ask about symptoms you may have each day. Please complete the daily diary *each evening at approximately the same time*.

For each symptom *please choose the number* that best describes the symptom when it was most severe *during the past 24 hours*. Please be sure to complete the severity for each symptom and to answer each question.

	None	Mild	Moderate	Severe	Very severe
1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4
2. Feel full soon after beginning to eat	0	1	2	3	4
3. Prolonged fullness (feeling of food sitting in stomach long after you finish eating a meal)	0	1	2	3	4
4. Bloating (seeing your belly get large and firm or feeling like you need to loosen your clothes)	0	1	2	3	4
5. Upper abdominal pain (above the navel)	0	1	2	3	4

For the next two questions, please record the number of times you have vomited (question #6) or dry heaved (question #7) in the past 24 hours. For example, please record zero if you have not vomited; record 1 if you have vomited once, record 2 if you have vomited twice, etc.

	Number
6. How many times did you vomit (throwing up with food or liquid coming out) in the past 24 hours?	_____
7. How many times did you try to vomit, but nothing came out (dry heave or retching) in the past 24 hours?	_____

Appendix B. Global Severity of Gastroparesis Symptoms (GSGS)

14.5 Appendix 5: Global Severity of Gastroparesis Symptoms Question for Investigators

Using the 0 to 10 scale below where 0 is ***Not at All Severe*** and 10 is ***Very Severe***, please mark an "X" in the box (☒) which best describes your medical assessment of the severity of the subject's gastroparesis symptoms at this visit.

Overall, how severe are the subject's gastroparesis symptoms?										
Not at All Severe ▼										**Very Severe** ▼
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Appendix C. Change in Gastroparesis Symptom Severity (CGSS)

14.4 Appendix 4: Change in Gastroparesis Symptom Severity Question for Subjects

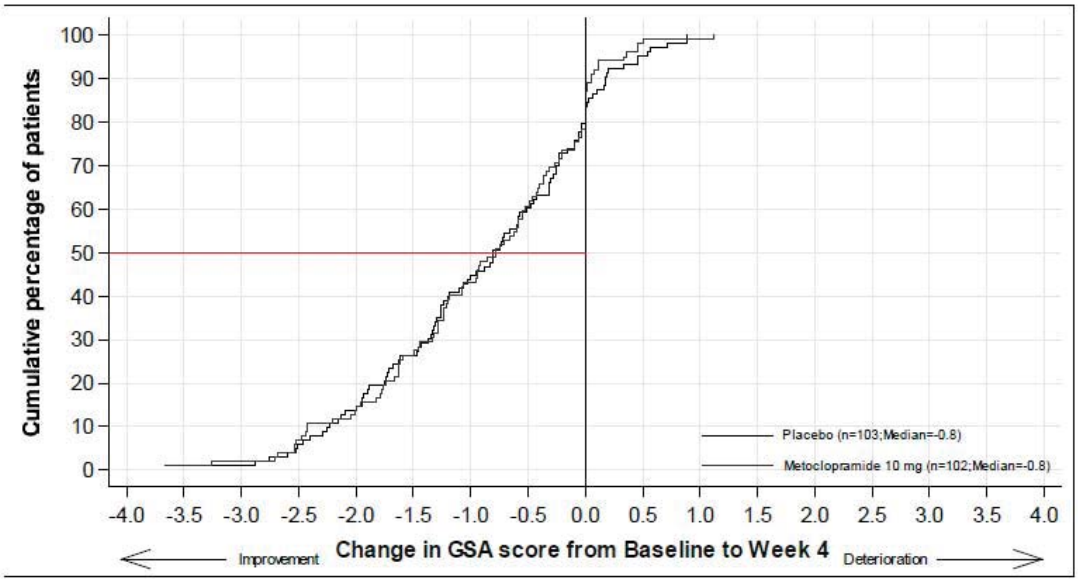
This question asks about the overall change you may have experienced in the severity of your symptoms since your last visit. Please answer the question by choosing the response that best describes your symptoms over the past week.

With respect to your gastroparesis symptoms, how would you describe your symptoms over the past week compared to the week before?

- ☐1 Very much improved
- ☐2 Much improved
- ☐3 Minimally improved
- ☐4 No change
- ☐5 Minimally worse
- ☐6 Much worse
- ☐7 Very much worse

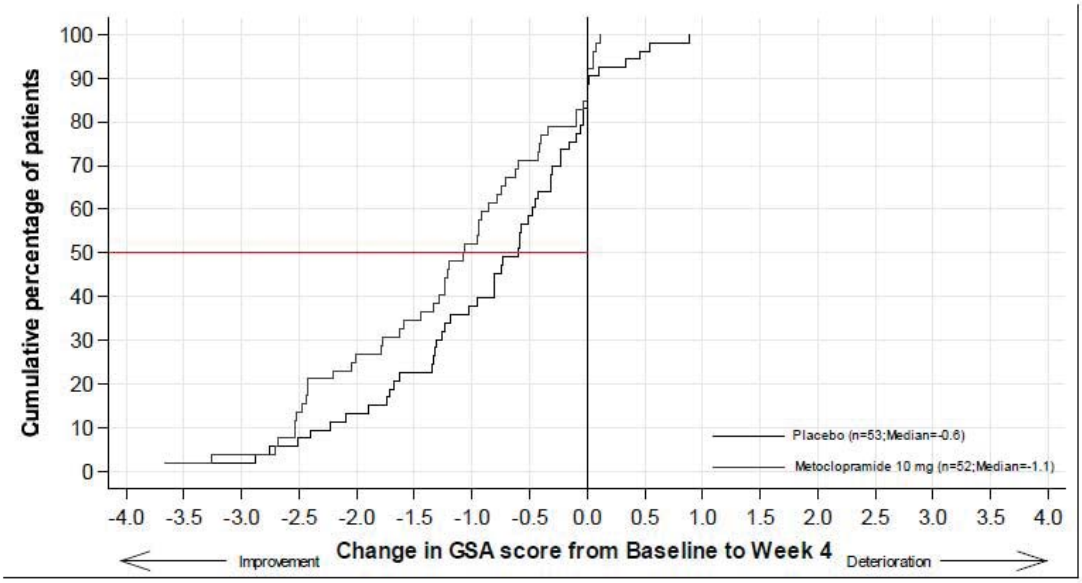
Appendix D. eCDF curves by treatment arms in the ITT population

Figure 3.1.1: Empirical Cumulative Distribution of change in Gastroparesis Symptom Assessment (GSA) total score from baseline to week 4 by treatment (ITT population)



Appendix E. eCDF curves by treatment arms in subjects with baseline GSA score>2.7

Figure 3.2.1: Empirical Cumulative Distribution of change in Gastroparesis Symptom Assessment (GSA) total score from baseline to week 4 by treatment (subgroups of subjects with baseline GSA score >2.7)



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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Metoclopramide Utilization in the Sentinel Distributed Database

Date:	March 7, 2019
Reviewer/ Team Lead:	Patricia L. Bright, MSPH, PhD Division of Epidemiology I
Associate Director:	Wei Hua, PhD Division of Epidemiology I
Drug Name:	Metoclopramide hydrochloride (HCL): • oral tablet (5 mg, 10 mg) • oral solution (5 mg/5 mL) • injectable solution (5 mg/mL)
Subject:	Summary statistics for pharmacy prescription claims for incident metoclopramide use among women age 40 years and over in the Sentinel Distributed Database
Application Type/Number:	NDA 209388 Gimoti (metoclopramide) nasal spray
Applicant/sponsor:	Evoke
OSE RCM #:	2018-1161

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This Division of Epidemiology (DEPI) review provides utilization data on incident metoclopramide use from the Sentinel Distributed Database (SDD) among women age 40 years and older, with subgroup analyses for those with type 2 diabetes codes and with a combination of type 2 diabetes and gastroparesis codes. This review will help inform the Office of New Drugs (OND), Division of Gastroenterology and Inborn Error Products (DGIEP) of metoclopramide use among women to provide context for DGIEP's assessment of Gimoti (metoclopramide) proposed for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.

Metoclopramide is a dopamine receptor antagonist indicated for the treatment of gastroesophageal reflux in adults who fail to respond to conventional therapy and for symptom relief in adults with acute and recurrent diabetic gastroparesis. Metoclopramide contains a boxed warning about the risk of tardive dyskinesia and cautions against treatment for longer than 12 weeks duration because of the increased risk of developing tardive dyskinesia with longer-term use.

DEPI obtained data from the SDD for the period of January 1, 2009, to September 30, 2015. Cohort members were comprised of: women, age ≥ 40 years, and with medical and drug coverage for at least 365 days prior to the first valid metoclopramide prescription claim. Members were excluded if they had evidence of a live birth delivery within 301 days following the index metoclopramide dispensing.

DEPI also conducted a subgroup analysis on two progressively nested cohorts:

1. Women who had an ICD-9-CM code for type 2 diabetes within the prior 365 days
2. Women who had an ICD-9-CM code for type 2 diabetes and an ICD-9-CM code for gastroparesis within the prior 365 days

The utilization data on incident metoclopramide use in SDD showed:

- Metoclopramide use among women ≥ 40 years was common; 1,436,794 incident users had 3,120,140 dispensings between January 2009 through September 2015
- Approximately 1/3 (n=502,877) of users had a code for type 2 diabetes
- A much smaller proportion (3.7%, n=52,937) had a code for both gastroparesis and type 2 diabetes
- Among women with codes for diabetes and gastroparesis, 25% of metoclopramide treatment episodes exceeded 45 days in duration (i.e., threshold defined a typical single prescription with 30 days of supply and 50% gap allowance)
    - This represents the proportion with diabetic gastroparesis that may utilize metoclopramide beyond a 4-week regimen
- Use appears to spike at 1-day and at 30-days (the analysis did not provide the granularity to distinguish between differing formulations or routes of administration)
- Although it comprised a small proportion of the overall use, some patients use

metoclopramide beyond 12-weeks of duration without breaks (not adhering to the boxed warning)

- 135,890 female incident users of metoclopramide in the base cohort had continuous treatment episodes over 12 weeks duration between January 2009 through September 2015 (excluding patients with gaps between dispensings).

1 INTRODUCTION

1.1 Background

This Division of Epidemiology-I (DEPI) review provides utilization data on incident metoclopramide use from the Sentinel Distributed Database[a] (SDD) among women age 40 years and older, with subgroup analyses for those with type 2 diabetes codes and with a combination of type 2 diabetes and gastroparesis codes. This review will help inform the Office of New Drugs (OND), Division of Gastroenterology and Inborn Error Products (DGIEP) of metoclopramide use among women to provide context for DGIEP's assessment of the Gimoti (metoclopramide) submission proposed for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.

Metoclopramide is a dopamine receptor antagonist (a synthetic substituted benzamide), indicated for the treatment of gastroesophageal reflux in adults who fail to respond to conventional therapy and for symptom relief in adults with acute and recurrent diabetic gastroparesis. Metoclopramide is available as Reglan (initial approval in 1979) and as a generic.

A boxed warning for metoclopramide for tardive dyskinesia was added in 2009 as follows:

WARNING: TARDIVE DYSKINESIA

- **Reglan can cause tardive dyskinesia (TD), a serious movement disorder that is often irreversible. There is no known treatment for TD. The risk of developing TD increases with duration of treatment and total cumulative dosage *[see Warnings and Precautions (5.1)]*.**
- **Discontinue Reglan in patients who develop signs or symptoms of TD. In some patients, symptoms may lessen or resolve after Reglan is stopped *[see Warnings and Precautions (5.1)]*.**

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[a] The Sentinel Distributed Database (SDD) is an active surveillance monitoring system for medical products. The SDD uses linked administrative and insurance claims databases. Data partners contribute administrative, medical, and pharmacy insurance claims and some demographic data. Approximately half of individuals covered in SDD are between ages 18 and 65 years; most individuals covered in the SDD are privately insured.

- **Avoid treatment with Reglan for longer than 12 weeks because of the increased risk of developing TD with longer-term use *[see Warnings and Precautions (5.1) and Dosage and Administration (2.2, 2.3)].***

Evoke (b) (4) has submitted an application for Gimoti (metoclopramide), formulated as a nasal spray, proposed for adult women with delayed or erratic gastric emptying and/or nausea and vomiting due to gastroparesis. The sponsor is proposing administration of Gimoti up to four times a day for a (b) (4) week duration.

To provide context for a (b) (4) week regimen, DEPI obtained utilization data from the SDD[b] for other modes of metoclopramide administration (oral tablet, oral solution, injectable solution).

2 REVIEW METHODS AND MATERIALS

DEPI staff conducted this review with attention to criterion included in the Guidelines for Good Pharmacoepidemiology Practices (GPP) by the International Society of Pharmacoepidemiology (ISPE)[1].

3 REVIEW RESULTS

3.1 Overview

This review provides data from the SDD from 17 health plans over a period from January 1, 2009, to September 30, 2015. The time period was selected to include a large number of health plans contributing to SDD, but to avoid the shift from International Classification of Diseases, Ninth Revision to Tenth Revision (ICD-9 to ICD-10)[c]. (See Appendix 1 for a list of dates of available data from each data partner contributing to SDD.)

This assessment provides summary statistics on duration of metoclopramide treatment.

3.2 Objective

The objective of this assessment was to obtain metoclopramide utilization data in SDD among members who met inclusion and exclusion criteria. In specific, the study was designed to provide data on metoclopramide use in a patient population that might approximate potential users of Gimoti, a metoclopramide product currently under DGIEP consideration for approval.

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[b] The Centers for Medicare and Medicaid Services (CMS) contributed to the data analyses presented in this review as one of the data partners.

[c] The study period was designed to avoid the ICD-9 to ICD-10 transition to reduce the complexity of the assessment and given that the inclusion of ICD-10 codes would likely only gain a small incremental proportion of additional users.

The review provides data on women ≥ 40 years of age who were not pregnant at the time of and for 301 days following the index metoclopramide dispensing[d]. Subgroup analyses provide data on such women who also have 1) a type 2 diabetes code and 2) with a combination of type 2 diabetes code and code for gastroparesis. (For full eligibility parameters for the cohorts assessed, see section 3.3.2 for eligibility criteria.)

3.3 Methods

3.3.1 Design and Setting

DEPI designed this inquiry to calculate summary statistics on duration of metoclopramide use corresponding to treatment dispensed in any care setting as captured in the SDD.

3.3.2 Eligibility Criteria

Members included in this cohort were comprised of:

- Women
- Age ≥ 40 years
- With one or more pharmacy prescription claims for metoclopramide
- With medical and drug coverage for at least 365 days prior to the first valid metoclopramide prescription claim (with gaps of enrollment coverage allowed up to 45 days)

Members were excluded if they:

- Had evidence of a live birth delivery within 301 days following the index metoclopramide dispensing[d][2]

In addition to the above "base cohort," two subgroup analyses further required:

1. Women to have an ICD-9-CM code for type 2 diabetes within the prior 365 days
2. Women to have an ICD-9-CM code for type 2 diabetes and an ICD-9-CM code for gastroparesis within the prior 365 days

(See Appendix 2 for ICD-9-CM codes used in the analysis.)

3.3.3 Exposure

The exposure of interest was oral and/or injectable metoclopramide, defined using National Drug Codes (NDCs) and Healthcare Common Procedure Coding System (HCPCS) procedure codes

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[d] DEPI made an attempt to exclude pregnant women from this assessment to avoid capturing metoclopramide use that might be used for indications associated with pregnancy. The 301-day period for excluding subsequent live births after the index metoclopramide dispensing corresponds to the longest gestation calculated by Sentinel's Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) algorithm[2].

(Appendix 3). Exposure episode length was defined using the days' supplied per dispensing to create a continuous sequence of exposure.

- Stockpiling of overlapping dispensings was applied separately for the oral and injectable NDC.
- One day supply was assigned for dispensings described by a procedure code.
- Same day dispensings were converted to the maximum days supplied.
- Dispensing gaps were allowed within an episode if the days' supply was less than 50% of the prior dispensing. Examples:
    - two dispensings of a 3-day supply would bridge a 1-day gap and be counted as contributing to one continuous treatment episode,
    - whereas two dispensings of 20-days' supply would bridge a gap of 9 days between the two dispensings and contribute to one continuous treatment episode.
- Exposure episodes were included until the occurrence of any of the following:
  1) disenrollment
  2) death
  3) date partner end date or
  4) the end of the query period.

"Metoclopramide" was the only generic name used in this SDD assessment; see Appendix 2 for the NDC codes.

3.3.4 Outcomes

This assessment did not evaluate outcomes corresponding to metoclopramide use.

3.3.5 Other Variables

DEPI also conducted a sensitivity analysis to evaluate continuous metoclopramide use without breaks; only episodes were included that had a zero-day gap in order to restrict the assessment to overlapping dispensings and abutting dispensings. Such dispensings that contributed to a continuous exposure episode could be used to identify continuous use beyond 12 weeks that didn't accommodate breaks between treatment episodes (not adhering to the boxed warning).

3.3.6 Sample Size and Statistical Analysis

No sample size or statistical analysis was required for this report on drug utilization patterns.

3.4 Study Results

Of 1,436,794 women 40 years of age and older in the SSD with an incident metoclopramide pharmacy claim (defined as no metoclopramide in the prior 365 days) between January 2009 and September 2015 and with no evidence of a liveborn delivery in the next 301 days, 35% (n=502,877) had an ICD-9-cm diagnosis code of type 2 diabetes. Of the 1,436,794 base cohort, only 3.7% (n=52,937) had codes for both type 2 diabetes and gastroparesis (Table 1).

Table 1: Women, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, and with no evidence of a liveborn delivery in the next 301 days.

Cohort	N	% of all
All women	1,436,794	100.0%
Diabetic women	502,877	35.0%
Diabetic women with gastroparesis	52,937	3.7%

Diabetic women with gastroparesis codes had a slightly higher proportion of women in 65-74 years of age (table 2). For further granularity on age distribution, along with the mean and median days' supply, for the base and two nested cohorts, see table 3.

Table 2. Diabetic women with gastroparesis, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, (stratified by age group) and with no evidence of a liveborn delivery in the next 301 days.

Diabetic women with gastroparesis		
Age (years)	**N**	**%**
40-54	12,322	23.3
55-64	12,017	22.7
65-74	15,829	29.9
75+	12,769	24.1

Mean days' supply per metoclopramide dispensing increased with age (table 3). Among women 40-45 years of age, the mean dispensing was 12 days (median 3) which increased to a mean of 21.9 days (median of 30) among those over 80 years of age.

Mean days' supply per metoclopramide dispensing was higher for those with diagnoses codes for type 2 diabetes or with codes for gastroparesis (table 3).

Table 3. Mean and median days supplied per metoclopramide dispensing* in women, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, (stratified by age group) and with no evidence of a liveborn delivery in the next 301 days.

Mean, **Median,**

(Number of total dispensings)			
Age groups	Base cohort	Subgroup having type 2 diabetes ICD-9-cm code	Subgroup having type 2 diabetes ICD-9-cm code and with ICD-9-cm code for gastroparesis
40-44	12.0, 3 (n=227,058)	16.6 10 (n=57,799)	23.0 30 (n=12,380)
45-49	13.9, 6 (n=264,514)	18.3 20 (n=81,580)	24.3 30 (n=17,596)
50-54	15.5 8 (n=310,184)	19.8 27 (n=112,488)	25.6 30 (n=23,216)
55-59	17.5 15 (n=309,858)	20.8 30 (n=133,179)	26.7 30 (n=25,266)
60-64	18.5 15 (n=282,115)	21.4 30 (n=135,611)	27.0 30 (n=24,834)
65-69	18.6 15 (n=436,579)	21.2 30 (n=208,440)	28.3 30 (n=33,654)
70-74	19.2 20 (n=408,442)	21.6 30 (n=201,445)	28.4 30 (n=30,344)
75-79	20.2 25 (n=328,970)	22.1 30 (n=166,668)	27.9 30 (n=23,685)
80+	21.9 30 (n=552,420)	22.8 30 (n=250,081)	27.4 30 (n=29.923)
Total dispensings	(n=3,120,140)	(n=1,347,291)	(n=221,298)

* No summation or bridging across dispensings, multiple dispensings may be listed per patient.

There were fewer "treatment episodes" than metoclopramide dispensings because multiple dispensings could contribute to a single treatment episode. However, patients could also contribute multiple treatment episodes if the gap between days' supply in the dispensing exceeded 50% of the prior dispensing.

Table 4 and 5 show the number and duration of episodes for the subgroup that had both diabetes and gastroparesis codes. Approximately 25% of episodes in this subcohort exceeded a duration of 45 days (table 5).

Table 4. Treatment episodes* per patient and metoclopramide prescriptions (RXs**) per treatment episode by age group in diabetic women with gastroparesis, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, (stratified by age group) and with no evidence of a liveborn delivery in the next 301 days.

Diabetic women with gastroparesis			
Age (years)	**N**	**Episodes per patient**	**RXs per episode**
40-54	12,322	2.6	1.7
55-64	12,017	2.3	1.8
65-74	15,829	2.1	1.9
75+	12,769	1.9	2.2
All	52,937	2.2	1.9

*Episode period defined by the days of treatment supplied by consecutive prescriptions, allowing treatment gaps <50% of prior supply. A patient can have more than one episode if gap >50% of prior supply.

**RXs per episode Count of prescription claims / Count of treatment episodes

Table 5. Treatment episode duration in diabetic women with gastroparesis, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, (stratified by age group) and with no evidence of a liveborn delivery in the next 301 days.

Diabetic women with gastroparesis				
		Duration (days), % of episodes		
Age (years)	**Episodes, N**	**≤ 45**	**46-89**	**≥ 90**
40-54	31,605	80.0	8.7	11.3
55-64	27,389	75.3	10.1	14.6
65-74	33,610	73.4	10.4	16.2
75+	24,225	70.2	11.4	18.5
All	116,829	75.0	10.1	14.9

Similar to dispensings, mean days' supply per metoclopramide treatment episode increased with age (table 6) and for those with additional codes indicating type 2 diabetes or with codes for gastroparesis (table 6).

Table 6. Mean and median days of metoclopramide treatment episode duration in women, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, (stratified by age group) and with no evidence of a liveborn delivery in the next 301 days.

Mean, Median, (Number of total episodes)			
Age		Subgroup having type 2	Subgroup having type 2 2iabetes ICD-9-cm code and with ICD-9-cm code for

groups	Base cohort	diabetes ICD-9-cm code	gastroparesis
40-44	14.9 1 (n=186,743)	23.5 5 (n=42,221)	38.1 30 (n=7,716)
45-49	18.3 1 (n=207,269)	26.9 7 (n=57,067)	41.6 30 (n=10,601)
50-54	21.1 2 (n=235,422)	30.4 10 (n=75,755)	46.4 30 (n=13,288)
55-59	24.9 5 (n=224,722)	32.8 11 (n=87,566)	50.1 30 (n=14,154)
60-64	27.2 7 (n=198,106)	34.6 12 (n=86,524)	52.5 30 (n=13,235)
65-69	26.9 6 (n=311,981)	33.5 10 (n=136,247)	55.6 30 (n=17,776)
70-74	28.5 7 (n=285,598)	35.2 13 (n=127,804)	56.3 30 (n=15,834)
75-79	32.0 10 (n=214,807)	38.4 15 (n=99,084)	59.0 30 (n=11,572)
80+	41.7 15 (n=299,385)	46.3 20 (n=127,341)	66.9 30 (n=12,653)
Total episodes	(n= 2,163,033)	(n=839,609)	(n=116,829)

The cumulative exposure duration reports total treatment duration across all treatment occurrences for each patient by age group. (A patient is only captured once in cumulative duration but this duration may be comprised of multiple episodes and multiple dispensings for that patient.) Cumulative duration reported in table 7 allows for breaks between treatment and for bridging and is not restricted to continuous use.

The assessment identified episodes with a duration greater than 12 weeks allowing for bridging between episodes with gaps of < 50% of prior dispensing -- so does not necessarily reflect continuous use. (For episodes greater than 12 weeks duration without gaps [continuous use], see table 8.)

- Of the 839,609 episodes that met the requirements for the base cohort and had a diagnosis of type 2 diabetes (table 7), 9.6% (n=80,742) had an episode greater than 12 weeks.
- Of the 116,829 episodes that met the requirements for the base cohort and had a diagnosis of type 2 diabetes and gastroparesis (table 7), 15% (n=17,701) had an episode greater than 12 weeks).

Table 7. Mean and median days of cumulative metoclopramide treatment duration (with 50% gap allowance) in women, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, (stratified by age group) and with no evidence of a liveborn delivery in the next 301 days.

Mean, Median, (Number of patients with given treatment duration [across all treatment occurrences for that patient])			
Age groups	Base cohort	Subgroup having type 2 diabetes ICD-9-cm code	Subgroup having type 2 diabetes ICD-9-cm code and with ICD-9-cm code for gastroparesis
40-44	22.3 2 (n=124,942)	43.7 4 (n=22,681)	99.6 30 (n=2,952)
45-49	27.9 2 (n=135,880)	50 5 (n=30,728)	107.3 30 (n=4,111)
50-54	32.2 1 (n= 154,171)	55.4 5 (n=41,514)	117.3 30 (n=5,259)
55-59	38.8 2 (n=144,317)	58.5 7 (n=49,045)	117.9 30 (n=6,021)
60-64	41.8 2 (n=129,111)	59.3 7 (n=50,544)	116.0 30 (n=5,996)
65-69	39.9 2 (n=210,423)	53.9 6 (n=84,564)	118.9 30 (n=8,314)
70-74	42.0 2 (n=193,217)	56.2 7 (n=80,069)	118.7 30 (n=7515)
75-79	47.6 5 (n=144,167)	61.2 10 (n=62,201)	116.9 30 (n=5,845)
80+	62.2	72.3	122.3

	10 (n=200,566)	19 (n=81,531)	30 (n=6,924)
Total cumulative episodes	(n=1,436,794)	(n= 502,877)	(n=52,937)

Patient distribution by duration of cumulative metoclopramide treatment (with 50% gap allowance) is shown in figure 1. Unlike the data in table 7, the data for duration in figure 1 was reported by the groups for duration in days: 1, 2-7, 8-14, 15-21, 22-28, 29-45, 46-60, 61-89, 90+. Therefore, a spike driven by a single day would reflect an increase across the associated duration group.

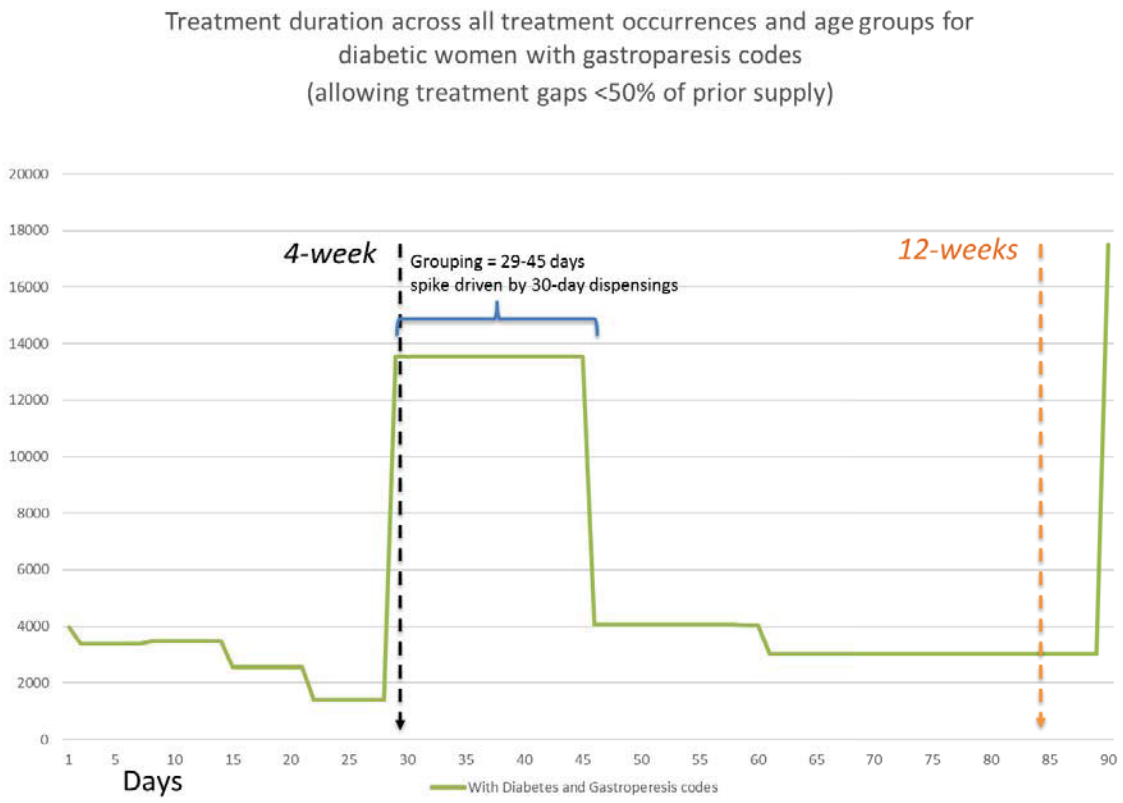

Figure 1: Diabetic women with gastroparesis: Cumulative metoclopramide treatment duration (with 50% gap allowance) in women, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, and with no evidence of a liveborn delivery in the next 301 days (data not stratified by age).

To evaluate whether some patients use metoclopramide continuously (without breaks) against the caution issued for long term duration of use in the boxed warning, DEPI conducted a sensitivity analysis to evaluate episodes that only had a zero-day gap in order to restrict the assessment to overlapping dispensings and abutting dispensings.

Table 8. Episodes beyond 12-weeks duration when restricted to only overlapping and abutting prescriptions (no gap or break in use) in women, ≥ 40 years, with a new metoclopramide prescription dispensed in the SDD between January 1, 2009, and September 30, 2015, and with no evidence of a liveborn delivery in the next 301 days.

Duration Groups (Days)	Base cohort	Subgroup having type 2 diabetes ICD-9-cm code	Subgroup having type 2 diabetes ICD-9-cm code and with ICD-9-cm code for gastroparesis
85-89	1650.0	932	195
90+	134,240	72,274	15,732

4. DISCUSSION

Frequent metoclopramide use in the base cohort

Metoclopramide use appears to be substantial in the base cohort with 1,436,794 female users identified (table 1). These 1,436,794 women had 3,120,140 dispensings (table 3) and corresponded to 2,163,033 episodes (table 6, multiple dispensings could contribute to an episode if the days' supply was less than 50% of the prior dispensing).

Frequent metoclopramide use among nested cohort of diabetic women

Of 1,436,794 women in the base cohort, 35% (n=502,877) had an ICD-9-cm diagnosis code of type 2 diabetes. These 502,877 women had 1,347,291 dispensings (table 3) and corresponded to 839,609 episodes (table 6, multiple dispensings could contribute to an episode if the days' supply was less than 50% of the prior dispensing).

Metoclopramide use among nested cohort of diabetic women with gastroparesis (subcohort of interest to DGIEP)

The subcohort of women with codes for diabetes and gastroparesis most closely approximates the target population of women that may seek relief for symptoms of diabetic gastroparesis. This subcohort was comprised of 52,937 women with an ICD-9-cm diagnosis code of type 2 diabetes and for gastroparesis. These 502,877 women had 1,347,291 dispensings (table 3) and corresponded to 839,609 episodes (table 6, multiple dispensings could contribute to an episode if the days' supply was less than 50% of the prior dispensing).

Duration of metoclopramide use among diabetic women with gastroparesis

In this subcohort of women with codes for diabetes and gastroparesis, 25% of metoclopramide treatment episodes exceeded 45 days in duration (i.e., threshold defined a typical single prescription with 30 days of supply and 50% gap allowance) (table 5). This represents the proportion with diabetic gastroparesis that may utilize metoclopramide beyond a 4-week regimen.

Continuous metoclopramide use beyond 12 weeks duration without breaks

DEPI conducted a sensitivity analysis restricted to only overlapping and abutting prescriptions (no gap or break in use) (table 8). In the base cohort of all women that met eligibility criteria, there were 135,890 continuous metoclopramide episodes beyond 12 weeks that didn't encompass breaks between treatment episodes (inconsistent with the boxed warning); 73,206 of these women also had a code for diabetes. Of the 135,890 with continuous use beyond 12 weeks that didn't encompass breaks, 15,927 (11.7%) had codes for both diabetes and gastroparesis.

Lack of validation

Chart validation was not conducted for this analysis so diagnosis codes for diabetes and gastroparesis are not confirmed by medical records. Similarly, age was determined from the claims data, but was not verified against medical records.

The potential for misclassification of diabetic patients with missing gastroparesis codes but using metoclopramide for gastroparesis symptoms is described below.

Target population and potential misclassification due to missing gastroparesis codes

DGIEP had a particular interest in the subcohort of women with diabetes and gastroparesis. This subcohort appears to be the closest approximation to the target population of women that may seek relief for symptoms of diabetic gastroparesis. However, there is the potential that women with diabetes may also use metoclopramide for symptom relief of gastroparesis, even if no code was recorded for gastroparesis in the prior 365 days. There is no mechanism to assess the proportion of diabetes patients with gastroparesis symptoms but without accompanying billing code for gastroparesis. Depending on how frequent such misclassification occurs, the actual number of symptomatic users may lie between the numbers reported for the subcohort with both diabetes and gastroparesis codes and the subcohort with only diabetes codes.

Lack of granularity for route of administration

A limitation of this analysis is that it encompassed both oral and injectable metoclopramide. However, SDD data that contributed to this assessment included limited hospital in-patient dispensings. Therefore, metoclopramide use in this analysis will likely correspond to metoclopramide dispensings administered mostly outside of hospital stays, such as at home, in the doctor's office, or in an urgent care setting. This assessment is unlikely to be dominated by postoperative metoclopramide use corresponding to in-patient hospital stays. Although this assessment does not capture a perfect proxy for the population of women interested or likely to use an inhaled metoclopramide product, the information may provide some context for duration of metoclopramide use in women 40 and over.

Capture in SDD

This assessment reflects only those patients with data captured by the SDD prior to September 2015. If trends in use changed following 2015, such trends were not captured.

Also, if patients disenrolled or switched health care plans, metoclopramide duration of use was censored upon disenrollment from the health plan. This would truncate the longitudinal data and not show the full metoclopramide duration for such individuals.

5 CONCLUSIONS

The utilization data on incident metoclopramide use in SDD showed:

- Metoclopramide use among women ≥ 40 years was common; 1,436,794 incident users had 3,120,140 dispensings between January 2009 through September 2015
- Approximately 1/3 (n=502,877) of users had a code for type 2 diabetes
- A much smaller proportion (3.7%, n=52,937) had a code for both gastroparesis and type 2 diabetes
- Among women with codes for diabetes and gastroparesis, 25% of metoclopramide treatment episodes exceeded 45 days in duration (i.e., threshold defined a typical single prescription with 30 days of supply and 50% gap allowance)
    - This represents the proportion with diabetic gastroparesis that may utilize metoclopramide beyond the 4-week regimen proposed for Gimoti
- Use appears to spike at 1-day and at 30-days (the analysis did not provide the granularity to distinguish between differing formulation or route of administration)
- Although it comprised a small proportion of the overall use, some patients use metoclopramide beyond the 12-week duration without breaks (in dissonance with the boxed warning)
    - 135,890 female incident users of metoclopramide in the base cohort had continuous treatment episodes over 12 weeks duration between January 2009 through September 2015 (excluding patients with gaps between dispensings).

6 REFERENCES

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[1] International Society of Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP), Pharmacoepidemiol Drug Saf. 2008 Feb;17(2):200-8.
[2] Li Q, Andrade SE, Cooper WO, et al. Validation of an algorithm to estimate gestational age in electronic health plan databases. Pharmacoepidemiol Drug Saf. 2013;22:524–532.

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APPENDIX 1: Latest date of available data for each data partner until the query end date (September 30, 2015).

The start date for this assessment was January 1, 2009. Therefore, although most data partners contributed data to SDD prior to January 2009, this review only involves data between January 1, 2009, and September 30, 2015.

DP ID	DP Start Date	DP End Date
DP01	1/1/2008	9/30/2015
DP02	1/1/2012	9/30/2015
DP03	1/1/2006	9/30/2015
DP04	1/1/2000	9/30/2015
DP05	1/1/2000	9/30/2015
DP06	1/2/2000	5/31/2015
DP07	1/1/2000	9/30/2015
DP08	6/1/2007	9/30/2015
DP09	1/1/2000	9/30/2015
DP10	1/1/2000	9/30/2015
DP11	1/1/2005	9/30/2015
DP12	1/1/2000	9/30/2015
DP13	1/1/2000	9/30/2015
DP14	1/1/2004	9/30/2015
DP15	1/1/2008	9/30/2015
DP16	1/1/2000	9/30/2015
DP17	1/1/2010	9/30/2015

APPENDIX 2: List of Diagnosis and Procedure Codes Used to Define the Inclusion Criteria in this Request

Code	Code Category	Code Type	Description
Type 2 Diabetes			
250.00	Diagnosis	ICD-9-CM	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
250.10	Diagnosis	ICD-9-CM	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled
250.20	Diagnosis	ICD-9-CM	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled
250.30	Diagnosis	ICD-9-CM	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
250.40	Diagnosis	ICD-9-CM	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
250.50	Diagnosis	ICD-9-CM	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled
250.60	Diagnosis	ICD-9-CM	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
250.70	Diagnosis	ICD-9-CM	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled
250.80	Diagnosis	ICD-9-CM	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
250.90	Diagnosis	ICD-9-CM	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled
250.02	Diagnosis	ICD-9-CM	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
250.12	Diagnosis	ICD-9-CM	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled
250.22	Diagnosis	ICD-9-CM	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled
250.32	Diagnosis	ICD-9-CM	Diabetes with other coma, type II or unspecified type, uncontrolled
250.42	Diagnosis	ICD-9-CM	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
250.52	Diagnosis	ICD-9-CM	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
250.62	Diagnosis	ICD-9-CM	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled
250.72	Diagnosis	ICD-9-CM	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
250.82	Diagnosis	ICD-9-CM	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled
250.92	Diagnosis	ICD-9-CM	Diabetes with unspecified complication, type II or unspecified type, uncontrolled
Gastroparesis			
536.3	Diagnosis	ICD-9-CM	Gastroparesis

APPENDIX 3: List of National Drug Codes (NDCs) used to define the exposure in this request

The only procedure code (HCPCS) used for this assessment was J2765: Injection, metoclopramide HCl, up to 10 mg.

NDC	Generic Name	Brand Name	Form	Route	Strength	Unit	Manufacturer
10019045002	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00703450204	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
76045010120	METOCLOPRAMIDE	metoclopramide HCl	syringe	syringe	injection	5	mg/mL
00409341418	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00703450294	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
23155024031	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00703450201	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
23155024041	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00703450281	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
58196022663	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
24200017444	METOCLOPRAMIDE	metoclopramide HCl	syringe	syringe	injection	5	mg/mL
10019045039	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00409217332	METOCLOPRAMIDE	metoclopramide HCl	syringe	syringe	injection	5	mg/mL
00409341301	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00703450284	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00409341401	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00703450291	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
00409341461	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	injection	5	mg/mL
60977045117	METOCLOPRAMIDE	Reglan	solution	solution	injection	5	mg/mL
60977045103	METOCLOPRAMIDE	Reglan	solution	solution	injection	5	mg/mL
60977045102	METOCLOPRAMIDE	Reglan	solution	solution	injection	5	mg/mL
60977045171	METOCLOPRAMIDE	Reglan	solution	solution	injection	5	mg/mL
58016481101	METOCLOPRAMIDE	Reglan	solution	solution	injection	5	mg/mL
60977045101	METOCLOPRAMIDE	Reglan	solution	solution	injection	5	mg/mL
60977045182	METOCLOPRAMIDE	Reglan	solution	solution	injection	5	mg/mL
66689003150	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
68115023660	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00182189889	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00591222905	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
61919015090	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00677132305	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
63629161804	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
42254026630	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
52959048000	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490591200	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg

55887065320	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
50111051701	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
52959084930	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
63739048210	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
51079088819	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54868187302	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
51079062920	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
49884068905	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
50111043002	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
21695034660	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63739017203	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00591222801	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
51079028301	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63304084610	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63739017215	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63739048201	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
68084067611	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63739017115	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
63739017201	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54738093801	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
49999005730	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00115165202	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
68115023630	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490591300	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
16714006212	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
49999005710	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
51079088820	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
62559011016	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
68094067662	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
00603461521	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00247051210	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54569043400	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490591206	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63304084505	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
55289063160	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
16714006104	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
60432062216	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
63304084501	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00440777190	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00603461528	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490936604	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
00591246801	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00182189800	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
16714006204	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490591303	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg

00591246805	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00093220310	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
66336088090	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
68094068058	METOCLOPRAMIDE	metoclopramide HCl	syringe	syringe	oral	0.9	mg/0.9 mL
50111043001	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
58016072915	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00591246705	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
54868187304	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
17856057605	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
23490936603	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
00591222901	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23629015210	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63629161803	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
50111043003	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
51079062901	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
18837008930	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
63739017103	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
66336080230	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00115165102	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
21695034620	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
58016072920	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00472500659	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
54868003408	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
68084009111	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00440777106	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00440777130	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00591222805	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
23490591309	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00603461432	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
43353050780	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
59911581502	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54868003402	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
47463503530	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
16590015130	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63187040403	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00603143558	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
63739048110	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00904107061	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
43353080860	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
51079088817	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00904107080	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54868003404	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
49999075830	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
54868187300	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
63739017101	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg

43353050760	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490591306	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00440177115	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
58016073360	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
61919015130	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
53489038401	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
54868003403	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
49999005712	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63739017110	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00247051230	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
51079088601	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
54868003400	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54738093701	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00603461530	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
68084000911	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
59911581501	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54868348500	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
42769139500	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
63629161801	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00440777104	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
43386058130	METOCLOPRAMIDE	metoclopramide HCl	tablet,disintegrating	tablet,disintegrating	oral	5	mg
00247051240	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
42291059590	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00591222910	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
51079028320	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00182178989	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00093220301	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00115165103	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00121057616	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
00440777191	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00591246701	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
43386058131	METOCLOPRAMIDE	metoclopramide HCl	tablet,disintegrating	tablet,disintegrating	oral	5	mg
00440777115	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
16714006206	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
51079088801	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54868187301	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
16714006111	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
55887024960	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
16590015090	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00093220401	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
58016072900	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00603461532	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg

62559019016	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
00228226950	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
42769139400	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
43353080853	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63304084605	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63739010310	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
49999005760	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
55289016990	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
55289016920	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
42291059690	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54868003405	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
57866404204	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
42769139405	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
68084009101	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63629300901	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
00440777120	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
16714006211	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00440777008	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
21695048530	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00115165201	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
21695034615	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490936601	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
42254026660	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
43353080760	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
42254019630	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
51079028317	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00093220305	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00472500660	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
58016073330	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
55289016930	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00591246810	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23629015310	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
66689003101	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
16714006210	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
57866404101	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
16714006205	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
43353050753	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54838050880	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
00603461421	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
21695034690	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00603461520	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490591201	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
49884068901	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
52959048030	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
53489038405	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg

68084067601	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00121157610	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
58864072890	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
16590015190	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
49999075860	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
54868187303	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
55887024930	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
54868003407	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
21695048590	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00228226910	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
16714006110	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00440777006	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00904107060	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
43386058031	METOCLOPRAMIDE	metoclopramide HCl	tablet,disintegrating	tablet,disintegrating	oral	10	mg
43353027453	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
62559110606	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
68084000901	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00247051206	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
21695034630	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
43386058030	METOCLOPRAMIDE	metoclopramide HCl	tablet,disintegrating	tablet,disintegrating	oral	10	mg
68094067659	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
00093220405	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
23629015410	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
23490591209	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
16590015030	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
00603461428	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
50111051702	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
54738093802	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00247051220	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
16590015060	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
51079088620	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
49999005700	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
57866404201	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
58016072912	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
49884068505	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00440777108	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
23490936602	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
54738093702	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
63739017210	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
16714006105	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
63739029310	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
58016072930	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg

16590015160	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00677132301	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	5	mg
58864072830	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63629161802	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
54868003409	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00115165101	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
51079028319	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
00440777195	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
55289016915	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
17856057602	METOCLOPRAMIDE	metoclopramide HCl	solution	solution	oral	5	mg/5 mL
49884068501	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
63304084601	METOCLOPRAMIDE	metoclopramide HCl	tablet	tablet	oral	10	mg
65649043102	METOCLOPRAMIDE	Metozolv ODT	tablet,disintegrating	tablet,disintegrating	oral	5	mg
65649043202	METOCLOPRAMIDE	Metozolv ODT	tablet,disintegrating	tablet,disintegrating	oral	10	mg
62559016501	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	5	mg
68220015110	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	10	mg
00091670563	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	5	mg
54868051301	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	10	mg
00091670163	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	10	mg
68220015010	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	5	mg
62559016601	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	10	mg
54868051300	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	10	mg
00091670170	METOCLOPRAMIDE	Reglan	tablet	tablet	oral	10	mg

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/s/

PATRICIA L BRIGHT
03/07/2019 03:01:57 PM

WEI HUA
03/07/2019 03:58:50 PM

DEPARTMENT OF HEALTH HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone: 301-796-2200
FAX: 301-796-9855

PEDIATRIC LABELING REVIEW

From:&	Carolyn L. Yancey, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:&	Hari Cheryl Sachs, MD, Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director, DPMH
NDA Number:&	209388
Sponsor:&	Evoke Pharma, Incorporated
Drug:&	Gimoti (metoclopramide nasal spray)
Drug Class:&	Motility modifier
Dosage Form and Route of Administration:&	10 mL glass vial with a metered nasal spray pump attached with a safety clip and cap. Each metered spray delivers 15 mg of metoclopramide.
Dosing Regimen:&	One spray in one nostril 30 minutes before each meal and at bedtime time (maximum of 4 sprays per day) for 2 to (b)(4) weeks.
Proposed Indication:&	For the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.

Reviewer Comments: The sponsor is seeking an indication only in women because the effect size in men was smaller than in women and not sufficient to show effectiveness. In addition, lower exposures were noted in men. DPMH defers to DGIEP to determine if an approval in women only is appropriate given other forms of metoclopramide are approved in adults regardless of gender.

Consult Request:&	The Division of Gastroenterology and Inborn Errors of Metabolism (DGIEP) requests the DPMH Pediatric Team review of pediatric labeling for new drug application (NDA) 209388 Gimoti (metoclopramide nasal spray) by Evoke Pharma, Incorporated, submitted via a 505(b)(2) regulatory pathway relying on the listed drug Reglan (metoclopramide hydrochloride) Tablets (NDA 017854). Labeling for Reglan was converted to the Physician Labeling Rule (PLR) format and the Pregnancy and Lactation Labeling Rule (PLLR)

format on August 29, 2017. DGIEP also requests DPMH assistance on preparation for the Pediatric Research Equity Act (PeRC) Meeting. The consult is due on February 23, 2019 (consult is dated June 19, 2018).

Background

The labeling under review is for Gimoti (metoclopramide nasal spray), NDA 209388, manufactured by Evoke Pharma, Incorporated. This NDA was submitted on June 1, 2018 via a 505(b)(2) regulatory pathway (as cited above) based on the findings of safety and effectiveness for Reglan (metoclopramide) Tablets, FDA-approved on December 30, 1980, for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis. A bioequivalence (BE) study conducted under Investigational New Drug (IND) 025512 is submitted under NDA 209388 (Gimoti) in support of the proposed metoclopramide nasal spray formulation.[1]

Metoclopramide hydrochloride is a dopamine-2-receptor antagonist that stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions.[2] The exact mechanism of action of metoclopramide in the treatment of gastroesophageal reflux, and acute and recurrent diabetic gastroparesis has not been fully established.[2]

Gimoti (metoclopramide nasal spray) would be marketed as an alternative to oral and injectable formulations of metoclopramide. The safety, efficacy, and pharmacokinetics (PK), and pharmacodynamics (PD) of Gimoti (15 mg, 16 mg, and 17 mg doses) were evaluated across six clinical studies in adults.[3] The primary efficacy endpoint, modified Gastroparesis Cardinal Symptom Index - Daily Dairy (mGCSI-DD) total score change from Baseline to Week 4 was not achieved for both males and females and lacked statistically significant improvement in male patients with gastroparesis symptoms for Gimoti 15 mg and 16 mg compared with placebo. The BE study/PK data was insufficient to establish a bridge to the approved oral tablet, Reglan, in men based on systemic exposure for area under the plasma concentration-versus-time curve (AUC) to Reglan Tablets 10 mg. The applicant acknowledges stalled male enrollment in studies META-IN-004 (males) and META-IN-002 (males and females) and notes that these male enrollment challenges may reflect the lower incidence of diabetic gastroparesis in males compared to females.[4] Efficacy for the primary endpoint mGCSI-DD [in studies META-IN-002 (males and females), META-IN-003 (females), and META-IN-004 (males)] was not demonstrated for the overall population (males and females). Prespecified analysis by sex (study META-IN-002, males and females) and by severity (study META-IN-003, only females) supported efficacy for Gimoti 10 mg in females with diabetic gastroparesis and females with moderate to severe diabetic gastroparesis.[3]

Selection of the 15 mg to-be-marketed dose of Gimoti is based on data from the comparative bioavailability study META-IN-006 that demonstrated that the 15 mg and 16 mg Gimoti doses in women provide equivalent systemic exposure levels (AUC) to Reglan Tablets 10 mg, and the 15 mg Gimoti dose has nearly equivalent exposure regarding the C_{max}. For Gimoti 15 mg, AUC is 50% higher in females than in males, and C_{max} is 76% higher.[5] Safety data from three studies (META-IN-002, -003, and -004) in patients with acute and recurrent diabetic gastroparesis were pooled and reported showing that metoclopramide nasal spray was generally well tolerated at doses from 10 mg to 20 mg with a safety profile consistent with Reglan (metoclopramide) Tablets.

<u>Reviewer Comments</u>: As cited earlier in this review, PK study demonstrated a lower C_{max} for Gimoti than

[1] NDA 209833 GIMOTI (metoclopramide nasal spray) by Evoke Pharma, Inc., received by FDA/DGIEP on June 1, 2018.
[2] NDA 017854 REGLAN (metoclopramide) Tablets for oral use most recent FDA-approved labeling, dated August 29, 2017.
[3] NDA 209833 GIMOTI (metoclopramide) nasal spray by Evoke Pharma, Inc., Module 2.5 Clinical Overview, page 35 to 42.
[4] Jung HK et al. The prevalence and outcomes of patients in Olmstead County, Minnesota from 1996 to 2006. Gastroenterol. 2009;136(4):1225-1233.
[5] NDA 209388 Gimoti (metoclopramide nasal spray). Module Clinical Summary, section 4.2.6, page 40-41.

Reglan Tablets prompting concern that the nasal spray may not be delivering the comparable amount of metoclopramide per the oral route (Reglan Tablets). Clinical Pharmacology reports that 5% of the study subjects had extremely low concentration of Gimoti, some subjects had virtually no exposure while other subjects had very high exposure raising concerns for incomplete drug delivery. A Human Factor study may identify usability issues that may have contributed to the variability in systemic exposure.

Pediatric Research Equity Act Requirements
Under the Pediatric Research Equity Act (PREA), (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Gimoti (metoclopramide) nasal spray represents a new dosage form and a new route of administration for metoclopramide. However, diabetic gastroparesis is on the FDA-Automatic Waiver List of adult-related conditions because this diagnosis is rarely or never occurs in pediatric patients and, as such, studies would be impossible or highly impractical in pediatric patients.

Regulatory History
See DPMH Review of Reglan (metoclopramide) Tablets written by Carolyn L. Yancey, M.D., dated July 19, 2017, for the regulatory background of metoclopramide.

DPMH Pediatric Labeling Recommendations
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric population. Like the innovator (Reglan), Gimoti (metoclopramide nasal spray) has no indication(s) in pediatric patients of any age. Consistent with the Reglan labeling, Gimoti proposed labeling for Section 1, Indications and Usage, includes Limitations of Use:

- GIMOTI is not recommended for use in pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates

(b) (4)

DPMH supports cross-referencing the first entry on pediatric patients under Limitations of Use to subsection 8.4 Pediatric Use to inform prescribers of the risks associated with use of metoclopramide in pediatric patients, including neonates. This review focuses on labeling sections and revisions that directly address pediatric use. These recommendations are based on the DGIEP substantially complete proposed GIMOTI labeling (dated December 11, 2018) which is in PLR/PLLR format. DPMH's recommended information to be added to the labeling is <u>underlined</u>. Information to be deleted has a ~~strikethrough~~. Comments and rationale for DPMH's recommendations to the labeling are in *italics*.

HIGHLIGHTS OF PRESCRIBING INFORMATION

GIMOTI (metoclopramide nasal spray)
Initial U.S. Approval: 1979

INDICATIONS AND USAGE

GIMOTI is indicate for the relief of symptoms in adult (b) (4) with acute and recurrent diabetic gastroparesis.

(1)

Limitations of Use:

- GIMOITI is not recommended for use in pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates. (1, 8.4)

(b) (4)

Reviewer Comments: DPMH recommends/agrees with retaining Limitations of Use language as in Reglan labeling that informs prescribers that metoclopramide is not recommended for use in pediatric patients due to the risk of TD and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GIMOTI is indicated for the relief of symptoms in adult (b) (4) with acute and recurrent diabetic gastroparesis. (1)

Limitations of Use:

GIMOTI is not recommended for use in pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates *[see Use in Specific Populations (8.4)]*.

(b) (4)

Reviewer Comments: See above DPMH comments to Highlights of Prescribing Information section that applies to the Full Prescribing Information, Section 1 Indications and Usage.

5 WARNINGS AND PRECAUTIONS

5.1 Tardive Dyskinesia

5.2 Other Extrapyramidal Symptoms

Reviewer Comments: DPMH does not recommend any changes to Warnings and Precautions, sections (5.1) and (5.2) on dystonias and other extrapyramidal symptoms, respectively, noted in subsection 8.4 Pediatric Use.

8 USE IN SPECIAL POPULATIONS

8.4 Pediatric Use

Metoclopramide is not recommended for use in pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates. The safety and effectiveness of GIMOTI is pediatric patients have not been established.

Dystonias and other extrapyramidal symptoms associated with metoclopramide are more common in pediatric patients than in adults *[see Warnings and Precautions (5.1, 5.2)]*. In addition, neonates have reduced levels of NADH-cytochrome b_5 reductase, making them more susceptible to methemoglobinemia, a possible adverse

reaction of metoclopramide use in neonates *[see Use in Specific Populations (8.8)]*.

Reviewer Comments: DPMH recommends retaining the language in subsection 8.4, as written in the listed product, Reglan Tablets. The risks of dystonias and other extrapyramidal symptoms are cross-referenced in Warnings and Precautions section (5.1) and (5.2), respectively.

DPMH Actions and Labeling Recommendations

DPMH reviewed Evoke Pharma, Incorporated proposed labeling for Gimoti (metoclopramide nasal spray) and participated in meetings with the DGIEP Clinical Team from July 20 to February 7, 2019. The most recent proposed labeling revisions per DPMH are dated December 11, 2018. DPMH labeling recommendations were provided in track changes for DGIEP consideration to revise the Gimoti nasal spray labeling to align with the listed drug labeling for Reglan and to conform to the *Draft Guidance for Industry and Review Staff* on Pediatric Labeling.[6] DPMH's input will be reflected in the final labeling and the action letter from the DGIEP. Should this product be approved, final labeling will be negotiated with the applicant, and may differ from recommendations in this DPMH labeling review.

[6] *Draft Guidance for Industry and Review Staff* - Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling, February 2013

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/s/

CAROLYN L YANCEY
02/22/2019 03:05:31 PM
DPMH Labeling Review for GIMOTI (metoclopramide) Nasal Spray, NDA 209388, 505(b)(2)

HARI C SACHS
02/22/2019 03:24:03 PM
I agree with these recommendations.

JOHN J ALEXANDER
02/22/2019 05:07:52 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 14, 2019

TO: Dragos Roman, M.D.
Director (Acting)
Division of Gastroenterology and Inborn Errors Products (DGEIP)
Office of Drug Evaluation III
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
DNDBE
OSIS

SUBJECT: Routine inspection of Spaulding Clinical Research, LLC., West Bend, WI.

1 Inspection Summary

OSIS arranged an inspection of study METO-IN-006 (NDA 209388) conducted at Spaulding Clinical Research, LLC., West Bend, WI.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

After reviewing the inspectional findings, I conclude the data from the audited study are reliable.

2 Inspected Study:

NDA 209388

Study Number: METO-IN-006
Study Title: "A Four-Period, Four-Treatment, Four-Sequence Randomized Crossover Study of the Comparative

Bioavailability of Metoclopramide After Nasal and Oral Administration to Healthy Volunteers Under Fasted Conditions”

Dates of conduct: 7/26/2017 – 9/20/2017

Clinical site: Spaulding Clinical Research, LLC.
525 S Silverbrook Drive
West Bend, WI 53095

ORA investigator Denise L. Burosh (BIMOW) inspected Spaulding Clinical Research, LLC., West Bend, WI from October 10-12 and 15-16, 2018.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

At the conclusion of the inspection, investigator Burosh did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

4. Conclusion:

After reviewing the inspectional findings, I conclude the data from study METO-IN-006 (NDA 209388) are reliable.

Based on the inspectional findings, studies of similar design conducted between the previous inspection (02/2017) and the end of the current surveillance interval should be considered reliable without an inspection.

Srinivas R. Chennamaneni, Ph.D.
Staff Fellow

Final Classification:

NAI - Spaulding Clinical Research, LLC.
West Bend, WI
FEI#: 3008921101

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Chennamaneni
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: SRC 1/8/2019
Edit: GB 1/10/2019; CRB 1/10/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Spaulding Clinical Research, LLC., West Bend, WI, USA

OSIS File #: BE 8141
FACTS: 11856300

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SRINIVAS RAO N CHENNAMANENI
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01/14/2019 05:56:53 PM

Clinical Inspection Summary

Date	January 8, 2019
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Anil Nayyar, M.D., Medical Officer, DGIEP
NDA #	209388
Applicant	Evoke Pharma, Inc.
Drug	Metoclopramide nasal spray
NME	No
Division Classification	GI motility modifying drugs
Proposed Indication	Acute and recurrent diabetic gastroparesis in adult women
Consultation Request Date	July 16, 2018
Summary Goal Date	February 1, 2019
Action Goal Date	April 1, 2019
PDUFA Date	April 1, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA were conducted at three clinical investigator (CI) sites. The data from the study are considered reliable. Two of the clinical sites have the final classification of No Action Indicated (NAI) and one clinical site has the final classification of Voluntary Action Indicated (VAI). No significant regulatory findings or data integrity issues were noted.

II. BACKGROUND

The sponsor submitted this NDA for metoclopramide in a nasal spray formulation for the indication of treatment of acute and recurrent diabetic gastroparesis in adult women. Metoclopramide, a dopamine type 2 receptor antagonist, increases lower esophageal pressure, esophageal muscle contractions, gastric emptying rate, and small bowel transit time without increasing gastric secretions. The FDA approved treatment for this condition is an oral dosage formulation of Reglan® (metoclopramide tablets, USP).

Drug:=metoclopramide nasal spray=

Studies: Protocol numbers and titles for all studies that were inspected=

Protocol META-IN-003 entitled "A Multicenter, Randomized, Double-Blind, Placebo-= Controlled, Parallel-Group Clinical Study to Evaluate the Efficacy and Safety of= Metoclopramide Nasal Spray in Women with Symptoms Associated with Diabetic= Gastroparesis"=

- Number of subjects: 205 subjects=
- Number of sites: 41 sites=
- Number of countries where subjects were enrolled: U.S. only=
- Dates that study was conducted: (b) (6)
- Efficacy endpoint: Change in the Daily Global Symptom Assessment (GSA) total score= from Baseline to Week 4=
- Sites were chosen based on enrollment, inspectional history, and number of INDs in the= OSI database=

III. RESULTS (by site):

Name and Type of Inspected= Entity/Address=	Protocol #/ Site #/= # of Subjects= randomized=	Inspection= Dates=	Classification=
CI: Bal Raj Bhandari, M.D.= 3424 Medical Park Drive #6= Monroe, LA 71203=	META-IN-003= Site #305= Subjects:=14=	September= 17 to 20,= 2018=	NAI=
CI: Richard McCallum, M.D.= 4801 Alberta Ave= El Paso, TX 79905=	META-IN-003= Site #347= Subjects:=13=	September= 11 to 13,= 2018=	NAI=
CI: Taddese Desta, M.D.= 292 Euclid Ave #115= San Diego, CA 92114=	META-IN-003= Site 356= Subjects:=10=	October 29= to= November= 7, 2018=	VAI=

Compliance Classifications=
NAI= No deviation from regulations.=
VAI= Deviation(s) from regulations.=
OAI= Significant deviations from regulations.=Data may be unreliable.=

1.= Bal Raj Bhandari, M.D.=
3424 Medical Park Drive #6, Monroe, LA 71203=

For Protocol METO-IN-003 at this site, 26 subjects were screened, and 14 subjects= were enrolled and completed the study.=Review of 100% of all screened and enrolled= subject records was conducted for informed consent process, staff training, test article= accountability, efficacy parameters, protocol deviations, concomitant medications,= eligibility criteria, and adverse events. Source documents for protocol adherence and= data verification were compared to line listings from the NDA. No significant= deviations or discrepancies were noted, and no Form 483 was issued. There was no= evidence of under reporting of adverse events.=

The study appears to have been conducted adequately at this site and the data= generated by this site may be used in support of the respective indication.=

2.= Richard McCallum, M.D.=
4801 Alberta Ave, El Paso, TX 79905=

For Protocol METO-IN-003 at this site, 15 subjects were screened, and 13 subjects= were enrolled and completed the study.=Review of 100% of enrolled subject records= was conducted for informed consent process, staff training, test article accountability,= efficacy parameters, protocol deviations, concomitant medications, eligibility criteria,= and adverse events. Source documents for protocol adherence, data verification, and= test article accountably records were compared to line listings from the NDA. No= significant deviations or discrepancies were noted, and no Form 483 was issued. There= was no evidence of under reporting of adverse events.=

The study appears to have been conducted adequately at this site and the data= generated by this site may be used in support of the respective indication.=

3.= Taddese Desta, M.D.=
292 Euclid Ave #115, San Diego, CA 92114=

At this site, for Protocol METO-IN-003, 43 subjects were screened, and ten subjects= were randomized and completed the study. A total of ten subjects' records were= reviewed.=The data in the line listings was compared with the source documents.=No= significant deviations or discrepancies were noted. There was no evidence of under= reporting of adverse events.=

A Form FDA 483, Inspectional Observations, was issued at the close of the= inspection.=Key findings are that an investigation was not conducted in accordance= with the signed statement of investigator and investigational plan because the=

following protocol violations were noted:

1. Laboratory analysis of serum human chorionic gonadotropin for Subject (b) (6) at screening on (b) (6) and for Subject (b) (6) at screening on (b) (6) was not requested or performed as required by protocol Section 8.2.1, Visit 1: Screening Period. Additionally, a urine pregnancy test for Subject (b) (6) was not performed at study Visit 4 as required by protocol Section 8.2.4, Visit 4: Randomization Visit. Subjects (b) (6) and (b) (6) were female subjects of child bearing potential.
2. Concomitant medications taken by subjects within six months of study entry and throughout the study were not always documented on electronic case report forms, as required by protocol Section 8.3, Concomitant Medications. For example,
   a. Subject (b) (6) discontinued taking trazodone in (b) (6) discontinued omeprazole and Prevpak in (b) (6), and was screened on (b) (6). These medications were not documented on electronic case report forms.
   b. Subject (b) (6) received treatment of prochlorperazine within six months of screening on (b) (6). The medication was not documented on an electronic case report form.

Dr. Desta adequately responded to the inspection findings in a letter dated November 21, 2018.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm.
Review Division /Acting Division Director/Dragos Roman
Review Division /Medical Team Leader/Juli Tomaino
Review Division /Project Manager/Maureen Dewey
Review Division/Medical Officer/Anil Nayyar
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/ Susan D. Thompson
OSI/DCCE/GCP Reviewer/ Susan Leibenhaut
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

SUSAN LEIBENHAUT
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: January 4, 2018 **Date Consulted:** June 19, 2018

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

To: Maureen Dewey, Regulatory Project Manager (RPM)
Division of Gastroenterology and Inborn Error Products (DGIEP)

Drug: Gimoti (metoclopramide)

NDA: 209388

Indication: Relief of symptoms in adult women with acute and recurrent diabetic gastroparesis

Applicant: Evoke Pharma, Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 209388 submitted on June 1, 2018
- DPMH review of Reglan (metoclopramide) Tablets USP (NDA 017854) by Christos Mastroyannis, MD, dated August 22, 2017.[1]

Consult Question: DGIEP requests review of PLLR labeling for this new NDA

[1] The cross-reference to the Reglan consult is included to avoid duplicating background information relevant to this class of products. DPMH's recommendations for the Gimoti labeling discussed below are based solely on information from literature that is not specific to a particular metoclopramide product.

INTRODUCTION

On June 1, 2018, the applicant, Evoke Pharma, submitted a new drug application (NDA) for Gimoti (metoclopramide) via the 505 (b) (2) regulatory pathway. The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on June 19, 2018, to assist with the labeling review for the *Pregnancy*, *Lactation,* and *Females and Males of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- The applicant is relying on the FDA's finding of safety and effectiveness for Reglan (metoclopramide) Tablets USP (NDA 017854) as the listed drug relied upon.[2]
- Metoclopramide received initial U.S. market approval in 1979.
- The proposed indication for Gimoti is the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.

Gimoti Drug Characteristics[3]

- *Drug Class:* dopamine-2-receptor antagonist
- *Mechanism of action:* sensitize tissues to the action of acetylcholine
- *Dosage and administration:* 15 mg per nasal spray administered before each meal and at bedtime for 2 to (b)(4) weeks.
- *Molecular weight:* 354 Daltons
- *Bioavailability:* 47.4%
- *Protein binding:* 30%
- *Half-life:* 8 hours
- *Adverse reactions:* dysgeusia, headache, fatigue, restlessness, drowsiness, and lassitude.

Current State of the Labeling[4]

- Reglan (metoclopramide) Tablet USP (NDA 017854), the listed drug relied upon, currently approved labeling is in the Physicians Labeling Rule (PLR) format and the PLLR format.

REVIEW

Applicant's Review of the Published Literature

The applicant did not specify the search criteria, but submitted the following relevant articles:

- In a register-based cohort study,[5] among 28, 486 women exposed to metoclopramide in the first trimester, there was no increased risk of major congenital malformations overall, for any of the 20 individual malformation categories assessed, spontaneous abortion, or stillbirth.

---

[2] The cross-reference to the Reglan consult is included to avoid duplicating background information relevant to this class of products. DPMH's recommendations for the Gimoti labeling discussed below are based solely on information from literature that is not specific to a particular metoclopramide product.

[3] Gimoti proposed package insert

[4] Reglan currently approved labeling from 8/29/17. Drugs@FDA

[5] Pasternak B, et al. Metoclopramide in Pregnancy and Risk of Major Congenital Malformations and Fetal Death. JAMA. 2013; 310 (15): 1601-1611.

- In a large cohort of infants (n=81,703) exposed to metoclopramide in the first trimester, exposure was not associated with significantly increased risks of any of several adverse outcomes, including congenital malformations, low birth weight, and preterm delivery.[6]

DPMH's Review of the Published Literature

The clinical experience data on metoclopramide use in pregnancy, lactation, and fertility were previously reviewed by DPMH in 2017.[7] DPMH concluded the following:

- *Pregnancy:* The available data from published retrospective cohort studies, national registry studies, and meta-analyses (reflecting over 20 years of use in thousands of pregnant women) failed to demonstrate an association of adverse developmental outcomes with metoclopramide use during pregnancy. There were adverse reactions reported, however, these are not dissimilar to those expected and already described in the Warnings and Precautions section of the Reglan labeling.

- *Lactation:* Metoclopramide is present in the breastmilk. Metoclopramide has been used off-label to induce lactation and improve milk production in women who wish to breastfeed; however, the data are insufficient to support that the drug increases milk production. No adverse reactions have been observed in breastfed infants of mothers who were taking metoclopramide while breastfeeding except for intestinal discomfort (n=2). Metoclopramide may cause extrapyramidal signs (dystonias) and methemoglobinemia in breastfeeding neonates (neonates have reduced levels of NADH-cytochrome b5 reductase, making them more susceptible to methemoglobinemia). Therefore, these neonates should be closely being monitored.

- *Fertility:* Publications identified during this review report on metoclopramide use in fertility, but do not report any specific fertility-related adverse reactions. Theoretically, metoclopramide elevates prolactin levels and this in turn suppresses hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. Suppressed hypothalamic GnRH can inhibit reproductive function by impairing gonadal steroidogenesis in both female and male of reproductive potential. Serum prolactin levels typically return to normal in 1 week and adverse effects typically resolve within a few weeks to months following metoclopramide discontinuation. Metoclopramide does not cause an increase to major congenital malformations and miscarriage in humans; therefore, there are no recommendations for contraception and need for pregnancy testing. Section 8.3, Females and Males of Reproductive Potential, will not be included in Reglan labeling.

Reviewer's Comment

The applicant proposed PLLR labeling for Gimoti similar to currently approved PLLR labeling for Reglan tablets, with the addition of a Human Data subheading in 8.1 Pregnancy. DPMH concludes the Risk Summary in 8.1 adequately describes the available human pregnancy data for metoclopramide. Therefore, DPMH recommends Gimoti PLLR labeling that is consistent with Reglan tablets.

---

[6] Matok I., et al. The safety of metoclopramide use in the first trimester of pregnancy. NEJM 360; 24. 2009.

[7] DPMH review of Reglan (metoclopramide) Tablets USP (NDA 017854) by Christos Mastroyannis, MD, dated August 22, 2017.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling

DPMH Proposed Gimoti Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Published studies, including retrospective cohort studies, national registry studies, and meta-analyses, do not report an increased risk of adverse pregnancy-related outcomes with use of metoclopramide during pregnancy. There are potential risks to the neonate following exposure in utero to metoclopramide during delivery *(see Clinical Considerations)*. In animal reproduction studies, no adverse developmental effects were observed with oral administration of metoclopramide to pregnant rats and rabbits at exposures about 6 and 12 times the maximum recommended human dose (MRHD) *(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 the clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Metoclopramide crosses the placental barrier and may cause extrapyramidal signs and methemoglobinemia in neonates with maternal administration during delivery. Monitor neonates for extrapyramidal signs *[see Warnings and Precautions (5.1,5.2), Use in Specific Populations (8.4)]*.

Data
Animal Data
Reproduction studies have been performed following administration of oral metoclopramide during organogenesis in pregnant rats at about 6 times the MRHD calculated on body surface area and in pregnant rabbits at about 12 times the MRHD calculated on body surface area. No evidence of adverse developmental effects due to metoclopramide were observed.

8.2 Lactation
Risk Summary
Limited published data report the presence of metoclopramide in human milk in variable amounts. Breastfed infants exposed to metoclopramide have experienced gastrointestinal adverse reactions, including intestinal discomfort and increased intestinal gas formation *(see Data).* Metoclopramide elevates prolactin levels *[see Warnings and Precautions (5.7)];* however, the published data are not adequate to support drug effects on milk production. The developmental

and health benefits of breastfeeding should be considered along with the mother's clinical need for Gimoti and any potential adverse effects on the breastfed child from Gimoti or from the underlying maternal condition.

Clinical Considerations

Monitor breastfeeding neonates because metoclopramide may cause extrapyramidal signs (dystonias) and methemoglobinemia *[see Warnings and Precautions (5.1, 5.2), Use in Specific Populations (8.4)]*.

Data

In published clinical studies, the estimated amount of metoclopramide received by the breastfed infant was less than 10% of the maternal weight-adjusted dose. In one study, the estimated daily amount of metoclopramide received by infants from breast milk ranged from 6 to 24 mcg/kg/day in early puerperium (3 to 9 days postpartum) and from 1 to 13 mcg/kg/day at 8 to 12 weeks postpartum.

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/s/

KRISTIE W BAISDEN
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 15, 2018
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 209388
Product Name and Strength:	Gimoti (metoclopramide nasal spray), 15 mg per spray
Product Type:	Single ingredient combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Evoke Pharma, Inc.
FDA Received Date:	June 1, 2018
OSE RCM #:	2018-1162
DMEPA Safety Evaluator:	Melina Griffis, R.Ph.
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 REASON FOR REVIEW

This review evaluates the proposed label and labeling for Gimoti (NDA 209388) for areas of vulnerability that could lead to medication errors. DGIEP requested this review as part of their evaluation of the 505(b)(2) submission for Gimoti. The reference listed drug (Reglan, NDA 17854) was approved in 1979.

1.1 Regulatory History

In a previous review, (RCM 2016-2888) DMEPA evaluated the results of Evoke Pharma's comprehensive use-related risk analysis to determine whether a human factors validation study is required for the proposed Gimoti (metoclopramide nasal spray). DMEPA's findings concluded that Evoke had adequately considered the risks associated with the proposed Gimoti (metoclopramide nasal spray) and that a human factors validation study was not needed.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed label and labeling for Gimoti for areas of vulnerability that may lead to medication errors and determined the label and labeling could be revised to improve clarity and prominence of information and to promote safe use of the proposed product.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We provide the recommendations in section 4.1 and 4.2 below and recommend that they are implemented prior to approval.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information
   1. Dosage and Administration Section
      a. The recommended dosing instructions should be expressed in number of sprays and indicate which nostril(s) (e.g. 1 nostril only or per nostril).

B. Full Prescribing Information
   1. Dosage and Administration Section
      a. A section entitled Administration Information should be added to include the priming requirement.
      b. The recommended dosing instructions should be expressed in number of sprays and indicate which nostril(s) (e.g. 1 nostril only or per nostril).

   2. How Supplied/Storage and Handling Section
      This section should be revised to include total # of sprays per bottle and numerical NDC number.

C. Instruction for Use

   1. The statement "[redacted] (b) (4)" in the Important Information section should be deleted. We note that an affirmative statement with respect to the correct route of the administration already exists in this section. Additionally, we are aware of post-marketing reports that negative statements (e.g.do not) may have the opposite intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative statement.[a]

4.2 RECOMMENDATIONS FOR EVOKE PHARMA

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Labels & Carton Labeling)
   1. The place holder NDC number in all locations should be updated to reflect the actual numerical NDC number.

B. Carton Labeling
   1. The statement "[redacted] (b) (4)" located on the side panel should be deleted. We note that an affirmative statement with respect to the correct route of the administration already exists on the principle display panel.

---

[a] Institute for Safe Medication Practices. Affirmative statements (do this) may be better understood that negative warnings (do not d0 that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3

Additionally, we are aware of post-marketing reports that negative statements (e.g.do not) may have the opposite intended meaning because the word "not" can be overlooked and the warning may be misinterpreted as an affirmative statement.[b]

2. Revise the discard after first use statement to read: "Date of first opening _/_/_. Discard unused portion 4 weeks after first use". In addition, this statement should be in bold font.

3. In accordance with 21 CFR 201.55 the "Usual Dose" statement should be added to the side panel.

C. Container Label

1. Revise the discard (b) (4) after first use statement to read: "Discard 4 weeks after first use.

[b] Institute for Safe Medication Practices. Affirmative statements (do this) may be better understood that negative warnings (do not d0 that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gimoti received on June 1, 2018 from Evoke, and the reference listed drug (RLD).

Table 2. Relevant Product Information for Gimoti and the Listed Drug		
Product Name	**Gimoti**	**Reglan**
Initial Approval Date	N/A	1979
Active Ingredient	metoclopramide	metoclopramide
Indication	For the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis	Treatment of documented gastroesophageal reflux in adults who fail to respond to conventional therapy. Releif of symptoms in adults with acute and recurrent diabetic gastroparesis.
Route of Administration	Intranasal	Oral
Dosage Form	Nasal spray	Tablet
Strength	15 mg per spray	5 mg and 10 mg
Dose and Frequency	Administer 15 mg (1 spray), 30 minutes before each meal and at bedtime (maximum of 60 mg per day) for 2 to 4 weeks	10 mg to 15 mg four times daily for 4 to 12 weeks. Maximum recommended daily dosage is 60 mg.
How Supplied	Supplied as a (b) (4) mg/mL solution of metoclopramide in 10 mL Type 1 amber glass bottle fitted with a metered spray pump attachment, a protective cap, and a safety clip	Bottle of 100 tablets
Storage	(b) (4)	Store at controlled room temperature, between 20°C and 25°C (68°F and 77°F)
Container Closure	Type 1 amber glass bottle fitted with a metered spray pump attachment, a protective cap, and a safety clip	N/A

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 1, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, Gimoti. Our search identified one previous review[c] and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Gimoti labels and labeling submitted by Evoke Pharma.

- Container label received on June 1, 2018
- Carton labeling received on June 1 ,2018
- Instructions for Use (Image not shown) received on June 1, 2018
- Medication Guide (Image not shown) received on June 1, 2018
- Prescribing Information (Image not shown) received on July 6, 2018

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[c] Abraham, S., Review of Human Factors Use-related risk Analysis for Gimoti IND 25512. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Dec 22. RCM No.: 2016-2888.

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MELINA N GRIFFIS
11/15/2018

SARAH K VEE
11/15/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7/16/2018

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209388

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

SHILA S NKAH
07/15/2018