CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209388Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **June 11, 2020**

From: **Caroline Strasinger, Ph.D.**
Reviewer, Branch IV
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV
Division of New Drug Products II
Office of New Drug Products

To: **IQA #2 of NDA 209388 (Dated 21-MAY-2020)**

Subject: **Final Recommendation - APPROVAL**

Summary:
The OPQ Integrated Quality Assessment (IQA) and Executive Summary dated May 21, 2020, was deemed *Not Ready for Approval per* 21 CFR 314.125(b)(6) . In that review it was noted that labeling negotiations had not been completed and that the labeling did not comply with the requirements under 21 CFR 201.

The previous labeling deficiencies for sections 3, 11, and 16 were conveyed to the applicant on June 3, 2020. On June 10, 2020 (sn 0040) a revised PI was submitted agreeing to all proposed changes. See the OPQ Labeling Review Addendum dated June 11, 2020 (Attachment 1 of this IQA).

OVERALL ASSESSMENT AND RECOMMENDATION:

NDA 209388 is now recommended for APPROVAL from the OPQ perspective.

Application Technical Lead Signature:
Caroline Strasinger, Ph.D.,
{see digital signature page}

Attachment 1: Labeling Review #1 Addendum (June 11, 2020)

Memorandum

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From: Caroline Strasinger, Ph.D.
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Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Products II
Office of New Drug Products

To: Labeling Review #1 of NDA 209388 (Dated 21-MAY-2020)

Subject: Final Approval Recommendation

Labeling Review #1 had noted the following pending issues with Sections 3, 11 and 16:

Section 3
- Remove (b) (4)
- Revise section for clarity as indicated above

Section 11
- Remove (b) (4) from metoclopramide HCl
- List ingredients in alphabetical order
- Revise product description for clarity as indicated above

Section 16
- Add dosage form
- Remove (b) (4)
- Revise storage conditions to read "Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]."
- Revise section for clarity as indicated above

On June 10, 2020 the above deficiencies were agreed to by the applicant and an updated PI was submitted. Relevant updated sections of the PI is included as an Attachment below.

OVERALL ASSESSMENT AND RECOMMENDATION:
NDA 209388 is now recommended for approval from the CMC labeling perspective. The Applicant provided updated Prescribing Information on June 10, 2020 (see Attachment 1).

Attachment 1: Final PI (Sections 3, 11, 16)

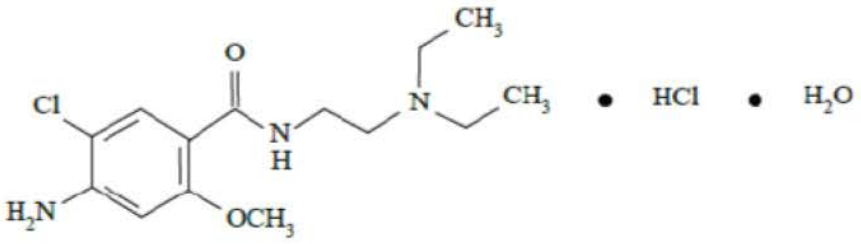
3 DOSAGE FORMS AND STRENGTHS

Nasal Spray: 15 mg of metoclopramide in each 70 microliter spray. GIMOTI is an aqueous solution supplied in an amber glass bottle fitted with a metered spray pump attachment.

11 DESCRIPTION

Metoclopramide hydrochloride, the active ingredient in GIMOTI, is a dopamine-2 receptor antagonist. Metoclopramide hydrochloride is a white, crystalline, odorless substance, freely soluble in water. Its chemical name is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate.

The molecular formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Its molecular weight is 354.3. The structural formula is:



GIMOTI (metoclopramide) nasal spray is for nasal administration. The product is supplied as an aqueous solution with a pH of 5.5 ± 0.5 in a 10 mL amber glass vial fitted with a metered spray pump attachment. Each unit contains 9.8 mL.

Each 70 microliter spray contains 15 mg metoclopramide, equivalent to 17.73 mg of metoclopramide hydrochloride. Inactive ingredients consist of benzalkonium chloride, citric acid monohydrate, edetate disodium dihydrate, purified water, sodium citrate dihydrate, and sorbitol.

16 HOW SUPPLIED/STORAGE AND HANDLING

GIMOTI (metoclopramide) nasal spray is supplied as a solution of metoclopramide in a 10 mL Type 1 amber glass bottle fitted with a metered spray pump attachment, a protective cap, and a safety clip. Each box of GIMOTI (NDC 72089-307-15) contains 1 bottle, with FDA-approved Patient Labeling (see Instructions for Use for proper actuation of the device).

Each actuation delivers 15 mg of metoclopramide. Each bottle contains 9.8 mL which is sufficient for 4 weeks of 4 times a day use.

Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F and 86°F) [*see USP Controlled Room Temperature*].

Discard GIMOTI 4 weeks after opening even if the bottle contains unused medicine.

Moo Jhong Rhee
Digitally signed by Moo Jhong Rhee
Date: 6/11/2020 09:00:19AM
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Caroline Strasinger
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Caroline Strasinger

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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	3/6/2020		
To:	Maureen Dewey		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	DGIEP
From:	Shanly Chen OPEQ/OHT3/DHT3C		
Through (Team):	Rumi Young, MS, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division): *optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: Product device engineering consult for NDA 209388 class 2 Resubmission		
Recommendation:	Device Constituents Parts of the Combination Product are Approvable		
PMC	1. To update the control strategy to include actuation force for the nasal spray in order to ensure that the product can be used by the target population.		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (optional)**

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	00015233
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/500t000000QnbjbAAB/view
ICC tracking #	ICC2000053
Submission Number	NDA 209388
Sponsor	Evoke Pharma
Drug/Biologic	Gimoti
Indications for Use	Relief of symptoms in adult women with acute and recurrent diabetic gastroparesis
Device Constituent	Nasal Spray
Related Files	ICC1800512

2. CDRH REVIEW

ICC Review Request from CDER/OND, DGIEP:	Review of the root cause analysis and response to sponsor questions regarding previous CR letter.
Device Presentation(s) being evaluated:	Nasal Spray
Objective of this Memo:	Evaluation of the root cause analysis and response to previously issued deficiencies in the CR letter.
Review Comments:	There are 2 sections to this review: the root cause analysis and our response to the sponsor questions.
Review Recommendation:	I agree with the sponsor that errors in the clinical study due to low dose is unlikely to be related to the device design or EPRs. Also the sponsor has addressed our deficiencies adequately.

History:

The original inter-center consult on Gimoti (NDA 209388) was completed by Jacqueline Gertz (ICC1800512). There were outstanding deficiencies from her consult along with others from CBER that resulted in a CR letter sent to the sponsor. The sponsor provided a CR response found in sequence 0026 module 1.11.4 to the previous deficiencies. A root cause analysis was provided by CBER, they are asking for a review and comments on the analysis.

Found in sequence 0028 module 3.2.p.8.1 Stability Summary and Conclusions, page 4

The container closure system has been identical throughout all of the stability studies performed to date. The (b) (4) *pumps differ only with respect to* (b) (4) *and there are no differences in the materials or construction. Minor differences in fill volume have been used throughout the development program as summarized in Table 2.*

Table 2: Summary of Fill Volumes Used Throughout Development

Dose Strength	Drug Content* (b) (4)	Dose Volume	Fill Volume (b) (4)
10 mg		50 µL	
14 mg		70 µL	
15 mg		70 µL	
16 mg		70 µL	
17 mg		70 µL	

Per the sponsor the container closure system has been identical, a streamline review memo was chosen, and review focus on the sponsor's response to the previous CR letter (seq 0026 mod 1.11.4) and root cause analysis (NDA 209388 Gimoti).

From Root Cause Analysis provided by CDER:

Problem Statement

Variability in Gimoti blood levels was observed in the four-way cross-over comparative bioavailability study, METO-IN-006, which included three doses of Gimoti (15 mg, 16 mg, and 17 mg) and Reglan Tablet 10 mg. Unexpected low levels of Gimoti (<5 ng/mL) were observed in 14 of 308 concentration-time profiles samples (4.5%) with no relationship to the Gimoti dose. The root cause for these aberrant results was investigated by identifying potential sources of error and evaluating the lines of evidence relevant to each source of error.

The preliminary results of the root cause analysis were submitted in the meeting package for the Type A End of Review meeting that occurred on July 25, 2019.

As captured in the meeting minutes (dated August 21, 2019), FDA responses included:

> *...the 'hesitant' behavior of administrators cannot completely address the potential cause of the low exposure. Although we consider that the data suggests that administers' behavioral variability could have contributed to the low exposure, the data are insufficient to completely rule out other possible causes. Additionally, your root cause analysis does not completely address the "inappropriate actuation force for full dose delivery" as a potential source of error. It is unclear whether your activation force specifications are appropriate for the user population to deliver a complete dose.*
>
> *...the Agency recommended establishing an activation force specification with an adequate justification for the specification range and performing a bench study to determine whether the 14 devices had significantly different activation force from the other devices in the study and whether all devices in the METO-IN-006 study were outside of a reasonable activation force specification. The Sponsor concurred and stated that they will submit the actual actuation force values with the resubmission.*

In response to the Agency's recommendation, a study designed to test the actuation force of the 14 pumps implicated in the low postdose drug levels in the METO-IN-006 comparative bioavailability study was conducted by (b) (4) (b) (4), a cGMP compliant laboratory specializing in analytical testing of drug delivery systems. Test results confirmed that there were no differences in actuation force in the implicated pumps compared to non-implicated pumps and pumps from the recent commercial scale manufacturing that were also included in the test protocol (b) (4) Report SR-2019-097 dated December 6, 2019 provided in Appendix 1).

The 14 implicated pumps were previously tested at (b) (4) to confirm their performance with respect to pump delivery and there were no pump failures. All pumps met shot weight acceptance criteria: (b) (4) actuations per pump; individual shot weights = (b) (4) % label claim; mean shot weights = (b) (4) % label claim ((b) (4) Report SR-2019-050 dated June 25, 2019 in Appendix 2).

Root Cause Analysis Findings and Conclusions

- *Extensive testing (shot weight, actuation force) of the same (b) (4) pumps used to administer Gimoti to the 12 subjects with 14 low post-dose drug levels by a cGMP compliant laboratory specializing in analytical testing of drug delivery systems has ruled out the (b) (4) pump as the source of error.*
- *In the comparative bioavailability study, training did not adequately address the need for all eight dose administrators to gain a level of comfort when approaching subjects to insert the tip of the nasal sprayer in the subject's nose to administer the full dose of Gimoti. Two of the dose administrators had more difficulty than the others when dosing study subjects. These two dose administrators were responsible for 86% of the low drug levels (<5 ng/mL).*
- *Training and behavior of the dose administrators were identified as primary contributors to the incidences of low drug levels.*
- *Unsuccessful drug delivery occurred infrequently, but was more than twice as common among the dose administrators (4.5%) compared to diabetic gastroparesis patients (<2%).*
- *Based on the findings in this root cause analysis, Evoke's conclusion is that the performance of particular study dose administrators was the cause of the aberrant delivery of drug and the incidences of low drug levels in the comparative bioavailability study, METO-IN-006.*

The potential sources of error and lines of evidence are presented in Table 1.

Updates to Table 1 include the results of the additional pump testing (actuation force) and a summary diabetic gastroparesis patient experience from market research as recommended by FDA at the Type A End of Review meeting that occurred on July 25, 2019.

An excerpt of Table 1 is included below, all other rows have been removed except for items pertaining to CDRH per the RPM of NDA 2000053 Gimoti. *The root cause analysis provided by the sponsor is in italics*. My analysis is provided directly below each row.

Potential Source of Error	Details	Supporting Evidence	Refuting Evidence	Likelihood of Error Source Contributing to Low Dose
Pump blockage caused by particulates	*The formulation may contain particulates that caused a pump blockage*	*None available*	• *Bulk solution (b) (4) (b) (4) during manufacture.* • *Bottles cleaned (b) (4)* • *Particulates are assessed as part of release testing.* • *Particulates were assessed as part of the stability program.*	*Unlikely*

			• *No particulate issues have been observed in any of the release and stability program testing.* • *Pumps in METO-IN-006 study were primed prior to dosing.*	
I agree that pump blockage cause by particulates are unlikely. If complete or partial blockages were to appear, then this issue should have been reflected in the plume geometry data over long-term storage (3.2.p.8.3 Stability data, page 19). The plume performance stability data reflect devices that have been stored (both upright and inverted positions) up to 36 months at storage conditions (25C/60%RH) and 6 months for accelerated (40C/75% RH). No evidence that participates in the METO-IN-006 study experienced pump failure issues per sponsor (1.11.4 Multiple…dated 4/1/2019, page 3).				

Inconsistent (b) (4) pump performance	*Performance issues with commercial use of (b) (4) pumps in CDER-approved drug products*	*None available*	• *No pump failures were noted during all of release testing and stability studies for clinical and registration batches.*
			• *Reliability testing supports robustness of design.*
			  ○ *Information Amendment submitted as SN0025 on March 28,2019.*
			  ○ *(b) (4) direct correspondence with the FDA on behalf of Evoke.*
				Unlikely

Agree that previous CDRH review of EPRs such as pump delivery, spray pattern, plume geometry, spray content uniformity does not show inconsistent (b) (4) pump performance. However, there was a CR deficiency regarding variations in droplet size distribution (ICC1800512 memo, page 18). The company provided new DSD data, which appears appropriate, see company response to CR deficiency below.				
Inconsistent (b) (4) pump performance (Comparative Bioavailability Study, METO-IN-006)	*Performance issues with (b) (4) pumps used in the study*	*None available*	• *Single lot of (b) (4) pumps used for study.* • *No pre-release failures in the lot of pumps intended for use in the study.* • *During development reliability testing, it was demonstrated that the pump was robust with respect to physical stresses that may be encountered during shipment.* • *Each nasal spray pump was used only once to deliver one dose to a study subject so an occurrence of 14 individual pump failures is highly unlikely.* • *On site, all pumps were primed in the study pharmacy one day before each dosing day and*	*Unlikely*

			all pumps used in study were confirmed to be working as intended. • *Re-testing of 14 pumps used to dose subjects that produced low PK levels did not show any pump failures. All pumps met shot weight acceptance criteria: (b) (4) actuations per pump; individual shot weights = (b) (4) % label claim; mean shot weights = (b) (4) % label claim.* ○ (b) (4) *Study Report SR-2019-050 dated June 25, 2019 is provided in Appendix 2.*	

In a real world scenario, nasal sprays will be used until the medication runs out and most nasal spray manufactures include overfill for priming sprays. The fact that each pump was only used once (after priming) to deliver medication to the patients represents an artificial best case scenario, however it is reasonable due to clinical testing requirements. I agree that 14 individual pump failures is extremely unlikely in a final finished product. The shot wait re-testing is summarized below (1.11.4 Multiple…dated 4/1/2019, page 60):

10.0 ACCEPTANCE CRITERIA

(b) (4)

After 14 samples were tested and 10 sprays actuated per sample, the average shot weight ranged from 97%-102% which is well within the acceptance criteria.

Faulty assembly of the constituent parts of the Clinical Trial Material (CTM)	*Incorrect assembly could affect combination product functionality (dose delivery)*	*None available*	(b) (4)	*Unlikely*

While possible, if faults were introduced during assembly, it would have been reflected in testing done by the manufacture. Upon review by CDRH documented in memo ICC1800512, the previous reviewer only had issues with droplet size distribution testing. However per ICC1800512, page 17, we had issues with the (b) (4) formulations. If there were faulty assembly issues, we would have expected to see problems across all formulation strengths and in other essential performance requirement testing.. I agree this is very unlikely. We will defer to CMC regarding their opinion on this matter.

Inappropriate actuation force for full dose delivery	*If force required is too great, it may not be possible to fully actuate pump*	*None available*	• *Study demonstrated the actuation force was appropriate to deliver the full dose:*
			  ○ *98% (176/180) of actuations delivered a dose in this actuation force assessment test in which volunteer subjects actuated Gimoti following training by* (b) (4) *(* (b) (4) *Training provided in Appendix 3).*
			  ○ *2% of actuations showed incomplete dose delivery, which is a lower incidence of incomplete actuations than observed in study METO-IN-006 (* (b) (4) *Report dated February 22, 2008 provided in Appendix 4).*
			• *An actuation force study was conducted with volunteers to confirm they were able to successfully actuate the* (b) (4) *pump. The pumps used were from* (b) (4) *commercially manufactured batches. The study showed that all actuations were successful (* (b) (4) *Report dated November XX, 2019 provided in Appendix 5).*
			• *Testing confirmed there were no differences in actuation force in the implicated pumps compared to non-implicated pumps from METO-IN-006, and pumps from the recent commercial scale manufacturing (* (b) (4) *Report SR-2019-097 dated December 06, 2019 provided in Appendix 1).*
				Unlikely

As stated in the problem statement "Unexpected low levels of Gimoti (<5 ng/mL) were observed in 14 of 308 concentration-time profiles samples (4.5%) with no relationship to the Gimoti dose." Only 2% of actuations showed incomplete dose delivery per study METO-IN-006 per Root Cause Analysis above. We would expect similar percentage between low levels of Gimoti in patients vs low actuation delivery.

In seq 27 mod 5.3.1.2.Root cause analysis, page 71 (b) (4) Report, the sponsor conducted an actuation force study with users and nasal sprays containing water (not final formulation) and the average actuation force was 37 N with a range from 20-70 N. They can apply this data to determine the EPR for an actuation force. However, the actual study would need to utilize the finished final product with the planned commercial strength of drug solution.

In seq 27 mod 5.3.1.2.Root cause analysis, page 27 (b) (4) report found no significant differences between the implicated pumps and non-implicated pumps regarding average peak forces. The study was done using automated actuation and not with users. However, since this study to was determine mechanical differences between pumps I agree with the sponsor's methodology.

I agree it is unlikely inappropriate actuation force could have resulted in the dose variability issues. However, an additional comment was asked of the sponsor to either include actuation force as an EPR or justify why it isn't needed, see additional comments item A below.

Deficiencies recommended by CDRH in the CR letter:

Your proposed specification for the drug product is inadequate since insufficient evidence has been provided to ensure that the quality control and essential performance characteristics of the combination product do not contribute to the observed clinical variability and lack of efficacy. Specifically, the method and acceptance criterion for droplet size distribution is not deemed robust enough to guarantee consistent delivery of the drug to the patient with each actuation. The proposed acceptance criterion for droplet size distribution of the 15 mg/mL strength (i.e., the mean droplet sizes and calculated ranges) are not justified particularly given the observed variability of PK data.

Recommendations to Address Deficiencies:

Upon resubmission, all proposed tests and acceptance criteria including the droplet sizes and other essential performance characteristics for the commercial product specification should be supported by three batches of drug product using the selected commercial formulation (including strength of the product) and the commercial device. We recommend that the three registration batches be manufactured at the proposed commercial manufacturing site, manufactured by the proposed commercial process, and tested using validated analytical methods at the proposed analytical site.

Evoke's Reponse:

To address the product quality/device quality deficiencies, Evoke has initiated manufacturing of three batches of drug product using the defined commercial formulation (equivalent to 15 mg dose) and the commercial device. The three registration batches will be manufactured at the commercial manufacturing site, manufactured by the commercial process at the planned commercial batch size, and tested using validated analytical methods at the proposed analytical sites.

To ensure that the acceptance criteria for droplet size and spray pattern are set appropriately Evoke will be taking a statistically-based approach to determining the acceptance criteria for droplet size distribution (DSD) and spray pattern. Evoke has used the transfer and validation data from the proposed release testing laboratory ((b) (4)) as the preliminary data set to assess method performance for DSD and spray pattern.

To determine the appropriate sample size estimate for the three-batch study recommended by FDA, Evoke will consider two quality control studies. (b) (4)

(b) (4)

The comparability report that details the data used to support the qualification of (b) (4) as the testing laboratory for commercial product release for DSD and spray pattern, as described in Section 3.2.R of the NDA, will be used as the initial data set for the study described above will also be provided as part of the resubmission.

Evoke is planning on submitting stability data up to 24 months from its ongoing stability program (see Comment C below for further details). These data will also be assessed against the proposed commercial specifications.

Evoke's Questions

Question #4

Evoke believes the approach described above will provide the requisite data sets required to ensure the droplet size distribution and spray pattern acceptance criteria for quality control and on-going stability are appropriately set. Does the Agency agree?

CDRH analysis:

From 3.2.P.5.6-1, page 12, the sponsor provided updated DSD testing on 3 batches of drug using the final finished device and drug formulation (15mg). All samples tested fell within the DSD acceptance criteria chosen by the sponsor.

Droplet size distribution	D90: (b) (4) D50: D10: Span: % (b) (4): NMT (b) (4)%

The average span was (b) (4) and the other results are displayed below:

	D90	D50	D10	% (b) (4): NMT (b) (4)%
Batch 1	147.6	73.79	30.35	0.2016
Batch 2	152.0	76.01	30.85	0.2399
Batch 3	129.0	63.19	25.78	0.2944

CDRH response:

The updated DSD data is acceptable.

Question #5

Are there any specific data needed, beyond droplet size distribution, spray pattern or shot weight, to address any other outstanding issues?

CDRH analysis:

See analysis for additional comments A below

CDRH response:

See Additional Comments A

ADDITIONAL COMMENTS from CR letter, not classified under deficiencies

PRODUCT QUALITY/DEVICE QUALITY

A. We recommend that actuation force be considered an essential performance requirement and to include a test and acceptance criterion for actuation force for the to-be-marketed combination product in the product release and stability specification. You should include verification and validation data to support that specification and describe why this force is appropriate for the intended user population. Alternatively, provide a rationale for why you do not consider actuation force an essential performance requirement for the device constituent and how you will control the product to assure this essential performance will be consistently achieved.

Evoke Response:

Evoke is collaborating with (b) (4), the device manufacturer, to develop an appropriate strategy to ensure that the actuation force for the to-be-marketed product is appropriately controlled for the combination product in a consistent manner and is applicable to the intended patient population.

(b) (4)

Question #6

Does the Agency have any additional comments or recommendations?

CDRH analysis:

In 3.2.P.7-7 they performed testing to validate the amount of force to actuate the nasal spray is repeatable between sprays and found the average peak force to actuate the nasal sprays was (b) (4) and the average difference in actuation forces between sprays to be 4%. This study was done with 3 analysis with 10 pumps, the genders are unknown.

In seq 27 mod 5.3.1.2.Root cause analysis, page 71 (b) (4) Report, the sponsor conducted an actuation force study with users and nasal sprays containing water (not final formulation) and the average actuation force was 37 N with a range from 20-70 N. It is important to note that while is study should not be the only study used to determine actuation force. This study was performed on 15 users (8 women, 7 men) x 5 nasal sprays x 1 spray each for a total of 75 measurements. Sponsor recorded how much force they used to actuate each nasal spray. It does not determine the minimum actuation force needed to actuate the final finished product. While there is no guidance on actuation force of nasal sprays, EPRs for syringes can be applicable. In 3.2.P.7 Container Closure System, page 6, the sponsor states the actuation force is to be NMT (b) (4) (b) (4). This force is too high to be an acceptable actuation force for their nasal spray.

We want to sponsor to lower the acceptance criteria for actuation force. However, we need the raw data of the users that actuated the sprays in the study. If most of the higher end forces were achieved by men, then we would be justified in asking the sponsor to lowering the actuation force. Per 1.2 Reviewer's Guide, page 9, the proposed indication is "GIMOTI is indicated for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis."

See IR #1 below

In testing done by (b) (4) (Study Report Reference: RE2019.152LPP El/1), you performed testing on your nasal spray to determine the range of forces users actuated your device at. However, you have not provided the raw data of the gender and age of the users corresponding to what forces they actuated the devices at. Provide the data that breaks down the age, gender and forces (in Newtons) of each user recorded in the study performed.

Evoke Response:

Seq 31 mod 1.11.1 Quality Information Amendment:
The sponsor provided the raw data and found that the average actuation for females vs males was 32.1 (stdev 7.6) vs 41.7 (stdev 12.9).

CDRH follow up IR response:

In your response to the previous deficiency you provided the raw data which shows that the average actuation force females vs males used for your device was 32.1 N (stdev 7.6) vs 41.7 (st dev 12.9). However, your essential performance requirement (EPR) for you nasal spray is no more than (b) (4) and your labeling clearly states your device is intended for adult women with diabetic gastroparesis. You should lower your EPR to no more than (b) (4) to ensure your target patient population can use your device effectively.

Evoke Response:

See Seq 33 Mod 1.11.1 Quality Information Amendment for full response

The Root Cause Analysis Report included in the NDA re-submission (SN0027) on December 19, 2019, provided clinical evidence that patients in the Gimoti target population are capable of successfully actuating the (b) (4) nasal spray pump is available from pharmacokinetic (PK) data collected in diabetic gastroparesis studies in the Gimoti development program where patients self-administered the nasal spray 4 times per day for 28 days in Phase 2 (METO-IN-002) and Phase 3 studies (METO-IN-003 and METO-IN-004). Patients self-administered approximately 55,000 nasal spray doses and there were no reported difficulties with dosing.

Post-first in-clinic dose, blood level data were available for 112 patients: 87 females from METO-IN-003 and 26 males from METO-IN-004. Following the first dose of the day, 98% of 112 patients had drug levels >5 ng/mL and, after dose #2, 99% of 114 patients had drug levels >5 ng/mL (Assessment of Real-life Patient Handling of Gimoti in Target Population, Root Cause Analysis Report, Appendix 7).

(b) (4) Method and Test Data

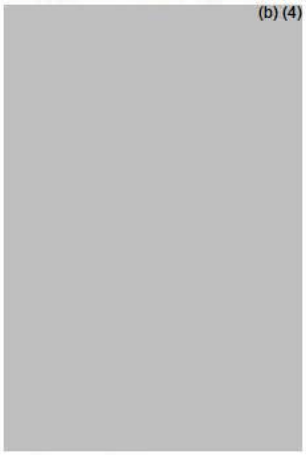
(b) (4)

(b) (4)

Additional Data

Further supportive evidence that users in the target patient population can effectively actuate a higher resistance device was demonstrated in an additional study conducted to assess the absolute Maximum Achievable force for different age and sex populations using an (b) (4) device with an identical hand actuation technique to the (b) (4) and attached to an (b) (4) sensor attached as seen in Figure 5.

Figure 5: Results of Study to Assess Absolute Maximum Achievable Force



In this study, the pump was engineered to require more force to actuate than the standard pump, although the study was not designed to go to failure, i.e., requiring such force that it could not be actuated, it did use pumps that required significantly more force.

The demographics of volunteers in the study were adults 20-59 years (n=17, 9 male, 8 female, various race/ethnicity), females ≥60 years (n=16), males ≥60 years (n=16), and children 10-12 years (n=16, 8 female, 8 male).

The results of the study showing maximum achievable trigger force using the (b) (4) method are shown in Table 4. As shown, all groups, including women greater than 60 years of age, could apply a significantly higher actuation force, if required to do so based on the resistance of the pump. Note, this study did not test pumps that required higher actuation forces than the ones detailed in Table 3 so do not represent the point of failure, i.e., unable to be actuated.

Table 4: Maximum Achievable Trigger Force Using (b) (4) Method

Maximum Achievable Trigger Force	Mean	Standard Deviation
Force Group 1 Children 10-12 yo	46.7 N	8.3 N
Force Group 2 Adults 20-59 yo	55.8 N	2.8 N
Force Group 3 Women > 60 yo	54.0 N	3.4 N
Force Group 4 Men > 60 yo	55.8 N	2.3 N

Determination of Acceptance Criteria

It has been established that the average actuation force required by a user to actuate the pump is (b) (4) N as determined by (b) (4) and this corresponds to (b) (4) using the (b) (4) method.

In addition, it has been shown that significantly higher actuation forces are readily achievable. Specifically, at least (b) (4) N has been shown to be achieved by women in the 51-60 age group. This is a 68% increase over the mean data from the original (b) (4) study.

Using these data, it can be concluded that an upper limit for the (b) (4) QC method could be set at an equivalent higher level, i.e. (b) (4), which would be equivalent to (b) (4) Understanding that this may be close to the maximum achievable actuation force (although the upper bound was never fully explored) an upper limit significantly lower to (b) (4) is proposed. This would equate to approximately (b) (4) by the (b) (4) method and well within the range of typical users as clearly shown in Figure 4.

The data provided herein, and the clinical evidence that the (b) (4) nasal spray pumps performed as expected in Evoke's Phase 3 diabetic gastroparesis studies, support the upper proposed acceptance criterion for the actuation force release specification for the (b) (4) nasal spray pump to be used by the target population of adult women with diabetic gastroparesis.

Analysis:

In normal measurements kilogram-force can be converted to Newtons by multiplying by standard gravity 9.8 m/s^2. However, the sponsor argues that for a nasal spray there is a set velocity, users must maintain at a certain actuation force in order induce an appropriate spray from the device. Per figure 3, footnote 1, this actuation is not applied in a freefall and occurs at constant velocity. Therefore, the sponsor argues that kg cannot be directly converted into N by using standard gravity for the (b) (4) data. Instead a force of (b) (4) by the (b) (4) method is equivalent to a force (b) (4) (b) (4) by the (b) (4) method. The sponsor agrees to an actuation force no more than (NMT) (b) (4) which correlates to approximately (b) (4). Per, page 9, table 4, the data shows the maximum achievable trigger force was (b) (4) for men over 60 years and then for women over 60 years was (b) (4) which is equivalent to (b) (4). The sponsor proposed lowering the actuation force to (b) (4) which is well within the range of forces achieved by the users.

Also, the sponsor provided clinical evidence that current actuation force requirements allow users to actuate the nasal spray without problems. Per sponsor, "*The Root Cause Analysis Report included in the NDA re-submission (SN0027) on December 19, 2019, provided clinical evidence that patients in the Gimoti target population are capable of successfully actuating the* (b) (4) *nasal spray pump is available from pharmacokinetic (PK) data collected in diabetic gastroparesis studies in the Gimoti development program where patients self-administered the nasal spray 4 times per day for 28 days in Phase 2 (METO-IN-002) and Phase 3 studies (METO-IN-003 and METO-IN-004). Patients self-administered approximately 55,000 nasal spray doses and there were no reported difficulties with dosing.*"

There is a post approval comment to add actuation testing to release and stability on the cover page:

To update the control strategy to include actuation force for the nasal spray in order to ensure that the product can be used by the target population.

Response is appropriate.

B. You provided a specification for the lowest allowable cap removal force, but without the highest allowable cap removal force. This information is recommended to demonstrate that the cap will not be too difficult for the user to remove. We recommend the upper cap removal force specification be defined.

Evoke Response:

Evoke is collaborating with (b) (4), the device manufacturer, to develop an appropriate strategy to ensure that the cap removal force will not be so high as to render it too difficult to remove by the patient population.

(b) (4)

Question #7

Does the Agency have any additional comments or recommendations?

CDRH analysis:

Response appropriate.

CDRH response:

3.2.P.7 Container Closure System the sponsor has provided acceptance criteria for the cap retention force of between (b) (4) . This is an appropriate range for the amount of force used to remove the cap and no post approval comment is needed.

C. The proposed shelf-life of (b) (4) months is not supported by the data submitted. Upon resubmission the proposed shelf life should be supported by three batches of the drug product using the selected commercial formulation (including strength of the product) and the proposed commercial device.

Evoke Response:

As discussed and agreed at the Type A Meeting on March 28, 2017, Evoke will be submitting additional stability data (12, 18 and 24 months at the long term storage condition of 25°C/60%RH) for the 17 mg dose strength that effectively brackets the commercial dose strength (15 mg) with the stability data already submitted in the NDA (14 mg strength dataset out to (b) (4) months) to support its justification for the proposed shelf-life of the commercial product. (Type A Meeting Minutes dated March 30, 2017)

Question #8

Does the Agency have any additional comments or recommendations?

CDRH analysis:

Per previous memo ICC1800512, page 17, we wanted the sponsor to bracket the commercial formulation (15mg) with higher (17mg) and lower strengths (14 mg). Response appropriate.

CDRH response:

We agree that the 17 mg dose strength with stability data to 24 months at long term storage condition of 25°C/60%RH would effectively bracket the commercial dose strength of 15 mg.

D. It is premature to agree to a reduced reporting category for an additional release and stability facility as proposed in your comparability protocol.

Evoke Response:

Evoke will be submitting the results from the comparability study and additional supporting documentation as detailed in the original NDA to support the reporting category for the additional testing facility.

CDRH analysis:

While this is listed under additional comments for PRODUCT QUALITY/DEVICE QUALITY, it was not a part of the deficiencies recommended by CDRH in ICC1800512, page 27.

CDRH response:

Not part of CDRH purview.

---END OF REVIEW---

3. APPENDIX

3.1. DOCUMENTS REVIEWED

Sequence	Module
0028	3.2.p.8.1 Stability Summary and Conclusions
0026	1.11.4 Multiple Module Information Admendent
0027	5.3.1.2.Root Cause Analysis Report
0033	1.11.1 Quality Information Amendment

3.2. INTERACTIVE REVIEW

	Date Sent: 3/24/2020	Date/Sequence Received: Click or tap to enter a date.
Information Request #1	In testing done by (b) (4) (Study Report Reference: RE2019.152LPP El/1), you performed testing on your nasal spray to determine the range of forces users actuated your device at. However, you have not provided the raw data of the gender and age of the users corresponding to what forces they actuated the devices at. Provide the data that breaks down the age, gender and forces (in Newtons) of each user recorded in the study performed.	
Sponsor Response	See Seq 33 Mod 1.11.1 Quality Information Amendment for full response	
Reviewer Comments	Response adequate, see page 14 above for analysis	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

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/

CAROLINE STRASINGER
05/21/2020 04:55:49 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response
☒ Not Ready for Approval as of this Review

NDA 209388
Assessment #2

Drug Product Name	GIMOTI (metoclopramide) nasal spray
Dosage Form	Nasal Spray
Strength	15 mg
Route of Administration	Nasal
Rx/OTC Dispensed	Rx
Applicant	Evoke Pharma, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission (0027)	19-JAN-2019	OPQ
Quality/Stability Information (0028)	21-FEB-2020	CDRH/DP
Quality Response to IR (0030)	26-MAR-2020	CDRH/DP
Quality Response to IR (0030)	1-APR-2020	CDRH
Quality Response to IR (0030)	13-APR-2020	CDRH/DP
Quality Response to IR (0034)	16-APR-2020	CDRH
Quality Response to IR (0035)	17-APR-2020	DP
Quality Response to IR (0037)	24-APR-2020	OPMA: Facilities
Multiple Submission (0039)	11-MAY-2020	LABELING/DP
Quality Response to IR (0040)	18-MAY-2020	CDRH/DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Duncan	Donna Christner
Drug Product	Caroline Strasinger	Moo-Jhong Rhee
Manufacturing	Peter Krommenhoek	Nallaperumal Chidambaram
Microbiology	Jianli Xue	
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Marquita Burnett	
Application Technical Lead	Caroline Strasinger	
CDRH	Shanley Chen	Rumi Young
Environmental	Caroline Strasinger	Moo-Jhong Rhee

RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	October 11, 2018	Reviewer: Hongbiao Liao LOA: Jan 26, 2016
	III			N/A[1]	N/A[1]	LOA: Jan 5, 2018
	III			N/A[1]	N/A[1]	LOA: Jan 5, 2018
	III			N/A[1]	N/A[1]	LOA: July 7, 2016

[1] Adequate information provided in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	25512	Metoclopramide Gel for treatment of diabetic gastroparesis from Evoke Pharma. Active since June 6, 2020

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response
☒ Not Ready for Approval as of this Review

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product including with respect to pump performance of this combination drug product. All previous Complete Response Issues have been resolved.

The Office of Process and Manufacturing Assessment (OPMA) has made a final overall "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The labeling for this NDA is inadequate for Sections 3, 11, and 16.

Therefore, from the OPQ perspective, this NDA is **not deemed ready** for approval per CFR 314.125(b)(6), until the labeling deficiencies are satisfactorily resolved. (see the List of Deficiencies)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Metoclopramide is an antiemetic dopamine-2 receptor antagonist. The reference listed drug, Reglan tablets, was approved in December 1980 (NDA 17854) for gastroesophageal reflux and diabetic gastroparesis in adults.

On April 1, 2019 NDA 209388 received a Complete Response recommendation which included several Product Quality and CDRH deficiencies. The applicant resubmitted the application on 19-DEC-2019 and has addressed all Product Quality and CDRH issues identified in the Complete Response Letter (CRL). This IQA (#2) is for the NDA

resubmission and the label and labeling of the drug product. For all other information, refer to the previous IQA dated 21-MAR-2019.

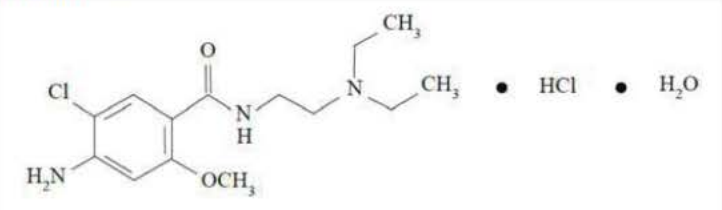
Proposed Indication(s) including Intended Patient Population	For relief of symptoms in adult women with acute and recurrent diabetic gastroparesis
Duration of Treatment	Administer 15 mg, 30 minutes before each meal and at bedtime for 2 to (b) (4) weeks
Maximum Daily Dose	60 mg per day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The active ingredient, metoclopramide hydrochloride, is a white to almost white, crystalline powder. It is freely soluble in water and ethanol. However, its solubility varies with pH. According to the manufacturer, there are no known polymorphs of the drug substance. Metoclopramide hydrochloride is manufactured by (b) (4)

Its chemical name is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. The molecular formula is C14H22ClN3O2•HCl•H2O. Its molecular weight is 354.3. The structural formula is:



The drug substance information is cross-referenced to DMF (b) (4). This DMF was reviewed most recently on 11-Oct-2018 by Hongbiao Liao and was found adequate (refer to DMF (b) (4) Review 12 in Panorama). The drug substance information provided in the DMF is adequate. The sponsor did not provide any drug substance updates in the resubmission. The NDA resubmission is recommended for approval from the perspective of drug substance quality.

Drug Product: Adequate

Metoclopramide nasal spray is supplied in a 10 mL amber glass vial with metered spray pump. The (b) (4) aqueous solution contains (b) ( ) mg of metoclopramide hydrochloride

monohydrate [redacted] as well as the following inactive ingredients: citric acid monohydrate and sodium citrate dihydrate [redacted], benzalkonium chloride [redacted] sorbitol [redacted] edetate disodium dihydrate [redacted] purified water [redacted]. Each pump actuation delivers 15 mg of metoclopramide in 70 µL of solution as a nasal spray.

With the resubmission the applicant has addressed the following Drug Product related deficiencies from the CR Letter:

Product Quality/Device Quality

- The applicant has reevaluated the acceptance criteria for the specification using batches manufactured at the proposed commercial strength, including for spray pattern and droplet size. The applicant has also added a test and acceptance criterion for actuation force to the finished product specification (as requested by CDRH). The provided specification is appropriately justified.

Additional Comment C

- A shelf life of 24 months is supported.
    - The applicant originally proposed a shelf-life of [redacted] months, however, given the uncertainty of the performance characteristics through [redacted] months due to the changes in testing facility, methods and criteria, only a 24 month shelf-life was granted. The applicant can request extensions of shelf life through annual reporting based on real-time stability data following an approved stability protocol. A 24 month shelf life was agreed to via an IR response dated April 17, 2020.
    - No out of specification (OOS) was observed through 3 months for any commercial batch under any storage condition. The 17 mg supportive stability batches likewise appear stable. The drop seen at 12 months for spray pattern across all 15 mg batches can be explained by a change in method and does not appear to be related to an undesirable stability trend.

Additional Comment D

- With the resubmission the new testing facility was incorporated into the resubmission. As such the comparability protocol proposed in the original submission (and discussed in the CRL) is now obsolete:

- The new testing facility was qualified through the provided comparability report and has received an adequate facility recommendation.

Refer to the Drug Product Review for more information on the above 3 items. Refer to the CDRH summary for additional assessment of the Product Quality/Device Quality and Additional Comments A and B of the CRL.

Labeling: Inadequate

The Labeling of NDA 209388 is inadequate due to the deficiencies in Sections 3, 11, and 16 of the PI. These labeling deficiencies were communicated to OND labeling review team on April 9, 2020.

Recommendation:
This application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the label/labeling perspective until the deficiencies noted are satisfactorily resolved.

Manufacturing: Adequate

(b) (4)

Biopharmaceutics: Choose an item.

N/A

Microbiology (if applicable): Adequate

The original submission was reviewed for product quality microbiology in N209388MR01.doc (deemed adequate) dated 12/21/2018. The applicant has provided additional stability data in the resubmission and a cursory review of the resubmission was performed this review cycle. The recommendation remains adequate.

CDRH: Adequate

With the resubmission the applicant has adequately addressed the following Device related deficiencies from the CR Letter:

Product Quality/Device Quality

The Applicant provided updated the acceptance criterion for droplet size dispersion (DSD) and justified it with the testing of 3 batches of drug using the final finished device and drug formulation (15mg). All samples were within the DSD acceptance criteria.

Additional Comment A

During this review cycle the applicant provided additional data to further support their selected acceptance criterion for actuation force and agreed to lower the criterion to (b) (4) and committed to including the test in the product specification as a post marketing commitment, which was sufficient for the CDRH reviewer to recommend approval.

In a late cycle IR response (18-MAY-2020) the Applicant added actuation force to the finished product specification (release and stability). The PMC as indicated in the CDRH review #2 below is no longer needed.

Refer to the updated drug product specification below.

Additional Comment B

The applicant has provided acceptance criteria for the cap retention force of between (b) (4). This is an appropriate range for the amount of force used to remove the cap and no post approval comment is needed.

The overall recommendation from CDRH: Device constituent parts of the combination product are approvable. Refer to the CDRH review for more information.

Specification Provided 18-MAY-2020 (SDN 0039)

Table 1: Specification for Gimoti (Metoclopramide Nasal Spray)

Parameter	Release Criteria
Appearance	A (b) (4) solution.
Packaging appearance	10 cc amber glass bottle with (b) (4) nasal spray pump. No visible leakage or blemishes on container/closure.
Identification	The retention time and the UV spectrum of the major peak in sample injection comply with that in reference standard injection.
Potency assay[1]	(b) (4) % (b) (4) of label claim
Related substances	Individual unspecified impurities (b) (4) % Individual specified impurities (b) (4) Total impurities (b) (4) %
Benzalkonium chloride content	(b) (4) of label claim
EDTA content	(b) (4) of label claim
Droplet size distribution	D90: (b) (4) D50: D10: Span % (b) (4) NMT (b) (4) %
Spray content uniformity	(b) (4)

Parameter	Release Criteria
	(b) (4)
Pump delivery	
Spray pattern	
Actuation force	NMT (b) (4)
Specific gravity	(b) (4)
pH	
Minimum fill	Conforms to USP. Labeled amount (b) (4)
Particulate matter	≥ (b) (4) µm: NMT (b) (4) per bottle ≥ µm: NMT (b) (4) per bottle
Microbial limit test	Total aerobic microbial count: NMT (b) (4) cfu/mL Total combined yeasts/molds count: NMT (b) (4) cfu/mL Absence of *P. aeruginosa* (b) (4) Absence of *S. aureus* (b) (4) Absence of *B. cepacia* (b) (4)

cfu = colony-forming unit; EDTA = ethylenediaminetetraacetic acid; ICH = International Conference on Harmonisation; LID/SID = longest/shortest internal diameter; NMT = not more than; USP = United States Pharmacopeia; UV = ultraviolet; w/v = weight/volume

[1] Free base

[2] Sample packaging fill = 4.6 mL

C. Risk Assessment

From Initial Risk Identification	Assessment

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach (b) (4)	Final Risk Evaluation	Lifecycle Considerations/ Comments
Metoclopramide Assay	Formulation, raw materials, container closure, process parameters, scale, equipment	L		L	
Benzalkonium chloride content	Formulation, stability, container closure	L		L	
EDTA Content	Formulation, stability, container closure	L		L	
spray content/dose uniformity	device performance parameters	L		L	
Droplet size distribution (DSD)	Device/actuator, viscosity of formulation	M		M	Review this data closely as shelf-life extensions are granted due to testing method and site change during the 2 review cycles (6-12 month data only provided)
Spray pattern					
Extractables / Leachables	Formulation, container closure, equipment	L		L	
Actuation Force	Device	L		L	
Microbial limits	Formulation, raw materials, process parameters, packaging defects	L		L	

Particulates	Particulates from excipients equipment, device components	L	(b) (4)	L	

D. List of Deficiencies for Complete Response

1. Labeling Deficiencies

Section 3
- Remove (b) (4)
- Revise section for clarity as indicated above

Section 11
- Remove (b) (4) from metoclopramide HCl
- List ingredients in alphabetical order
- Revise product description for clarity

Section 16
- Add dosage form
- Remove (b) (4)
- Revise storage conditions to read "Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]."
- Revise section for clarity

The above deficiencies are currently under negotiation with the applicant.

Application Technical Lead Name and Date: Caroline Strasinger, PhD 5/20/2020

26 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

On 11-MAY-2020 agreed to changes proposed by ONDP for the Carton/Container and the applicant confirmed the desired presentation of the name is GIMOTI (metoclopramide) nasal spray and not GIMOTI (metoclopramide nasal spray).

1.0 PRESCRIBING INFORMATION

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

GIMOTI (metoclopramide nasal spray)

Initial U.S. Approval: YYYY

----------DOSAGE FORMS AND STRENGTHS----------

Nasal Spray: 15 mg metoclopramide in each 70 microliter spray. (3)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	GIMOTI	ADEQUATE
Established name(s)	(metoclopramide nasal spray)	ADEQUATE On May 11, 2020 the applicant changed the presentation to **(metoclopramide) nasal spray**
Route(s) of administration	Nasal spray	ADEQUATE
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Nasal Spray: 15 mg metoclopramide in each spray	INADEQUATE/**ADEQUATE** Add volume of each spray (70 microliter) This was **satisfactorily** resolved on 5/11/20.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		*CMC defers to OND/Patient Labeling for the appropriateness of these instructions.*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

3 DOSAGE FORMS AND STRENGTHS

Nasal Spray: 15 mg of metoclopramide in each 70 microliter spray. GIMOTI (b) (4) (b) (4) is an aqueous solution (b) (4) supplied in an amber glass bottle fitted with a metered spray pump attachment. (b) (4) (b) (4)

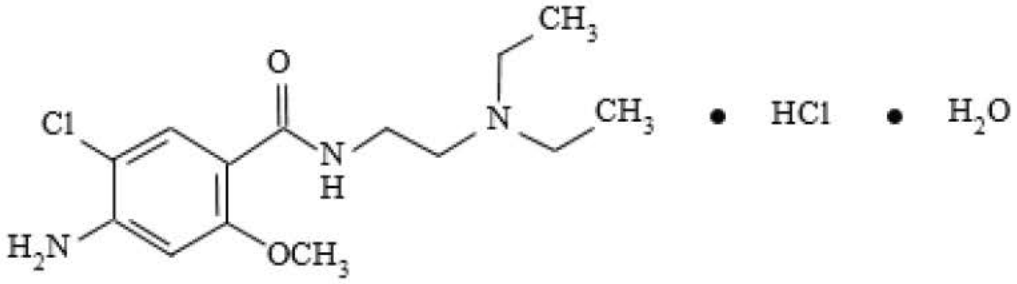
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Nasal spray	INADEQUATE For clarity revise as above
Strength(s) in metric system	15 mg	ADEQUATE
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not provided	15 mg metoclopramide is (b) (4) Per OND request and for clarity of the label, the equivalency statement is only included in section 11.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Aqueous solution in an amber glass bottle	ADEQUATE
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Supplied in amber glass bottle fitted with a metered spray pump attachment.	INADEQUATE For clarity revise as above

1.2.3 Section 11 (DESCRIPTION)

11 DESCRIPTION

Metoclopramide hydrochloride, the active ingredient in GIMOTI, is a dopamine-2 receptor antagonist. Metoclopramide hydrochloride [redacted] is a white, crystalline, odorless substance, freely soluble in water. Its chemical name is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate.

The molecular formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Its molecular weight is 354.3. The structural formula is:



GIMOTI (metoclopramide nasal spray) is for nasal administration. The product is supplied as an aqueous solution with a pH of 5.5 ± 0.5 in a [redacted] 10 mL amber glass vial fitted with a metered spray pump attachment. [redacted] Each unit contains 9.8 mL [redacted]

Each 70 microliter spray contains 15 mg metoclopramide, (equivalent to 17.73 mg of metoclopramide hydrochloride [redacted] Inactive ingredients consist of citric acid monohydrate, sodium citrate dihydrate, benzalkonium chloride, sorbitol, edetate disodium dihydrate, and purified water. [redacted]

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	GIMPOTI (metoclopramide nasal spray)	ADEQUATE On May 11, 2020 the applicant changed the presentation to **(metoclopramide) nasal spray.**
Dosage form(s) and route(s) of administration	Nasal spray, for nasal administration	ADEQUATE
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	15 mg metoclopramide (equivalent to 17.73 mg of metoclopramide hydrochloride (b) (4))	INADEQUATE Remove (b) (4) See Reformatting edits
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	citric acid monohydrate, sodium citrate dihydrate, benzalkonium chloride, sorbitol, edetate disodium dihydrate, and purified water	INADEQUATE List in alphabetical order
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/therapeutic class	a dopamine-2 receptor antagonist	ADEQUATE
Chemical name, structural formula, molecular weight	Chemical names and structures provided	ADEQUATE
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	(b) (4)	INADEQUATE Request rewording of drug product description. See edits above.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

16 HOW SUPPLIED/STORAGE AND HANDLING

GIMOTI (metoclopramide nasal spray) is supplied as a (b) (4) solution of metoclopramide in a 10 mL ~~Type 1~~ amber glass bottle fitted with a metered spray pump attachment, a protective cap, and a safety clip. Each box of GIMOTI (NDC 72089-307-15) contains 1 bottle, with FDA-approved Patient Labeling (see Instructions for Use for proper actuation of the device).

Each actuation (b) (4) delivers 15 mg of metoclopramide. Each bottle contains 9.8 mL which is sufficient (b) (4) for 4 weeks of 4 times a day use.

(b) (4)

Discard GIMOTI 4 weeks after opening even if the bottle contains unused medicine.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Not present	INADEQUATE Add nasal spray
Strength(s) in metric system	15 mg	ADEQUATE
Available units (e.g., bottles of 100 tablets)	Each box contains 1 bottle, each bottle contains 9.8 mL	ADEQUATE
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	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.	ADEQUATE
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Discard Gimoti 4 weeks after opening even if the bottle contains unused medicine.	ADEQUATE
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	(b) (4)	INADEQUATE Revise to read: Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59 to 86°F) [*see USP Controlled Room Temperature*].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	ADEQUATE
Include information about child-resistant packaging	N/A	ADEQUATE

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for Evoke Pharma Inc. by Patheon, a Division of Thermo Fisher	ADEQUATE

ASSESSMENT OF THE PI: ***INADEQUATE***

The following Items should be addressed for the PI. Refer to screen shots above for specifics of text and format.

Section 3

- Remove [redacted] (b) (4)
- Revise section for clarity as indicated above

Section 11

- Remove [redacted] (b) (4) metoclopramide HCl
- List ingredients in alphabetical order
- Revise product description for clarity as indicated above

Section 16

- Add dosage form
- Remove [redacted] (b) (4)
- Revise storage conditions to read "Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]."
- Revise section for clarity as indicated above

2.0 PATIENT LABELING

N/A

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Gimoti (metoclopramide nasal spray)	ADEQUATE On May 11, 2020 the applicant changed the presentation to **(metoclopramide) nasal spray**
Dosage strength	15 mg per spray	ADEQUATE
Route of administration	For nasal use only	ADEQUATE
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not present	INADEQUATE (b) (4) [redacted] This was **satisfactorily** resolved on 5/11/20.
Net contents (e.g. tablet count)	Not present on container Carton states: Net Weight 50 g 112 sprays	INADEQUATE/**ADEQUATE** Container: Include net content amount on label Carton: Net content amount should read 9.8 mL 112 metered sprays This was **satisfactorily** resolved on 5/11/20.
"Rx only" displayed on the principal display	Present	ADEQUATE
NDC number	Present	ADEQUATE
Lot number and expiration date	Present on vial Serialization area noted on carton	ADEQUATE

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	INADEQUATE/**ADEQUATE** Storage condition should read: Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]. This was **satisfactorily** resolved on 5/11/20.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	(b) (4)	ADEQUATE
Quantitative Ingredient Information (injectables)	Not an injectable however ingredients are listed	INADEQUATE/**ADEQUATE** For the Carton: List ingredients in alphabetical order This was **satisfactorily** resolved on 5/11/20.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Present	ADEQUATE

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Distributed by: Evoke Pharma, Inc Solana Beach, CA 92075	ADEQUATE
Medication Guide (if applicable)	See Instructions for Use and Medication Guide before using this product	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	ADEQUATE	

Assessment of Carton and Container Labeling: *ADEQUATE*
The below deficiency items were addressed by the applicant on 11-MAY-2020. The Container/Closure Label is now adequate.

The following Items should be addressed for the Carton/Container
The Below Comments Apply to Container (vial) and Carton:

1. *Include the net contents on the vial in addition to the carton. Net content amount should read as follows:*
   9.8 mL
   112 metered sprays

The Below Comments Apply to Carton:

2. *Include a salt equivalency statement and ensure the inactive ingredients appear in alphabetical order. Refer to the below for format and content.*
   Each 70 µL spray contains:
   metoclopramide……..15 mg
   (equivalent to 17.73 mg of metoclopramide hydrochloride)
   Inactive ingredients include benzalkonium chloride, citric acid monohydrate, edetate disodium dihydrate, purified water, sodium citrate dihydrate, and sorbitol
3. *Confirm location of lot number and expiration date*
4. *Storage condition should read:*
   Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

ITEMS FOR ADDITIONAL ASSESSMENT

LIST OF DEFICIENCES

Section 3

- Remove [redacted] (b) (4)
- Revise section for clarity as indicated above

Section 11

- Remove [redacted] (b) (4) metoclopramide HCl
- List ingredients in alphabetical order
- Revise product description for clarity as indicated above

Section 16

- Add dosage form
- Remove [redacted] (b) (4)
- Revise storage conditions to read "Store at 20°C to 25°C (68°F to 77°F) excursions permitted 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]."
- Revise section for clarity as indicated above

Overall Assessment and Recommendation:

On January 27, 2020, the Carton and Container deficiencies were communicated to the Applicant. The Applicant agreed to OPQ related Carton and Container deficiencies on MAY 11, 2020. However, the Labeling of NDA 209388 is inadequate due to the deficiencies noted below for Sections 3, 11, and 16 of the PI. These remaining labeling deficiencies were communicated to OND labeling review team on April 9, 2020.

Recommendation:

This application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the label/labeling perspective until the deficiencies noted above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Caroline Strasinger, Ph.D. 12-MAY-2020
OPQ, ONDP, DNDP II, B4

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Strasinger's assessment of the labeling and labels and concur with her recommendation that this application is ***not*** deemed ready for approval until the deficiencies noted in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D. 12-MAY-2020
Chief, Branch 4
DNDP II/ONDP/OPQ

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 5/21/2020 04:20:54PM
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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 5/18/2020 08:31:37AM
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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 209388

Drug Product Name / Strength: Gimoti™ (metoclopramide nasal spray)/15 mg

Route of Administration: Nasal

Applicant Name: Evoke Pharma Inc.
420 Stevens Avenue, Suite 370, Solama Beach, CA 92075

Manufacturing Site: (b) (4)

Method of Sterilization: N/A; the drug product is non-sterile

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

List Submissions Being Reviewed: 6/1/2018, 12/14/2018

Highlight Key Outstanding Issues from Last Cycle: An IR dated 11/30/2018 to address minor deficiencies was conveyed to the applicant following Product Quality Microbiology review. The information provided in the amendment dated 12/14/2018 in response to the IR is incorporated in the review.

Remarks: N/A

Concise Description Outstanding Issues Remaining: None

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

Reviewer's Assessment: *Adequate*

The drug product is non-sterile. Therefore, microbiology review will not be conducted for drug substance.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** [redacted] aqueous solution, multi-dose
- **Drug product composition –**

Component	Amount per bottle (mg)	Amount per ml (mg)	Amount per 70 µl actuation (mg)	Function	Quality standard
Metoclopramide hydrochloride [redacted]	[redacted]	[redacted]	17.73	API[a]	USP/EP
Citric acid monohydrate					USP/EP
Sodium citrate dihydrate					USP/EP
Benzalkonium chloride [redacted]					NF
Sorbitol [redacted]					USP
Edetate disodium dihydrate					USP/EP
Purified water					USP/EP

a: Equivalent to 15 mg metoclopramide base per 70 µl actuation.

[redacted]

- **Description of container closure system –** The drug product is contained in a 10 ml Type I amber glass bottle and mounted with a snap-on [redacted] metered nasal spray pump with a protective cap and safety clip.

Description of primary packaging components

Component	Description	Manufacturer
Glass bottle	10 ml Type 1 [redacted] amber glass bottle	[redacted]
Nasal spray pump	[redacted] pump with safety clip and cap	

Exhibit batches # 7003: [redacted] L
Proposed commercial batch: [redacted] L

Reviewer's Assessment: *Adequate*

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Primary Microbiology Reviewer Name and Date:

Jianli Xue, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA
12/21/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Neal J. Sweeney, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA
12/21/2018

Jianli Xue

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Date: 12/21/2018 12:12:07PM
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Neal Sweeney

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Date: 12/21/2018 12:25:27PM
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QUALITY ASSESSMENT

Recommendation: As of this review, this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(1) and 21 CFR 314.125(b)(6).

NDA 209388

OPQ Review #1

Drug Name/Dosage Form	Gimoti (metoclopramide) nasal spray
Strength	15 mg per actuation
Route of Administration	Nasal spray
Rx/OTC Dispensed	Rx
Applicant	Evoke Pharma, Inc.; Solana Beach, CA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Jun 01, 2018	OPQ
Amendment	Aug 21, 2018	Drug Product
Amendment	Sep 6, 2018	Drug Product
Amendment	Oct 15, 2018	Drug Product
Amendment	Dec 14, 2018	Drug Product
Amendment	Feb 21, 2019	Labeling

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Labeling	Caroline Strasinger	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Yaodong Huang	CDER/OPQ/OPF/ DPAIII/PABVIII
Microbiology	Jianli Xue	CDER/OPQ/OPF/ DMA/MABII
Facilities	Yaodong Huang	CDER/OPQ/OPF/ DPAIII/PABVIII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Environmental Assessment (EA)	Caroline Strasinger	CDER/OPQ/ONDP/ DNDPII/NDPBV
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV

QUALITY ASSESSMENT

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4	(b) (4)	Active	Dr. Donglei Yu, October 11, 2018, adequate	LOA: Jan 26, 2016
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Jan 5, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Jan 5, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA: July 7, 2016

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	25512	Metoclopramide (b) (4) for treatment of diabetic gastroparesis from Evoke Pharma. Active since June 6, 2002

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	Complete	Recommended for NOT APPROVAL for the proposed indication	Feb 7, 2019	Dr. Jacqueline Gertz CDRH/ODE/DAGRID/ GHDB
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has ***not*** provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product in terms of pump performance of this combination drug product.

The Office of Process and Facilities (OPF) has made a final overall "**Approval**" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The labeling discussions are **precluded** from this review cycle.

Therefore, from the OPQ perspective, this NDA is ***not*** recommended for approval per CFR 314.125(b)(1) and CFR 314.125(b)(6), until above mentioned issues are satisfactorily resolved. **(see the List of Deficiencies)**

II. Summary of Quality Assessments

A. Product Overview

Metoclopramide is an antiemetic dopamine-2 receptor antagonist.

The reference listed drug, Reglan tablets, was approved in December 1980 (NDA 017854) from ANI Pharmaceuticals Inc., MN for gastroesophageal reflux and diabetic gastroparesis in adults.

Proposed Indication(s) including Intended Patient Population	Metoclopramide nasal spray is indicated for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis.
Duration of Treatment	Acute and Recurrent Diabetic Gastroparesis Administer 15 mg, 30 minutes before each meal and at bedtime (maximum of 60 mg per day) for 2 to (b)(4) weeks.
Maximum Daily Dose	60 mg per day
Alternative Methods of Administration	N/A

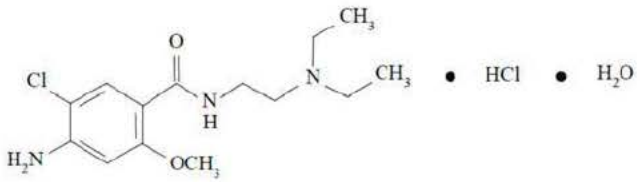
B. Quality Assessment Overview

Drug Substance:

The active ingredient, metoclopramide hydrochloride, is a white to almost white, crystalline powder. It is freely soluble in water and ethanol. However, it's solubility varies with pH. According to the manufacturer, there are no known polymorphs of the drug substance.

Metoclopramide hydrochloride is manufactured by (b) (4). The detailed CMC information regarding manufacture, purification, analytical methods, structure elucidation and stability is provided in DMF (b) (4) from the manufacturer. A letter of authorization dated January 26, 2016 from the manufacturer was included in the DMF. The DMF was last reviewed by Dr. Donglei Yu, October 11, 2018 and was deemed adequate.

Its chemical name is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. The molecular formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Its molecular weight is 354.3. The structural formula is:



The applicant has provided Certificate of Analyses (COA) of multiple batches of the drug substance used in the clinical studies as well as registration stability testing.

The identity, purity and quality of the drug substance, metoclopramide hydrochloride, is controlled by (b) (4) (b) (4) (b) (4) The drug substance specification complies with (b) (4) metoclopramide hydrochloride monograph. The drug substance specification is deemed adequate per drug substance reviewer, Dr. Martin Haber. (See **the Drug Substance** review)

The API is manufactured by (b) (4), and the Office of Process and Facilities (OPF) has made an "Adequate" recommendation for the drug substance manufacturing and testing facility. (See the **Facilities** review)

Drug Product:

Metoclopramide nasal pump, 15 mg per actuation is supplied as 10 mL metered spray pump. The (b) (4) aqueous solution contains (b) (4) of metoclopramide hydrochloride monohydrate (b) (4) as well as the following inactive ingredients: citric

acid monohydrate and sodium citrate dihydrate (b) (4), benzalkonium chloride (b) (4), sorbitol (b) (4), edetate disodium dihydrate (b) (4) (b) (4) and purified water (b) (4). Each pump actuation delivers 15 mg of metoclopramide in 70 µL of solution as a nasal spray.

The drug product is manufactured by (b) (4). The manufacturing process consists of: (b) (4) (b) (4) (b) (4) The selection of manufacturing process, in-process controls, drug product release tests, and the executed batch records were deemed satisfactory. The whole drug product manufacturing process was reviewed and deemed adequate. (See **Process** review)

Microbiology sections containing antimicrobial effectiveness testing, overall (b) (4) manufacturing operation, microbial limit test method and method validation, in-use stability and stability of the drug product were reviewed and deemed adequate. (See **Microbiology** review)

The overall control strategy for the drug product to ensure the identity, strength, purity and quality was based on (b) (4) (b) (4) n addition to USP methods, the applicant also developed and instituted non-compendial in-house analytical methods which were validated.

In addition to controlling the drug product, the pump performance such as droplet size distribution, spray pattern, spray content uniformity and pump delivery were also controlled in the drug product specification. These pump attributes are critical for consistent dose delivery by the metered pump to assure the safety and efficacy. The drug product reviewer concluded that limited data provided for these attributes were not adequate for assuring a consistent dose delivery. which may have compromised efficacy of the drug product, particularly when excessively wide inter and intra subject variability were observed in the pharmacokinetic data (although, it is not definitive at this time whether or not the pump performance contributes to the observed variability in the pK data).

Overall, the CMC information submitted in this application is deemed ***inadequate*** for assuring the statutory requirements for the drug product and, therefore, a recommendation of ***not*** approval of this NDA is made from the drug product perspective. (see **Drug Product** review)

Device:
Since this proposed drug is a combination drug product, CDRH was consulted for further evaluation on the performance of the metered pump.

The CDRH assessed: 1) the metered pump performance; 2) biocompatibility between the patient and pump components; and 3) release specification for the device constituents; and concluded that the pump performance requirements are ***not*** adequately met in terms of controlling droplet size distribution and pump actuation force; and therefore, ***not*** approval recommendation was made from the CDRH perspective. (see **CDRH Consult** memo)

Facility:
The Office of Process and Facilities (OPF) has made an "**Adequate**" recommendation for the drug product manufacturing and testing facilities. (See the **Facility** review)

Environmental Assessment:
Evoke Pharma, Inc. claimed a categorical exclusion from the requirement to prepare an Environmental Assessment under 21 CFR 25.31 (b) as the amount of waste to be generated is expected to be small and no extraordinary circumstances exist. The claim was supported by an EIC estimate of (b) (4) (less than 1 ppb) based on a peak sale for the next 5 years of (b) (4) per year. The claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 (b) was deemed acceptable. (See the **Drug Product** review)

Labeling:
The labeling discussions are precluded from this review cycle

C. Lifecycle Management Consideration (NDA only)

Drug Substance:
- Drug substance conforms to the current USP monograph for metoclopramide hydrochloride.

Drug Product:
- Upon resubmission, ALL proposed tests and acceptance criteria including the droplet sizes and other essential performance characteristics for the commercial product specification should be supported by 3 batches of drug product using the selected commercial formulation (including strength of the product) and the commercial device.

D. Special Product Quality Labeling Recommendations (NDA only)
None

E. Final Risk Assessment (see the Attachment)

III. List of Deficiencies:

Complete Response Deficiency:

The specification for the drug product is inadequate as insufficient evidence has been provided to ensure the combination product quality control and essential performance characteristics of the device do not contribute to the observed clinical variability and lack of efficacy. Specifically, the method and acceptance criterion for droplet size distribution are not deemed robust enough to guarantee consistent delivery of the drug to the patient with each actuation. The variability of the proposed acceptance criterion and the significant differences between the mean droplet sizes for the 14 mg per actuation, 15 mg per actuation and 17 mg per actuation strengths are not justified particularly given the observed variability of pK data.

Recommendation to Address the Deficiency:

Upon resubmission, all proposed tests and acceptance criteria including the droplet sizes and other essential performance characteristics for the commercial product specification should be supported by 3 batches of drug product using the selected commercial formulation (including strength of the product) and the commercial device.

Additional Comments:

The following comments are not approvability issues but should be addressed in the Resubmission.

- We recommend that actuation force be considered an essential performance requirement and to include a test and acceptance criterion for actuation force for the to-be-marketed combination product in the product release and stability specification. You should include verification and validation data to support that specification and describe why this force is appropriate for the intended user population. Alternatively, provide a rationale for why you do not consider actuation force an essential performance requirement for the device constituent and how you will control the product to assure this essential performance will be consistently achieved.

- You provided a specification for the lowest allowable cap removal force, but without the highest allowable cap removal force. This information is recommended to demonstrate that the cap will not be too difficult for the user to remove. We recommend the upper cap removal force specification be defined.

- A shelf-life of (b) (4) months is not supported.

Given the Complete Response is significantly related to efficacy, a reformulation, change in strength, or change in device may be anticipated upon resubmission of the application. In conjunction with the above information regarding specification, upon resubmission, the proposed shelf life should be supported by 3 batches of the drug product using the selected commercial formulation (including strength of the product) and the proposed commercial device.

- It is deemed premature to agree to a reduced reporting category for an additional facility for release and stability testing as proposed in your comparability protocol.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
February 25, 2019

Hitesh N. Shroff -S
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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 209388

Drug Product Name / Strength: Gimoti™ (metoclopramide nasal spray)/15 mg

Route of Administration: Nasal

Applicant Name: Evoke Pharma Inc.
420 Stevens Avenue, Suite 370, Solama Beach, CA 92075

Manufacturing Site: (b) (4)

Method of Sterilization: N/A; the drug product is non-sterile

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary:

List Submissions Being Reviewed: 6/1/2018, 12/14/2018

Highlight Key Outstanding Issues from Last Cycle: An IR dated 11/30/2018 to address minor deficiencies was conveyed to the applicant following Product Quality Microbiology review. The information provided in the amendment dated 12/14/2018 in response to the IR is incorporated in the review.

Remarks: N/A

Concise Description Outstanding Issues Remaining: None

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

Reviewer's Assessment: *Adequate*

The drug product is non-sterile. Therefore, microbiology review will not be conducted for drug substance.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** [redacted] aqueous solution, multi-dose
- **Drug product composition –**

Component	Amount per bottle (mg)	Amount per ml (mg)	Amount per 70 µl actuation (mg)	Function	Quality standard
Metoclopramide hydrochloride [redacted]	[redacted]	[redacted]	17.73	API[a]	USP/EP
Citric acid monohydrate				[redacted]	USP/EP
Sodium citrate dihydrate					USP/EP
Benzalkonium chloride [redacted]					NF
Sorbitol [redacted]					USP
Edetate disodium dihydrate					USP/EP
Purified water					USP/EP

a: Equivalent to 15 mg metoclopramide base per 70 µl actuation.

[redacted]

- **Description of container closure system –** The drug product is contained in a 10 ml Type I amber glass bottle and mounted with a snap-on [redacted] metered nasal spray pump with a protective cap and safety clip.

Description of primary packaging components

Component	Description	Manufacturer
Glass bottle	10 ml Type 1 [redacted] amber glass bottle	[redacted]
Nasal spray pump	[redacted] pump with safety clip and cap	

Exhibit batches # 7003: [redacted] L
Proposed commercial batch: [redacted] L

Reviewer's Assessment: *Adequate*

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Primary Microbiology Reviewer Name and Date:

Jianli Xue, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA
12/21/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Neal J. Sweeney, Ph.D.
Microbiologist
CDER/OPQ/OPF/DMA
12/21/2018

Jianli Xue

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Neal Sweeney

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 209388

a) Drug Product: Metoclopramide Nasal Spary, 15 mg per actuation

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation, Process Parameters	M	(b) (4)	The dose strength of the drug product is expected to be within the specification during the entire shelf life from product quality perspective. None	None
pH	API Solubility, particle size	M		The pH of the drug product is expected to remain within acceptable range during the shelf life of the product as demonstrated by the stability testing. None	None
Bioburden	Formulation,Manufacturing environment and processes	M		Bioburden is controlled in the drug product at release and stability. Low	None
Pump Performance	Pump performance parameters such as droplet size distribution, spary content uniformity, pump delivery and spary pattern.	M		(b) (4) Sufficent information on droplet size distribution for to-be marketed product was not provided. Thus consistent product delivery could not be assured which may affect safety and efficacy. High	The API must conform to the USP monograph. Upon any change of pump, all pump performance particularly for the droplet sizes and actuation performance must be be carefully evaluated with CDRH consult.

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/

MAUREEN D DEWEY
06/19/2020 04:33:31 PM

OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date	February 7, 2019
To	Maureen Dewey Maureen.Dewey@fda.hhs.gov OMPT/CDER/OND/ODEIII/DGIEP 301-796-0845
Requesting Division	DGIEP
From	Jacqueline Gertz CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Sarah Mollo, Injection Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for Submission # NDA209388 - Gimoti ICCR 2018-03099 ICC 1800512
Recommendation	Device Constituent Parts of the Combination Product are Not Approvable – See Section 13 for Outstanding Deficiencies

Digital Signature Concurrence Table	
Reviewer	
Team Leader/Branch Chief	

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	2018-03099
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=3392
ICC tracking # (Lead)	1800512
Submission Number	NDA 209388
Sponsor	Evoke
Drug/Biologic	Gimoti
Indications for Use	Diabetic gastroparesis in women.
Device Constituent	Nasal Spray
Related Files	N/A

Table 2. Review Team				
CDER/CBER Lead Review Division	DGIEP			
Submission RPM	Maureen Dewey			
Lead Device Reviewer	Jacqueline Gertz			
The CDRH review is being managed under ICC #: ICC 1800512				
Below is a list of the Discipline Specific ICCR#, ICC# and CON#.				
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**ICCR #**	**ICC #**	**CON #**
Compliance	Susannah Gilbert	2018-03120	1800512	1815607

Table 3. Important Dates		
Final Lead Device Review Memo Due	April 1, 2019	
Interim Due Dates	**Meeting Date**	**Due Date**
Filing	July 20, 2018	
Mid-Cycle	November 1, 2018	
Primary Review	February 23, 2019	
Wrap-up meeting	February 14, 2019	

Table of Contents

2. PURPOSE/BACKGROUND

2.1. Scope

Evoke Pharma is requesting approval of the Gimoti Nasal Spray. The device constituent of the combination product is a nasal spray.

CDER has requested the following consult for review of the device constituent of the combination product on 6/19/2018:

Review the device constituents of the combination product and pre-market facilities inspection.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors
- Sterility of the device constituent if applicable

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

CDRH has not interacted previously regarding this NDA.

2.3. Indications for Use

Combination Product	Indications for Use
Gimoti	Acute and recurrent diabetic gastroparesis in adult women
Nasal Spray	Drug delivery

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Date - Version	Location
32p24-container-closure-system.pdf		3.2.p.2.4
specifications-1.pdf		3.2.p.5.1

description-and-composition.pdf		3.2.p.1
container-closure-system-1.pdf		3.2.p.7
container-closure-system-4.pdf		3.2.p.7
Quality information amendment – response to IR		009/1.11.1

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The following information is located in 3.2.p.2.4 container closure system:

Gimoti is intended for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis. The recommended Gimoti dose for the treatment of acute and recurrent diabetic gastroparesis is 15 mg 4 times daily 30 minutes before each meal and at bedtime. Gimoti is not recommended for use in adult men with acute and recurrent diabetic gastroparesis as benefit in this population has not been demonstrated.

The container closure system for Gimoti (metoclopramide nasal spray) comprises a 10 mL Type I amber glass bottle closed with an (b) (4) *nasal spray pump. This standard configuration was used throughout the development program and will also be used for commercial product.*

Information on the commercial container closure system is summarized in Table 1 below.

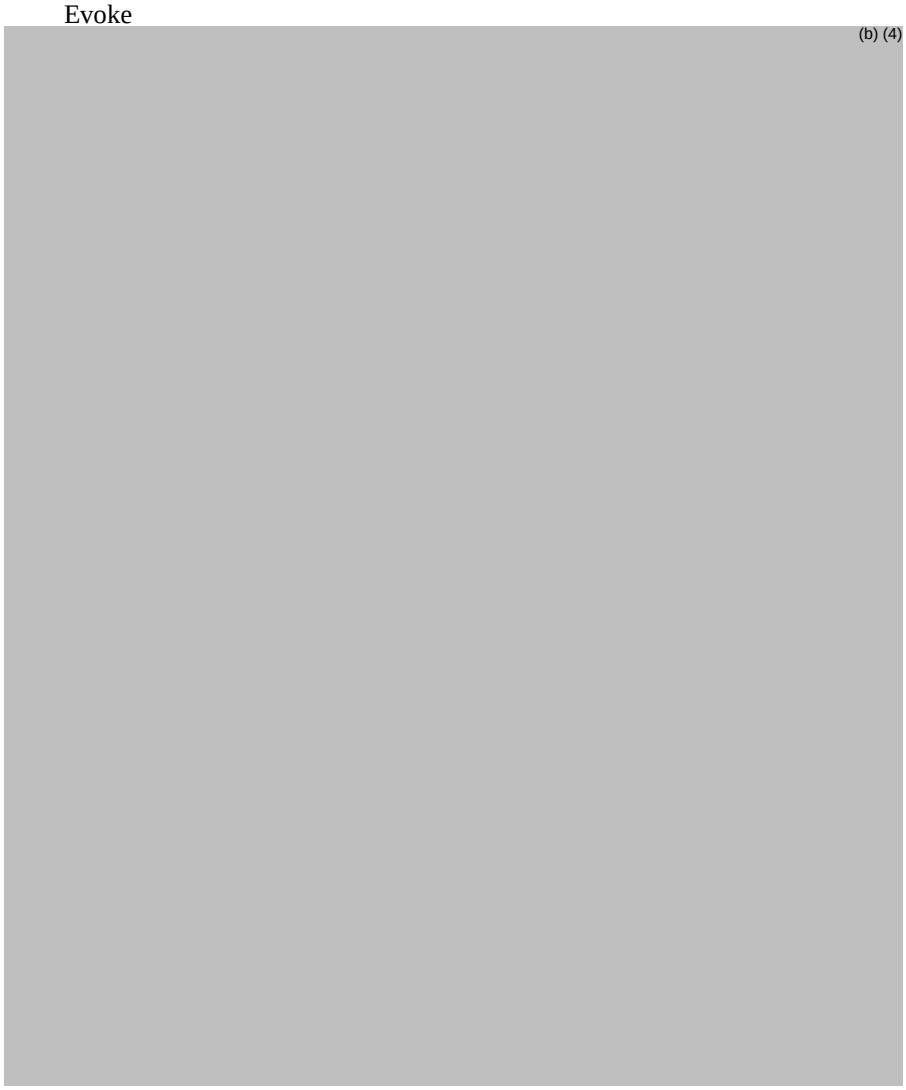
Table 1: Commercial Primary Packaging Configuration

Component	Description	Manufacturer	Product Code	DMF #
Container	10 mL glass round amber (b) (4)	(b) (4)		
Spray pump	(b) (4)			

DMF = Drug Master File

The (b) (4) *nasal spray pump, a commercially available unit, is an easy-to-use delivery system that provides a reproducible 70 µL dose (as demonstrated by pump delivery as part of routine product release testing) and is small enough to carry around in a pocket or purse. The 10 mL bottle volume enables a 4-week supply of drug to be filled and the Type I* (b) (4) *amber glass* (b) (4) (b) (4) *shelf-life of 3 years at controlled room temperature.*

The image is located in 3.2.p.7 document titled container-closure-system-4.pdf



Steps for using the device – information from instructions-for-use.pdf in 1.1.4
1st time

1. Remove the cap
2. Remove the safety clip
3. Prime the pump with 10 pumps (1st time only)
4. Place the spray nozzle under one nostril tip
5. Aim the tip slightly away from the center of your nose, lean forward slightly
6. Close the other nostril with your other index finger
7. Press down on the finger flange while breathing in gently
8. Remove nozzle from nostril
9. Wipe nozzle with a clean tissue
10. Replace protective cap
11. Replace the safety clip

Device Characteristic	Description / Specification
Nasal Spray Name	(b) (4) with spray actuator and safety clip

Priming Dose / Volume	10 sprays
Container Fill Volume	10mL
Pump Delivery (Spray Weight)	(b) (4)
Spray Pattern and Plume Geometry Shape	
Spray Content Uniformity (SCU)	
Droplet / Particle Size Distribution	

	(b) (4)
Insertion Site / Depth	
Achievable Flow Rates*	N/A
Audible / Visual Feedback	N/A
Cap Removal Force	(b) (4) kg; measured spec averages (b) (4) kg. there is no max cap removal force spec. Deficiency: You provided a specification for the lowest allowable cap removal force. You have not provided a specification for the highest allowable cap removal force. This information is recommended to demonstrate that the cap will not be too difficult for the user to remove. We recommend the upper cap removal force specification be defined.
Actuation Force	Human factors study with to-be-marketed product. Specification not provided. Specification cannot be verified/validated by HF study if a spec isn't provided Deficiency: We recommend that actuation force be considered an essential performance requirement. A specification for this requirement was not defined in the submission, and verification and validation data were not provided for the specification. Therefore, we recommend that you provide a specification for actuation force for the to be marketed form of the combination product along with verification and validation data to support that specification. Please describe why this force is appropriate for the intended user population. Alternatively, provide a rationale for why you do not consider actuation force an essential performance requirement for the device constituent.
Reliability (e.g. Emergency-Use Products ~99.99% Reliability)	N/A
Visibility of Medication Container*	Yes, bottle is amber
Last Dose Specifications and Safety Features*	Safety features: Safety clip, cap Last dose testing: Actuated 3 units (b) (4) times to simulate initial prime and full course of administration. Doses were within SCU spec until between actuation (b) (4). Droplet size distribution gets variable around (b) (4) sprays.

	Fill volume/weight is appropriate for the intended number of doses.
Type of Use (e.g. single use, disposable, reusable, other)	Use for repeated doses from the same vial
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self-administration
Mechanism of Action (e.g., manual piston, spring, gas, etc.)	(b) (4)
Method of Actuation (e.g. compress plunger, force against skin, button activated, etc.)	(b) (4)
Automated Functions	N/A
Drug Container Type	Amber bottle
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	Mg
Environments of Use	Not professional setting – home, restaurant, car, etc.
Storage Conditions and Date of Expiry	3 years at controlled room temperature
Graduation Marks / Fill Lines*	N/A
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Etc.	Prime with 10 sprays before first use
Electronics / Data transmission • Display • Control functions • Data transmission technology • Data being transferred	N/A
Material Composition	(b) (4)

*Typically reserved for multi-use nasal sprays

5. FILING REVIEW

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

Table 4: Design Control Documentation Check

Design Control Requirement	Signed/Dated Document Present	Submission Location

	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	x		Container-closure-system-1
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	x		Container-closure-system-1
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x		Container-closure-system-1
Validation Data • Human factors • Clinical data	x x		Container-closure-system-1
Traceability Documentation	x		Design history file

Filing Review Checklist				
Description		Present		
		Yes	No	N/A
Description of Device Constituent		x		
Essential Performance Requirements		x		
Manufacturing Controls* (e.g. release specifications, incoming inspection, in-process controls, etc.) *Manufacturing Controls should provide confirmation that the attributes of the co-packaged syringe consistently meet the device requirements (e.g. dose accuracy, break loose / glide force, compatibility with tip cap).		x		
Letters of Authorization		x		
Performance Data Check	Pump Delivery (Spray Weight)	x		
	Actuation Force		x	
	Spray Pattern and Plume Geometry Shape	x		
	Spray Content Uniformity (SCU)	x		
	Biocompatibility			x
	Droplet / Particle Size Distribution	x		
	Shelf Life, Aging and Transportation	x		
	Sterility and/or cleaning/disinfection instructions	x		
Full Test Reports for Performance Testing		x		
Device Constituent Labeling		x		

Reviewers comments:
The device part of the NDA is fileable.

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

The design inputs (requirements) and outputs of the combination product have been established. These are tabulated in Table 6. The inputs are predicated on patient needs as summarized above for the key aspects of the device constituent of the combination product. As part of this assessment, the Human Factors Evaluation (HFE) for the combination product was also reviewed (Gimoti Human Factors Assessment Report is detailed in Module 5.3.5.4). The design inputs and outputs adequately cover all the risks identified in the HFE (per FDA correspondence dated 03FEB2017).

Table 6 Design Inputs and Outputs

Design Input /User Need Requirement	Design Output Procedures	Design Output Documentation
High patient compliance and compatibility	Assess ease of use as part of HFE and review clinical study program for any patient compatibility concerns	Approved labeling providing instructions for use and listing potential adverse events from use of product
Ease of use in patient population	Assess ease of use as part of HFE	Approved labeling providing instructions for use
Pump performance reproducibility	Pump performance testing on final combination product: SCU, DSD, SP	Finished product specification
Ability to reproducibly deliver the required dose over the dosing period	Tail-off study to demonstrate pump performance near exhaustion.	Finished product specification
Ability to deliver the required number of doses	Tail-off study to support Minimum Fill specification as part of release testing	Finished product specification
Adequate in-use shelf life	In-use stability study of 28 days; pump performance confirmation testing over in-use period	Approved labeling
Ease of priming	Prime/reprime study	Approved labeling
Ability to hold prime if not used daily	Prime/reprime study	Approved labeling
Provide adequate product protection to ensure at least 2 years shelf life at controlled room temperature	ICH-compliant stability program	Approved labeling
Portable and convenient to use	Assess ease of use as part of HFE	Approved labeling
Compatible with the drug product solution with respect to drug product stability	ICH-compliant stability program	Approved labeling
Maintain prime when used as directed	Prime/reprime study	Approved labeling
Robust for day-to-day use and shipping purposes	Robustness study	Finished product specification
Appropriate materials of construction for leachables	Extractables/leachables study and stability assessment	Quality agreement with pump and bottle suppliers
Good container-closure integrity to avoid leakage etc.	Leak test as part of manufacturing process; ICH-compliant stability program	In-process control checks

DSD = droplet size distribution; HFE = Human Factors Evaluation; ICH = International Conference on Harmonisation; SCU = spray content uniformity; SP = spray pattern

6.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	

Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	x		Container closure system 1
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	x		3.2.p.2.4
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x		3.2.p.2.3
Validation Data • Human factors • Clinical data	x x		5.3.5.4 – Gimoti human factors assessment report
Traceability Documentation	x		Container closure system 1

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial?	x		
Selectable dose range on device matches the labeled dose range for the medication?	x		
Verification methods relevant to specific use conditions as described in design documents and labeling	x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	x		
Traceability demonstrated for specifications to performance data	x		
Adherence to FDA Guidance: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation*	x		
Adherence to FDA Guidance: *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* (For nasal sprays that act as jet injectors or have 'dial-a-dose'			X

capabilities)			
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry	x		

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		x				
Biocompatibility		x		CDER will be reviewing all of the patient/fluid contacting components		
Sterility		x		CDER will be reviewing the sterility of the primary container closure.		
Software / Cybersecurity			x			
Electrical Safety / EMC			x			
Human Factors			x			

*Other discipline specific consults may be necessary based on product characteristics

Standards / Guidance Conformance		**YES**	**NO**	**N/A**
Adherence to FDA Guidance	Infusion Pumps Total Product Life Cycle – Guidance for Industry and FDA Staff (2014)			X
	Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)			X
	Guidance for Industry and FDA Staff – Intravascular Administration Sets Premarket Notification Submissions (2008)			X
	Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2013)			X
	Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (2002)	x		
	Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	X		
	Mobile Medical Applications Guidance for Industry and			X

	Food and Drug Administration Staff (2015)			

*This table does NOT include discipline specific Guidance / Standards that may be applicable to the review

7.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device		X	
Bioequivalence Study utilized to-be-marketed device		X	
Simulated Actual Use Study utilized to-be-marketed device	x		

7.3. Design Verification Review

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Pump Delivery (Spray Weight)	(b) (4)	Y	Y	Y	Y	Y
Residual Volume		y	y	y	N	Y
Spray Pattern and Plume Geometry Shape		Y	Y	Y	Y	Y
Spray Content Uniformity (SCU)		Y	Y	Y	Y	Y
Droplet / Particle Size Distribution		Y	Y	Y	Y	Y

Insertion Depth	(b) (4)	Y	Y	N	N	N
Actuation force	No spec provided	N	N	N	N	N

Stability summary

From stability data-1 in 3.2.p.8.3:

Table 2: Summary of Fill Volumes Used Throughout Development

Dose Strength	Drug Content[1]	Dose Volume	Fill Volume
10 mg	(b) (4)	50 µL	(b) (4)
14 mg		70 µL	
15 mg		70 µL	
16 mg		70 µL	
17 mg		70 µL	

(b) (4)

Essential Performance Requirement	Specification	Product concentration, time points	Passed?
		3 batches (b) (4) mg/mL, 10mg with 36 months at real time and 6 months accelerated ageing.	
Pump Delivery (Spray Weight)	(b) (4)	3 batches of (b) (4) mg/mL, 14mg dose with 36 months at real time and 6 months accelerated 3 batches (b) (4) mg/mL, 10mg with 36 months at real time and 6 months accelerated ageing. 3 batches of (b) (4) mg/mL, 17mg dose with 9 months at real time and 6 months accelerated 1 batch of (b) (4) mg/mL, 15 mg dose, completed 6 months accelerated and real time.	Y
Residual Volume		3 batches of (b) (4) mg/mL, 14mg dose with 36 months at real time and 6 months accelerated	Y

		3 batches (b) (4) mg/mL, 10mg with 36 months at real time and 6 months accelerated ageing. 3 batches of (b) (4) mg/mL, 17mg dose with 9 months at real time and 6 months accelerated 1 batch of (b) (4) mg/mL, 15 mg dose, completed 6 months real time only.	
Spray Pattern and Plume Geometry Shape	(b) (4)	3 batches of (b) (4) mg/mL, 14mg dose with 36 months at real time and 6 months accelerated 3 batches (b) (4) mg/mL, 10mg with 36 months at real time and 6 months accelerated ageing. 3 batches of (b) (4) mg/mL, 17mg dose with 9 months at real time and 6 months accelerated 1 batch of (b) (4) mg/mL, 15 mg dose, completed 6 months real time only.	Y
Spray Content Uniformity (SCU)	(b) (4)	3 batches of (b) (4) mg/mL, 14mg dose with 36 months at real time and 6 months accelerated 3 batches (b) (4) mg/mL, 10mg with 36 months at real time and 6 months accelerated ageing. 3 batches of (b) (4) mg/mL, 17mg dose with 9 months at real time and 6 months accelerated 1 batch of (b) (4) mg/mL, 15 mg dose, completed 6 months real time only.	Y
Droplet / Particle Size Distribution	D90 (b) (4) D50 D10 (b) (4)	3 batches of (b) (4) mg/mL, 14mg dose with 36 months at real time and 6 months accelerated 3 batches (b) (4) mg/mL, 10mg with 36	No Droplet size distribution did not pass for the (b) (4) mg/mL or (b) (4) mg/mL formulations. Only 6 months of real time ageing

		months at real time and 6 months accelerated ageing. 3 batches of (b) (4) mg/mL, 17mg dose with 9 months at real time and 6 months accelerated 1 batch of (b) (4) mg/mL, 15 mg dose, completed 6 months real time only.	was provided for the (b) (4) mg/ml to be marketed formula.
Insertion Depth	(b) (4) mm	Not assessed	N – based on the risk of the device, this won't be requrest
Actuation force	No spec provided	Not assessed	n

Reviewer's comments:

Deficiency: The stability data included droplet size distribution, spray weight, spray content uniformity, spray pattern, and weight lost. The data did not include actuation force. We recommend that you include stability data to demonstrate that the actuation force specifications are maintained over the shelf life of the product.

Deficiency: The long-term stability data provided in the submission demonstrates that in several instances, the droplet size distribution is out of specification. Please conduct a root cause analysis and determine the cause of the specification failure. Implement any mitigation measures necessary to ensure the device is consistently within specification for the entire shelf life of the product. Reconduct any testing necessary to support the changes including validation, stability, and transportation.

From CDER: We previously agreed with the Applicant that we would consider the approach for fulfilling stability requirements and registration batches (b) (4), (b) (5) I think it may be best to put them on notice that we don't feel their criterion are supported/justified because of the limited data for the commercial strength (b) (4), (b) (5) , still likely not appropriate, but a possible explanation). Then we can roll remaining inadequacies of the method and acceptance criterion/lack of support into the CR Letter (assuming it isn't efficacious nor Bioequivalent) and tell them in the CR letter they will need to justify new acceptance criterion for the proposed commercial strength and formulation (b) (4), (b) (5) and to do that with three commercial batches through 12 months.
Also, they have provided method validation for droplet size; the validation protocol and report are in 3.2.P.5.3-16 and 3.2.P.5.3-17 respectively (It was validated each time there was a strength change), so I am afraid if we just ask them that, they will just respond with a link to the report again.

Revised deficiency: We acknowledge your proposed strategy of (b) (4)
(b) (4)

(b) (4)

[redacted]

CR deficiency: We acknowledge your proposed strategy of (b) (4)

(b) (4)

[redacted]

7.3.1. Biocompatibility Review

Biocompatibility Review Instructions

From GSR section 1.2 cover letters, doc original application reviewers guide.
FDA cleared device with the same materials from the same manufacturer and for similar intended use. Therefore, the patient-contacting materials are biocompatible during the intended use of this device. Additionally, CDER will be reviewing all fluid path components.

8. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

8.1. CDRH Compliance

Compliance email from Isabel Tejero, Lead consumer safety officer dated 7/25/2018:

> *I'm triaging this consult. This is a nasal spray for relief of symptoms in adult women with acute and recurrent diabetic gastroparesis, and won't need a compliance consult. I will complete the consult today.*
> *Isabel*

9. RISK ANALYSIS

9.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		

9.2. Summary of Risk Analysis

				(b) (4)	
Pumps	Appearance	H	If damaged may impact integrity of container closure system		L
	SCU	H	Pump is the delivery system of the FP for correct dosing		L
	Elemental Impurities	M	High elemental impurities may be a safety concern		L
	Particulate Matter	H	Presence of particulates could lead to presence in the finished product but content relatively low		L
	Microbial quality	H	"Pump microbial quality is impacting the microbial quality of the finished product. Nevertheless the material from the supplier has been used in several production without microbial issue detected linked to this material		M
	Spray Pattern	H	Pump is the delivery system of the FP		L

	DSD	H	Pump is the delivery system of the FP	(b) (4)	L

Reviewer's comments:
All device related risks have been mitigated through control at receipt, stability testing, and release testing.

10.LABELING

10.1. Device Labels

The following information is located in 1.14-labeling/draft/carton and container -

Carton:

(b) (4)

Vial:

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

10.3. Warnings/Precautions/Contraindications

No device related warnings/precautions/contraindications

Reviewer Comment
The labeling is acceptable

11.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5.1 – specification- 1:

Table 1 Specification for Gimoti Nasal Spray

Parameter	Release Criteria
Appearance	A (b) (4) solution
Packaging appearance	10 cc amber glass bottle with (b) (4) nasal spray pump. No visible leakage or blemishes on container/closure.
Identification:	The retention time and the UV spectrum of the major peak in sample injection comply with that in reference standard injection.
Potency assay[1]	(b) (4)% ((b) (4)% w/v) of label claim
Related substances	Individual unspecified impurities ≤ (b) (4)% Individual specified impurities ≤ (b) (4) Total impurities ≤ (b) (4)%
Benzalkonium chloride content	(b) (4)% (b) (4)% w/v) of label claim
EDTA content	(b) (4)% (b) (4)% w/v) of label claim
Droplet size distribution	D90 < µm: D50 < µm: D10 < µm: Span: (b) (4) % (b) (4) µm: NMT (b) (4)%

Spray content uniformity	(b) (4)
	(b) (4)
Pump delivery	
Spray pattern	
Specific gravity	
pH	5.5 ± 0.5
Minimum fill	Conforms to USP. Labeled amount 9.8 mL.
Particulate matter	≥ (b) (4) µm: NMT (b) (4) per bottle ≥ (b) (4) µm: NMT (b) (4) per bottle

Microbial limit test	Total aerobic microbial count: NMT (b) (4) cfu/mL Total combined yeasts/molds count: NMT (b) (4) cfu/mL Absence of *P. aeruginosa* (b) (4) Absence of *S. aureus* (b) (4) Absence of *B. cepacia* (b) (4)

cfu = colony-forming unit; EDTA = ethylenediaminetetraacetic acid; ICH = International Conference on Harmonisation; LID/SID = longest/shortest internal diameter; NMT = not more than; USP = United States Pharmacopeia; UV = ultraviolet; w/v = weight/volume

(b) (4)

Reviewer's comments:
The release specifications include:

Spray pattern, pump deliver/dose accuracy/potency assay, spray content uniformity, droplet size distribution. All specifications are the same for release and for all the other testing. The release specifications do not include, actuation force. This should be included.
Potency assay = spray weight/dose accuracy.

Deficiency: Release criteria should include all the essential performance requirements for the combination product. The release criteria for this product includes testing of the spray content uniformity, pump delivery, droplet size distribution, and spray pattern. Actuation force was not included and is considered an essential performance requirement. We recommend that you update the release specifications to include actuation force. Alternatively, provide information showing how you will control the product to assure this performance specification is consistently achieved.

12.INTERACTIVE REVIEW

12.1. Filing Information Requests

The actuation parameters of spray pattern, droplet/particle size distribution, and spray weight were all defined, verified and validated in the submission. Discussion or testing of the actuation force for the spray pump could not be located in the submission. This information is important to ensure the nasal spray pump is appropriate for the user population. Please provide actuation force testing for the to be marketed form of the combination product.

Sponsor's response received 9/6/2018:
Referenced an FDA cleared device with the same materials from the same manufacturer for a similar intended use. Human factors study with to-be-marketed product. They did not provide an actuation force specification.

12.2. 74-Day letter Information Requests

Are there 74-Day Letter information requests? ☐ No ☐ Yes

12.3. Mid-Cycle Information Requests

1. We acknowledge your proposed strategy of (b) (4) [redacted] (b) (4)

2. Provide updated stability data for all strengths.

12.4. Interactive Review

Are there other interactive review information requests? ☐ No ☐ Yes

13. COMPLETE RESPONSE DEFICIENCIES

The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

CDRH Information Request

1. We acknowledge your proposed strategy of (b) (4) [redacted] (b) (4)

   We recommend that you submit updated stability data to demonstrate that the to be marketed product will meet the specifications after stability testing.

2. We recommend that actuation force be considered an essential performance requirement. A specification for this requirement was not defined in the submission, and verification and validation data were not provided for the specification. Therefore, we recommend that you provide a specification for actuation force for the to be marketed form of the combination product along with verification and validation data

to support that specification. Please describe why this force is appropriate for the intended user population. Alternatively, provide a rationale for why you do not consider actuation force an essential performance requirement for the device constituent.

3. The stability data included droplet size distribution, spray weight, spray content uniformity, spray pattern, and weight lost. The data did not include actuation force. We recommend that you include stability data to demonstrate that the actuation force specifications are maintained over the shelf life of the product.

4. Release criteria should include all of the essential performance requirements for the combination product. The release criteria for this product includes testing of the spray content uniformity, pump delivery, droplet size distribution, and spray pattern. Actuation force was not included and is considered an essential performance requirement. We recommend that you update the release specifications to include actuation force. Alternatively, provide information showing how you will control the product to assure this performance specification is consistently achieved.

5. You provided a specification for the lowest allowable cap removal force. You have not provided a specification for the highest allowable cap removal force. This information is recommended to demonstrate that the cap will not be too difficult for the user to remove. We recommend the upper cap removal force specification be defined.

14.RECOMMENDATION

14.1. Recommendation to CDER

CDRH is recommending that the device constituent of the combination product is not approvable for the proposed indication due to no provided actuation force specification, stability testing, or release criteria. Additionally, droplet size distribution specifications were not met in the stability testing. See Section 13 for the deficiencies to include in the complete response letter.

Oumou Barry

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