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RESEARCH**

APPLICATION NUMBER:

215712Orig1s000

OTHER REVIEW(S)

Labeling Review for Nasonex 24HR Allergy Nasal Spray *Draft Labeling* Addendum

SUBMISSION DATE(S): February 7, 2022
February 10, 2022

NDA/SUBMISSION TYPE: NDA 215712

ACTIVE INGREDIENT(S): Mometasone Furoate, 50 mcg/spray

DOSAGE FORM(S): Nasal spray

SPONSOR: Perrigo Pharma International
Perrigo R&D Company (Authorized US Agent)
515 Eastern Ave, Allegan, MI 49010
Valerie Gallagher, Vice President Regulatory Affairs
269-673-9367

REVIEWER: Teegan Dellibovi-Ragheb, PhD, RAC

TEAM LEADER: Sergio Coelho, PhD

PROJECT MANAGER: Phong Pham, PharmD

BACKGROUND

Reference is made to the NDA 215712 submission on May 17, 2021, and the labeling amendments, dated September 3, 2021, October 20, 2021, November 15, 2021, January 12, 2022, and February 1, 2022. NDA 215712 was submitted for the partial switch of Nasonex (mometasone furoate monohydrate) Nasal Spray, 50 mcg/spray, from Rx to Over-the-Counter (OTC) status. The proposed OTC indication is “temporarily relieves these symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy nose.” The purpose for this product would be “Allergy Symptom Reliever.” Reference is also made to the labeling review entered into DARRTS on February 4, 2022 (Teegan Dellibovi-Ragheb, IDS Reviewer) in which the sponsor’s draft labeling was evaluated.

FDA requested clean labels (labeling that does not include any annotations, additional markings, or legends such as size specifications and/or color scheme) on February 2, 2022. These labels were submitted in an amendment to the supplement on February 7, 2022.

In addition, FDA sent the following information request to the sponsor on February 9, 2022, which was based on the recommendations made in the labeling review conducted by the DMEPA review team and entered into DARRTS on February 3, 2022:

As currently presented in all the proposed container labels and carton labeling, the format for the expiration date is not defined. To reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day formatted as YYYY-MM-DD if only numerical characters are used, or as YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month expressed as YYYY-MM if only numerical characters are used, or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

The sponsor submitted an amendment to the supplement on February 10, 2022 in which they state, “The format of the expiration date is included in the Master Packaging Records on the upper right hand side of the ‘Customer Packaging Order’ page. The format is currently listed as “Exp Date: MM/YYYY”. (b) (4). However, Perrigo is aware of the initiative in USP<7> that will require either the YYYY-MM or YYYY-MMM format and will comply by the effective date, which is currently September 1, 2023.” The DMEPA review team indicated in a review entered into DARRTS on February 16, 2022 that this response was acceptable from a medication error perspective.

This current addendum labeling review is for the amendments submitted by the sponsor on February 7 and 10, 2022.

Table 1: Draft Labeling Submitted for Review

Submitted Draft Labeling	Date Submitted
120 spray count blister card (secondary packaging)	2/7/2022
120 spray count container label	2/7/2022
60 spray count blister card (secondary packaging)	2/7/2022
60 spray count container label	2/7/2022
30 spray count blister card (secondary packaging)	2/7/2022
30 spray count container label	2/7/2022

Consumer Information Leaflet (Package Insert for all Nasonex 24HR Allergy SKUs)	2/7/2022
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REVIEWER'S COMMENTS

The sponsor submitted clean labeling files for the proposed blister card (outer container) and immediate container labeling and the consumer information leaflet (package insert) submitted on February 1, 2022, which were reviewed and recommended for approval in the labeling review entered into DARRTS on February 4, 2022. The sponsor did not make any further changes to these labels. This is acceptable.

RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted outer and immediate container labeling for Nasonex 24HR Allergy (mometasone furoate, 50 mcg/spray) nasal spray and request final printed labeling. The sponsor should be informed that the “New!” flag appearing in the upper right corner of the PDP must be removed after six months of marketing. Request that the sponsor submit final printed labeling (FPL) identical to the labeling listed in the following table.

Submitted Draft Labeling	Date Submitted
120 spray count blister card (secondary packaging)	2/7/2022
120 spray count container label	2/7/2022
60 spray count blister card (secondary packaging)	2/7/2022
60 spray count container label	2/7/2022
30 spray count blister card (secondary packaging)	2/7/2022
30 spray count container label	2/7/2022
Consumer Information Leaflet (Package Insert for all Nasonex 24HR Allergy SKUs)	2/7/2022

SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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

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/s/

TEEGAN A DELLIBOVI-RAGHEB
02/18/2022 02:58:48 PM

SERGIO N COELHO
02/18/2022 03:01:11 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 16, 2022
Requesting Office or Division: Division of Nonprescription Drugs I (DNPDI)
Application Type and Number: NDA 215712
Product Name and Strength: Nasonex 24HR Allergy (mometasone furoate monohydrate) nasal spray, 50 mcg per spray
Applicant/Sponsor Name: Perrigo Pharma International DAC
OSE RCM #: 2021-1241-1
DMEPA 2 Safety Evaluator: Grace P. Jones, PharmD, BCPS
DMEPA 2 Team Leader: Janine Stewart, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a response to our labels and labeling recommendation, received on February 10, 2022 for Nasonex 24HR Allergy, which the Division of Nonprescription Drugs I (DNPDI) requested that we review to determine if it is acceptable from a medication error perspective. The Applicant's response reflects a recommendation that we made during a previous label and labeling review.^a

2 CONCLUSION

We acknowledge the Applicant's response that the proposed currently listed expiration date is "MM/YYYY" and their plan to revise the format to either "YYYY-MM" or "YYYY-MMM" by September 1, 2023. We find this acceptable from a medication error perspective and have no additional recommendations at this time.

^a Jones, G. Label and Labeling Review for Nasonex 24HR Allergy (NDA 215712). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 FEB 02. RCM No.: 2021-1241.

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/

GRACE JONES
02/16/2022 03:49:25 PM

JANINE A STEWART
02/16/2022 05:07:29 PM

Labeling Review for Nasonex 24HR Allergy Nasal Spray *Draft Labeling*

SUBMISSION DATE(S): May 17, 2021
September 3, 2021
October 20, 2021
November 15, 2021
January 12, 2022
February 1, 2022

NDA/SUBMISSION TYPE: NDA 215712

ACTIVE INGREDIENT(S): Mometasone Furoate, 50 mcg/spray

DOSAGE FORM(S): Nasal spray

SPONSOR: Perrigo Pharma International
Perrigo R&D Company (Authorized US Agent)
515 Eastern Ave, Allegan, MI 49010
Valerie Gallagher, Vice President Regulatory Affairs
269-673-9367

REVIEWER: Teegan Dellibovi-Ragheb, PhD, RAC

TEAM LEADER: Sergio Coelho, PhD

PROJECT MANAGER: Phong Pham, PharmD

BACKGROUND

Nasonex (mometasone furoate monohydrate) Nasal Spray, 50 mcg/spray, is an intranasal glucocorticoid which has been available by prescription since October 1, 1997 under NDA 20762. Perrigo acquired right of reference to NDA 20762 and is submitting the current original NDA 215712 to partially switch Nasonex from Rx to Over-the-Counter (OTC) status. The proposed OTC indication is “temporarily relieves these symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy nose.” The purpose for this product would be “Allergy Symptom Reliever.”

The Rx NDA 20762 would remain active and be amended to support the remaining Rx indications for prophylaxis of seasonal allergic rhinitis and treatment of nasal polyps.

The sponsor is proposing to market the nonprescription drug product under the trade name “Nasonex 24HR Allergy”. A proprietary name review request was submitted to the agency on June 4, 2019 and a Proprietary Name Conditionally Acceptable letter was issued by FDA on November 20, 2019. Sponsor resubmitted the request for a proprietary name review for Nasonex 24HR Allergy on June 10, 2021 and a Proprietary Name Granted letter was issued by FDA on September 8, 2021.

Currently approved nonprescription intranasal glucocorticoid products include:

- Flonase Sensimist Allergy Relief (fluticasone furoate 27.5 mcg per spray)
 - Original NDA 22051 (Type 2- New Active Ingredient) approved 4/27/2007, Supplement 13 (Full Rx-to-OTC switch) approved 8/2/2016
- Flonase Allergy Relief (fluticasone propionate 50 mcg per spray)
 - Original NDA 20121 (Type 3- New Dosage Form) approved 10/19/1994, NDA 205434 (Partial Rx-to-OTC switch) approved 7/23/2014
- Nasacort Allergy 24HR (triamcinolone acetonide 55 mcg per spray)
 - Original NDA 20468 (Type 3- New Dosage Form) approved 5/20/1996, Supplement 35 (Full Rx-to-OTC switch) approved 10/11/2013
- Rhinocort Allergy Spray (budesonide 32 mcg per spray)
 - Original NDA 20746 (Type 3- New Dosage Form) approved 10/1/1999, Supplement 32 (Full Rx-to-OTC switch) approved 3/23/2015

Table 1: Draft Labeling Submitted for Review

Submitted Draft Labeling	Date Submitted
120 spray count blister card (secondary packaging)	5/17/2021 9/3/2021 10/20/2021 11/15/2021 1/12/2022 2/1/2022
120 spray count container label	5/17/2021 9/3/2021 10/20/2021 2/1/2022
60 spray count blister card (secondary packaging)	5/17/2021 9/3/2021 10/20/2021

	11/15/2021 1/12/2022 2/1/2022
60 spray count container label	5/17/2021 9/3/2021 10/20/2021 2/1/2022
30 spray count blister card (secondary packaging)	5/17/2021 9/3/2021 10/20/2021 11/15/2021 1/12/2022 2/1/2022
30 spray count container label	5/17/2021 9/3/2021 10/20/2021 2/1/2022
Consumer Information Leaflet (Package Insert for all Nasonex 24HR Allergy SKUs)	5/17/2021 9/3/2021 10/20/2021 1/12/2022 2/1/2022

INFORMATION REQUESTS (IRs)

A. 74 day letter dated July 29, 2021

FDA requested the following labeling information from the sponsor in the 74 day letter:

General Comments:

- (1) Provide a 3D rendering of the to-be-marketed product or physical (actual) samples of the product, including the immediate and secondary container labeling.
- (2) We remind you that the distributor labeling must be identical to the application holder's label and labeling, with the exception of trade dress and required manufacturer, packer, or distributor information as applicable under 21 CFR 201.1. It is the responsibility of the application holder to ensure that all distributor labeling is identical, with the exceptions noted, to the labeling approved under the NDA.

Principal Display Panel (PDP):

- (3) Revise the statement of identity on the PDP so that it is in bold face type, and the size of the text is at least 30% of the height of the most prominent printed matter on the PDP. In addition, use a font color that provides better contrast to the background color, (b) (4).
- (4) Revise the text of the statement of identity such that it reads, “Mometasone furoate, 50 mcg/spray allergy symptom reliever (glucocorticoid)* nasal spray”. Note that there is currently no USP monograph for “mometasone furoate nasal spray”.
- (5) Revise the asterisked statement at the bottom of the PDP which states “Mometasone furoate is a steroid medicine known as a glucocorticoid” so that the font is larger and in a color that provides better contrast to the background color, (b) (4).
- (6) Ensure that the size of the declaration of net quantity of contents (“0.57 fl. oz. (17.0mL)”) complies with the type specifications as laid out in 21 CFR 201.62(h). In addition, for all labels include the dimensions of the PDP (in square inches) and the height of the declaration (in inches) on your draft labeling.

Drug Facts Label:

- (7) Provide the maximum characters per inch of the Drug Facts text for all labels.

Immediate Container Label:

- (8) Consider using a peel-back label for the immediate container, so that you can include dosing information for adults and children 12 years of age and older, as well as important warnings, on the immediate container labeling.
- (9) Increase the size of the text on the immediate container labeling so that it is at least 6-point type.
- (10) Provide the maximum characters per inch for the text on the immediate container label.
- (11) Remove the asterisk at the end of the statement of identity.
- (12) Revise the declaration of net quantity of contents so that the font is in a color that provides better contrast to the white background.

The sponsor responded with the additional information and revised labeling on September 3, 2021. The sponsor made some of the labeling changes requested by FDA. However, the sponsor declined to revise the wording of the SOI as requested, and also declined to use a peel-back label for the immediate container, as recommended by FDA. The sponsor revised the text size of the immediate container label for the 30-spray count SKU from 4 point to only 4.5 point type, rather than 6 point type as requested, however the other immediate container SKUs were revised to 6 point type.

B. Information Request dated October 7, 2021

FDA requested the following labeling information from the sponsor:

Principal Display Panel (PDP):

- (1) We acknowledge that you increased the size and contrast of the statement of identity (SOI) on the PDP, however we remain concerned that it is not sufficiently prominent. We therefore reiterate our previous request to revise the SOI so that it is in bold face type. In addition, we request that you further increase the contrast of the font color compared to the white background, (b) (4).
- (2) We acknowledge that you increased the font size of the asterisked statement at the bottom of the PDP which states “Mometasone furoate is a steroid medicine known as a glucocorticoid” by 1 point size. However, we are concerned that this statement is still extremely small compared to the other printed matter on the PDP, and it conveys important information to the consumer as an adjunct to the statement of identity. Therefore, increase the size of this statement so it is in a size reasonably related to the most prominent printed matter on the PDP.

Drug Facts Label (DFL):

- (3) Under the subheading “When using this product” add the warning “stinging may occur for a few seconds right after use”. Postmarketing experience notes nasal burning and irritation as an adverse effect of using this product. A similar warning already exists in this product class.

Immediate Container Label:

- (4) We acknowledge receipt of the 3D rendering of your to-be-marketed product, which you submitted in response to our request. Upon review we noted that according to your current package configuration, the (b) (4) (b) (4), and the DFL is printed on the other side. We are concerned that consumers would (b) (4) (b) (4) (b) (4).
- Increase the size of the text on the 30 spray count immediate container label so that it is at least 6-point type, and the maximum characters per inch does not exceed 39. Currently, the text is too small to be legible to consumers. If you are unable to make the label legible to consumers, we recommend that you use a peel-back label for the immediate container, so that you can include dosing information for adults and children 12 years of age and older, as well as important warnings, on the immediate container labeling, for those consumers that do not have access to the full DFL on the outer container.

- Send two physical samples of the to-be-marketed 30 spray count product for review, which includes the immediate container in the outer packaging.

Please send to:

Phong Pham

(b) (4)

- (5) We acknowledge that you increased the contrast of the declaration of net quantity of contents in response to our request, however we still have concerns that the declaration is not sufficiently conspicuous. Revise the declaration so that the font is in a color that provides better contrast to the white background, (b) (4)

(b) (4)

The sponsor responded with the additional information and revised labeling on October 20, 2021. Rather than physical samples of the product, which the sponsor stated were not available at the time, the sponsor submitted a moveable 3D image of the product. In addition, the sponsor updated the package insert to include a (b) (4) discard date for the product as requested by the CMC review team. The sponsor noted that they may increase the number of days once the extended Antimicrobial Effectiveness Testing (AET) study is completed and submitted to FDA (no later than 1/16/2022).

C. Information Request dated November 9, 2021

FDA requested the following labeling information from the sponsor:

We acknowledge that you included the discard date on the package insert. We also request that you include this information (i.e., “Discard (b) (4) days after first use of the product”) on the Drug Facts Label as the last bulleted item under the “Other information” heading, immediately following the storage information.

The sponsor responded with the additional information and revised labeling on November 15, 2021.

On January 12, 2022 the sponsor submitted an additional amendment with the AET study report and updated labeling, which revised the discard date on the DFL and package insert for all SKUs to “discard 75 days after first use of the product”. The CMC review team determined that a 75 day discard date was supported by the AET data and confirmed that this labeling statement was acceptable at a team meeting on January 20, 2022 (based on Microbiology review 1/13/22).

D. Information Request dated January 25, 2022

FDA requested the following labeling information from the sponsor:

(1)

(b) (4)

- (2) Consider adding a statement to the Consumer Information Leaflet (package insert) informing the consumer that there is enough medication in the bottle to allow for priming sprays plus the number of sprays labeled on the bottle.

The sponsor submitted an amendment to the supplement on February 1, 2022. The amendment contained revised labeling, in which the (b) (4) was removed from the outer container and immediate container labeling, as well as the package insert. In addition, the recommended statement “NOTE: There is enough medicine in the bottle to allow for priming sprays plus the number of sprays labeled on the bottle” was added to the package insert under the heading “Prime”. The sponsor also updated the copyright information to ©2022.

REVIEWER'S COMMENTS

This is a review of the proposed blister card (outer container) and immediate container labeling and the consumer information leaflet (package insert) submitted on February 1, 2022.

A. Blister Card (secondary packaging), 30-, 60- and 120-spray count

i. Principal Display Panel (PDP)

The proprietary name is written as “Nasonex 24HR Allergy”. This name was found acceptable in a Proprietary Name Review entered into DARRTS on September 7, 2021. A Proprietary Name Granted letter was issued to the sponsor on September 8, 2021 indicating that this proprietary name is conditionally acceptable. Therefore, this is acceptable.

The statement of identity (SOI) is written as “Mometasone furoate nasal spray, 50 mcg/spray allergy symptom reliever (glucocorticoid)*” and at the bottom of the PDP there is the asterisked statement “*Mometasone Furoate is a steroid medicine known as a glucocorticoid”. Although the sponsor declined to revise the text of the SOI as recommended in the 74 day letter (such that the dosage form appears at the end of the statement), the language used in the draft labeling is consistent with the labeling for other drug products in this product class. In addition, in response to FDA’s requests in the 74 day letter and in a request for information dated October 7, 2021, the sponsor revised the SOI to bold face type, used a darker font that provides better contrast with the background, and increased the size to 25% of the Nasonex portion of the proprietary name. The sponsor also increased the size and contrast of the asterisked

statement at the bottom of the PDP so that it is sufficiently prominent. Therefore, this is acceptable.

The Perrigo logo and NDC number appear at the top of the PDP. This is acceptable.

The promotional statement “Convenience Pack” appears at the top of the PDP of the 30 spray count label. Similar promotional material has been approved for other OTC products. Therefore, this is acceptable.

The statement “non-drowsy / scent-free mist” appears in the upper right corner of the PDP. These are accurate statements and consistent with the labeling claims used for other products in this class. Therefore, these are acceptable.

A “New!” flag appears in the upper right corner of the PDP. Any such new flag must be removed after six months of marketing. This is acceptable.

The statements “Allergy + Congestion” and “Full Prescription Strength” appear in the center of the PDP. These are accurate descriptions of the product’s indication and dosage strength and are consistent with the labeling claims used for other products in this class. Therefore, this is acceptable.

The statement “24HR RELIEF of: nasal congestion / runny nose / sneezing / itchy nose” appears on the lower half of the PDP. This description of the product’s indication is accurate and uses the same language as the “Uses” statement on the DFL. Therefore, this is acceptable.

The spray count and the declaration of net quantity of contents appear at the bottom of the PDP, as listed below. The declaration meets the format specifications in 21 CFR 201.62. Therefore, this is acceptable.

- 30 Sprays, 0.25 FL. OZ. (7.5mL)
- 60 Sprays, 0.34 FL. OZ. (10.0mL)
- 120 Sprays, 0.57 FL. OZ. (17.0mL)

ii. Top and Back Panel

The top panel contains the statement “Allergy X Congestion”, similar to the statement on the PDP. This is acceptable.

The back panel contains the proprietary name “Nasonex 24HR Allergy” and the statement “24HR RELIEF of: nasal congestion / runny nose / sneezing / itchy nose”. These are similar to the statements on the PDP and are acceptable.

The back panel contains the distributor and copyright information “Distributed By Perrigo Allegan, MI 49010 ©2022. All rights reserved.” This is acceptable.

The back panel contains recycling info, a barcode and location for lot number and expiration date. This is acceptable. However, DMEPA has recommended the format for the expiration date be defined for all submitted labeling prior to approval (DMEPA review 2/3/22).

The back panel contains the statement “Nasonex, the Nasonex logo, the bottle and cap designs, and other design elements are trademarks of Merck Sharp & Dohme Corporation or its affiliates and used under license.” Perrigo states they have acquired right of reference to NDA 20762 from Merck Sharp & Dohme and the rights to partially switch the NDA from Rx to OTC status. Therefore, this is acceptable.

Immediately above the DFL on the back panel there is the statement “See below for important information about use in children.” This is consistent with the labeling for other products in this class and is acceptable.

iii. Drug Facts Label (DFL)

The Active ingredient (in each spray) section states “Mometasone furoate monohydrate (glucocorticoid) 50 mcg” and the Purpose section states, “Allergy symptom reliever”. This is consistent with other products in this class and is acceptable.

The Uses section mirrors previously approved OTC nasal glucocorticoids and is acceptable.

The warnings included in the different subsections under the heading Warnings are acceptable. They are based on the warnings and information in the Patient Information section of the currently approved Rx labeling. In addition, these warnings closely mirror the previously approved labeling of currently marketed OTC nasal glucocorticoids in both content and placement. They are also consistent with FDA’s recommendations during pre-NDA meetings, and include the warning “stinging may occur for a few seconds right after use”, which was requested by FDA in an information request on October 7, 2021.

The Directions section is written in a way that is consistent with other drugs in this class, and the language is clear and simple. It refers consumers to the package insert for additional directions and information. It includes the dosage for adults and children 12 years of age and older, and the dosage for children 2 to 11 years of age. It includes limitations of use for children, which is important for the safe use of this product in pediatric populations. It does not limit the use of this product in adults and

children 12 years of age and older, however the DPACC review team indicated during team meetings held on July 8, 2021 and September 22, 2021 that this is consistent with clinical practice and a limitation of use for this population is not necessary.

The bulleted information in the Other Information section is accurate and is consistent with currently approved labeling for other drugs in this class. In response to a request for information dated November 9, 2021, the sponsor included the discard information “discard 75 days after first use of the product” as the last bulleted item immediately following the storage information. The CMC review team has determined that this is acceptable based on the results of the AET study submitted on January 12, 2022 (Microbiology review 1/13/22). Therefore, this is acceptable.

The label meets format specifications in 21 CFR 201.66(d).

B. Immediate Container Label (30-, 60- and 120-spray count)

The proprietary name “Nasonex 24HR Allergy” and the SOI “Mometasone Furoate Nasal Spray 50 mcg per spray **Allergy Symptom Reliever** (glucocorticoid)” appear in the center of the immediate container label. This is acceptable.

The spray count and declaration of net quantity of contents appear below the SOI (for the 60 and 120 spray count) or to the right of the SOI (for the 30 spray count). The declaration complies with 21 CFR 201.62 for the 60 and 120 spray count. The height of the declaration is under 1/16 inch on the 30 spray count label, which does not comply with 21 CFR 201.62(h)(1). However, the declaration is legible and is at least 6 point type, which was the minimum font size requested by FDA. Therefore, this is acceptable.

The label contains the statement “IMPORTANT: Read Drug Facts label and enclosed materials for important information. Children 2-11: 1 spray per nostril per day. Talk to a doctor if your child needs to use for longer than two months a year. Keep out of reach of children. Only for use in the nose, do not spray into eyes. Store between 20°-25°C (68°-77°F). Shake well before each use.” The sponsor declined to use a peel-back label in order to include additional information for the safe and effective use of this product on the immediate container label (such as dosing directions for adults and children 12 and over, and important warnings). However, the information that is included in the limited space available is consistent with previously approved immediate container labeling for other drugs in this class, and the consumer is referred to the full usage information on the DFL and package insert. Therefore, this is acceptable.

The label contains the distributor and copyright information “Distributed By Perrigo Allegan, MI 49010 ©2022. All rights reserved.” This is acceptable.

The label contains the contact information “*Questions or comments?* Call toll-free 1-800-864-9649” (60 and 120 spray count) or “*Questions?* 1-800-864-9649” (30 spray count). This is acceptable.

The label contains the location for a lot number and expiration date. This location is acceptable. However, DMEPA has recommended the format for the expiration date be defined for all submitted labeling prior to approval (DMEPA review 2/3/22).

The text on the immediate container label is at least 6 point type, provides sufficient contrast with the white background, and has no more than 39 characters per inch. This is acceptable.

C. Package Insert (30-, 60- and 120-spray count)

The labeling text of the package insert is as follows. The text corresponds to diagrams in the package insert to aid in consumer comprehension:



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Reviewer Comments: The package insert contains detailed directions on how to shake, prime the bottle, use the spray, and clean the nozzle. It includes dosage information for children age 2-11 and users age 12 or older, as well as other important information and some key warnings. In addition, it includes limitations of use for children, which is important for the safe use of this product in pediatric populations. As requested by FDA, the discard information “discard 75 days after first use of the product” is included on the package insert as well as the DFL. Also as recommended by FDA, the statement “NOTE: There is enough medicine in the bottle to allow for priming sprays plus the number of sprays labeled on the bottle” was added to the package insert under the heading “Prime”. The information on the package insert is accurate and is consistent with the currently approved Rx labeling. In addition, the information closely mirrors the currently approved labeling for the package insert for other nasal glucocorticoids in both content and placement. For instance, in section A (Getting Started), Steps 1-5 (Shake, Prime, Blow, Aim, Breath and Spray) use the same headings and much of the same language as the approved labeling for other drugs in this product class. The directions and diagrams are clear, use plain language, and are laid out in a logical flow of information with sufficient white space to aid with navigation and comprehension of the information.

RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted outer and immediate container labeling for Nasonex 24HR Allergy (mometasone furoate, 50 mcg/spray) nasal spray and request final printed labeling. The sponsor should be informed that the “New!” flag appearing in the upper right corner of the PDP must be removed after six months of marketing. Request that the sponsor submit final printed labeling (FPL) identical to the labeling listed in the following table, with the exceptions noted below under “Outstanding Issues”:

Submitted Draft Labeling	Date Submitted
120 spray count blister card (secondary packaging)	2/1/2022
120 spray count container label	2/1/2022
60 spray count blister card (secondary packaging)	2/1/2022
60 spray count container label	2/1/2022
30 spray count blister card (secondary packaging)	2/1/2022
30 spray count container label	2/1/2022
Consumer Information Leaflet (Package Insert for all Nasonex 24HR Allergy SKUs)	2/1/2022

OUTSTANDING ISSUES

The sponsor will need to submit clean labeling files without any proprietary information.

In addition, in there February 3, 2022 review, DMEPA has recommended the format for the expiration date be defined for all submitted labeling prior to approval.

SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

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

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/

TEEGAN A DELLIBOVI-RAGHEB
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SERGIO N COELHO
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	February 2, 2022
Requesting Office or Division:	Division of Nonprescription Drugs I (DNPDI)
Application Type and Number:	NDA 215712
Product Name, Dosage Form, and Strength:	Nasonex 24HR Allergy (mometasone furoate monohydrate) nasal spray, 50 mcg per spray
Product Type:	Single Ingredient Product
Rx or OTC:	Over-the-Counter (OTC)
Applicant/Sponsor Name:	Perrigo Pharma International DAC
FDA Received Date:	February 1, 2022, January 12, 2022, November 15, 2021, and October 20, 2021
OSE RCM #:	2021-1241
DMEPA 2 Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA 2 Team Leader:	Janine Stewart, PharmD

1 REASON FOR REVIEW

As part of the approval process for Nasonex 24HR Allergy (mometasone furoate monohydrate) nasal spray, the Division of Nonprescription Drugs I (DNPDI) requested that we review the proposed Nasonex 24HR Allergy container labels, carton labeling, and Consumer Information Leaflet (CIL) for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY & BACKGROUND

Mometasone furoate monohydrate nasal spray, 50 mcg, was originally approved on October 1, 1997, under NDA 020762 as a prescription product. Perrigo Pharma International DAC (Perrigo) acquired right of reference to NDA 020762 and now seeks a partial Rx-to-OTC switch for the proposed OTC use of mometasone furoate monohydrate for the temporary relief of symptoms of hay fever or other upper respiratory allergies (nasal congestion, runny nose, sneezing, and itchy nose), under NDA 215712. The Rx indications for the prophylaxis of seasonal allergic rhinitis and treatment of nasal polyps will remain under NDA 020762. Perrigo seeks to market the proposed OTC product under the proposed proprietary name, Nasonex 24HR Allergy, which we found acceptable on September 3, 2021^a.

2 MATERIALS REVIEWED

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

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

^a Jones G. Proprietary Name Memorandum for Nasonex 24HR Allergy (NDA 215712). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 03. PNR ID No.: 2021-1044724016.

Jones G. Proprietary Name Review for Nasonex 24HR Allergy (PIND 142446). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 07. PNR ID No.: 2019-32179513

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Nasonex 24HR Allergy container labels, carton labeling, and CIL, which is the package insert. Of note, Perrigo indicates that the only difference between the Rx formula and the proposed OTC formula is the (b) (4)

The proposed product would be a fifth in class Rx-to-OTC switch for intranasal corticosteroids. Additionally, Perrigo is proposing an (b) (4)

The proposed Nasonex 24HR Allergy (b) (4) container labels, carton labeling, and CIL are consistent with the information contained in the prescription Prescribing Information (PI) and Instructions for Use (IFU) that provide product dosing and usage instructions. Additionally, the proposed CIL follows a similar format and contains similar usage information as the currently marketed OTC intranasal corticosteroids (e.g., Flonase Allergy Relief and Flonase Sensimist Allergy Relief). The proposed CIL also includes a statement noting that enough medication is in the bottle to allow for both priming sprays and the number of labeled sprays. The *Other Information* section of the Drug Facts Label (DFL) also contains the bullet, "keep package and insert. They contain important information," which is consistent and similar to language that is listed for other currently marketed OTC intranasal corticosteroid products. The additional information in the *Other Information* section of the DFL, "discard 75 days after first use of the product" is included based on the in-use stability data that Perrigo submitted, which OPQ confirmed.

We note the proposed container labels and carton labeling contain a placeholder for the lot number and expiration date, but the format for the expiration date is not provided. Thus, to ensure the safe use of the product and to minimize confusion and risk for deteriorated drug medication errors, we provide a recommendation below.

DMEPA had previously reviewed the submitted use-related risk analysis (URRA) and comparative analysis under IND 142446, which Perrigo submitted to support that results of a human factors (HF) validation study would not be needed for the NDA submission. DMEPA's evaluation of the URRA and known use issues with currently marketed products found that the potential risks with using the proposed product have been considered and mitigated with no identifiable or unique risks and determined that HF validation study results are not needed to

support the NDA.^b Under the NDA submission, Perrigo states that the product user interface has not been modified. Thus, additional HF related data is not necessary at this time.

4 CONCLUSION & RECOMMENDATIONS

We determined that the proposed CIL for Nasonex 24HR Allergy (b) (4) are acceptable from a medication error perspective. The proposed container labels and carton labeling for Nasonex 24HR Allergy (b) (4) may be improved to minimize confusion and risk for deteriorated drug medication errors. Thus, we provide a recommendation in Section 4.1.

4.1 RECOMMENDATIONS FOR PERRIGO PHARMA INTERNATIONAL DAC

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

A. Container Labels & Carton Labeling

1. As currently presented in all the proposed container labels and carton labeling, the format for the expiration date is not defined. To reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format, if only numerical characters are used, or in YYYY-MMM-DD format, if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as, YYYY-MM, if only numerical characters are used, or YYYY-MMM, if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

^b Little C. Use-Related Risk Analysis and Comparative Analyses Review for Nasonex 24HR Allergy (mometasone furoate monohydrate) IND 142446. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 17. RCM No.: 2020-53.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nasonex 24HR Allergy received on January 12, 2022 from Perrigo Pharma International DAC.

Table 2. Relevant Product Information for Nasonex 24HR Allergy	
Initial Approval Date	10/01/1997
Active Ingredient	mometasone furoate monohydrate
Indication	<p>Drug Facts Label (DFL) <i>Uses:</i></p> <p>Uses temporarily relieves these symptoms of hay fever or other upper respiratory allergies:</p> <ul style="list-style-type: none"> ■ nasal congestion ■ runny nose ■ sneezing ■ itchy nose
Route of Administration	nasal
Dosage Form	nasal spray
Strength	50 mcg per spray
Dose and Frequency	<p>Drug Facts Label (DFL) <i>Directions:</i></p> <p>Directions Read insert (inside package) for how to:</p> <ul style="list-style-type: none"> ■ prime the bottle ■ use the spray ■ clean the nozzle ■ shake well before each use ■ use this product only once a day ■ do not use more than directed <p>Adults & children 12 years of age and older</p> <ul style="list-style-type: none"> ■ 2 sprays in each nostril once daily while sniffing gently <p>Children 2 to 11 years of age</p> <ul style="list-style-type: none"> ■ the growth rate of some children may be slower while using this product. Children should use for the shortest amount of time necessary to achieve symptom relief. Talk to your child's doctor if your child needs to use the spray for longer than two months a year. ■ an adult should supervise use ■ 1 spray in each nostril once daily while sniffing gently <p>Children under 2 years of age</p> <ul style="list-style-type: none"> ■ do not use
How Supplied	30-spray, 60-spray, and 120-spray count bottles
Storage	store between 20-25°C (68-77°F) discard 75 days after first use of the product

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 19, 2022, we searched for previous DMEPA reviews relevant to this current review using the term, Nasonex. Our search identified three previous reviews^{c,d,e}, and we considered our previous recommendations to see if they are applicable for this current review.

^c Chan I. Labeling Review for Nasonex (NDA 020762/S-037). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 MAR 18. RCM No.: 2009-1663.

(b) (4)

^e Little C. Use-Related Risk Analysis and Comparative Analyses Review for Nasonex 24HR Allergy (mometasone furoate monohydrate) IND 142446. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 17. RCM No.: 2020-53.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Nasonex 24HR Allergy labels and labeling submitted by Perrigo Pharma International DAC.

- Container labels received on October 20, 2021 (b) (4) and February 1, 2022 (b) (4)
- Carton labeling received on January 12, 2022 (b) (4) and February 1, 2022 (b) (4)
- 3D-rendered images received on November 15, 2021
- Consumer Information Leaflet received on February 1, 2022

G.2 Label and Labeling Images

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

^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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

Pharmacovigilance Review

Date: December 16, 2021

Reviewer: Allison Lardieri, PharmD, BCPPS
Division of Pharmacovigilance II

Team Leader: Lynda McCulley, PharmD, BCPS
Division of Pharmacovigilance II

Deputy Division Director: S. Christopher Jones, PharmD, MS
Division of Pharmacovigilance II

Product Name: Nasonex (mometasone furoate monohydrate) nasal spray

Application Type/Number: NDA 215712
Partial Rx-to-OTC Switch

Applicant: Perrigo

OSE RCM #: 2021-2038

TABLE OF CONTENTS

Executive Summary	1
1 Introduction.....	2
1.1 Regulatory History	2
1.2 Relevant Product Labeling.....	2
2 Methods and Materials	3
2.1 FAERS Search Strategy	3
2.2 Sponsor’s Data	4
3 Results.....	4
3.1 FAERS Case Selection.....	5
3.2 Adverse Events of special interest (AESI).....	8
3.3 Sponsor’s Data	9
4 Conclusion	10
5 References.....	11
6 Appendices	12
6.1 Appendix A. FDA Adverse Event Reporting System (FAERS)	12
6.2 Appendix B. Preferred Terms for Adverse Events of Special Interest (AESI).....	13
6.3 Appendix C. FAERS Line Listing of Nasonex Case Series (n=71)	14

EXECUTIVE SUMMARY

On May 17, 2021 Perrigo (sponsor) submitted a New Drug Application (NDA 215712) for the partial prescription (Rx) to over-the-counter (OTC) switch of Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg. The Office of Nonprescription Drug Products (ONDP) consulted the Division of Pharmacovigilance (DPV) to evaluate reports of serious adverse events associated with Nasonex and assess the findings from the sponsor's 120-Day Safety Update. To conduct this evaluation, we reviewed adverse events reported to the FDA Adverse Event Reporting System (FAERS), the sponsor's 120-Day Safety Update, and the most recent Periodic Adverse Drug Experience Report (PADER).

Of note, ONDP requested an evaluation of the adverse events of special interest (AESI) including local nasal events, mycotic/fungal infections including candidiasis, ocular events including visual disturbances, effects on the hypothalamic pituitary adrenal (HPA) axis, effects on growth and/or bone metabolism, effects on glucose metabolism, overdose, and nonprescribed/nonmedical use exposure. These AESI were identified in the Nasonex NDA 215712 application because they were considered medically important/medically significant based on suggestions by the FDA during a Pre-NDA meeting.¹

Overall, 56/71 (78.9%) cases reported a serious adverse event (SAE), though no deaths were reported. Six of the SAE cases were from the US, of which 4 were confounded by concomitant medications. All 56 SAE cases were confounded by concomitant medications, comorbidities, or lacked information for assessment.

The majority of cases in this case series contained an AESI (57/71, 80.3%), which was similar to the sponsor's finding in their 120-Day Safety Update. In addition, the proportion of each AESI is also similar to the sponsor's FAERS search results. No new safety signals were identified from these reports of AESIs. Analysis was limited due to most cases with missing information (i.e., temporality) or cases with multiple concomitant medications and comorbidities.

Our review confirms that the sponsor's FAERS data reported in the 120-Day Safety Update is consistent with the adverse events reported in our FAERS searches. The most commonly reported PTs (*Asthma, Dyspnoea, Wheezing*) occurred in patients with allergic rhinitis, for which Nasonex is indicated. Even though we identified adverse events of special interest, analysis of the cases was limited due to missing information (i.e., temporality) or multiple concomitant medications and comorbidities. Furthermore, the low number of domestic serious adverse events, including adverse events of special interest reported with Nasonex indicate no increase in adverse events in FAERS. This data is consistent with the sponsor's data analysis.

1 INTRODUCTION

On May 17, 2021 Perrigo (sponsor) submitted a New Drug Application (NDA 215712) for the partial prescription (Rx) to over-the-counter (OTC) switch of Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg. The Office of Nonprescription Drug Products (ONDP) consulted the Division of Pharmacovigilance (DPV) to evaluate reports of serious adverse events associated with Nasonex and assess the findings from the sponsor's 120-Day Safety Update. The Prescription Drug User Fee Act (PDUFA) Goal date for this product is March 17, 2022. To conduct this evaluation, we reviewed adverse events reported to the FDA Adverse Event Reporting System (FAERS), the sponsor's 120-Day Safety Update, and the most recent Periodic Adverse Drug Experience Report (PADER).

Of note, ONDP requested an evaluation of the adverse events of special interest (AESI) including local nasal events, mycotic/fungal infections including candidiasis, ocular events including visual disturbances, effects on the hypothalamic pituitary adrenal (HPA) axis, effects on growth and/or bone metabolism, effects on glucose metabolism, overdose, and nonprescribed/nonmedical use exposure. These AESI were identified in the Nasonex NDA 215712 application because they were considered medically important/medically significant based on suggestions by the FDA during a Pre-NDA meeting.¹

1.1 REGULATORY HISTORY

Nasonex, an intranasal corticosteroid, was approved as a prescription product in 1997 for the treatment of nasal symptoms and nasal congestion associated with seasonal allergic rhinitis, prophylaxis of seasonal allergic rhinitis, and treatment of nasal polyps. The prescription dose ranged 2 sprays in each nostril once or twice daily, depending on indication for adults and 1 spray in each nostril once daily for children ages 2 to 11 years old.²

The Perrigo submission for Nasonex NDA 215712 Rx-to-OTC switch includes the following proposed indications for consumers ≥ 2 years of age:

Temporarily relieves these symptoms of hay fever or other upper respiratory allergies:

- nasal congestion
- runny nose
- sneezing
- itchy nose

The recommended dose is 2 sprays in each nostril once daily for adults and children ≥ 12 years; and 1 spray in each nostril once daily for children ages 2 to 11 years old.

The remaining two indications (i.e., prophylaxis of seasonal allergic rhinitis and treatment of nasal polyps) will remain with the Rx NDA 20762. However, the Rx Nasonex product was discontinued in May 2021 [REDACTED] (b) (4) per communication from Merck Sharp & Dohme (MSD), its current application holder.

1.2 RELEVANT PRODUCT LABELING

The following is relevant product labeling from the proposed Drug Facts Label (DFL) for Nasonex NDA 215712³:

(b) (4)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

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

Table 1. FAERS Search Strategy*	
Date of search	October 14, 2021
Time period of search	September 8, 2020 [†] - March 31, 2021 [†]
Search type	FBIS Quick Query
Product terms	Product Name: Nasonex; Nasonex (mometasone furoate monohydrate)
MedDRA search terms (Version 24.0)	<p>Search 1: all MedDRA search terms</p> <p>Search 2: PTs[‡] for local nasal event</p> <p>Search 3: PTs[‡] for mycotic/fungal infections including candidiasis</p> <p>Search 4: PTs[‡] for ocular events including visual disturbances, SMQ (Narrow) Glaucoma, SMQ (Narrow) Optic nerve disorder, SMQ (Narrow) for Lens disorders, SMQ (Narrow) Retinal disorders</p> <p>Search 5: PTs[‡] for effects on the hypothalamic pituitary adrenal (HPA) axis</p> <p>Search 6: PTs[‡] for effects on growth and/or bone metabolism</p> <p>Search 7: PTs[‡] for effects on glucose metabolism, SMQ (Narrow) Hyperglycaemia/New onset diabetes mellitus, SMQ (Narrow) Hypoglycaemia</p> <p>Search 8: PTs[‡] for overdose</p> <p>Search 9: PTs[‡] for nonprescribed/nonmedical use exposure.</p>
<p>* See Appendix A for a description of the FAERS database.</p> <p>[†] Time period of search was selected to match the time period included in the sponsor's 120-day safety update FAERS searches. The 120-day safety update spanned from September 8, 2020 through May 17, 2021. However, the sponsor used openFDA, which is updated quarterly and therefore their FAERS section only included data through March 31, 2021.</p> <p>[‡] See Appendix B for complete list of PTs included in searches 2-9. These search strategies mirror the sponsor's FAERS searches in their 120-day safety update.</p> <p>Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardised MedDRA Query, PT=Preferred Term</p>	

2.2 SPONSOR'S DATA

In addition to the FAERS data, DPV reviewed the following data submitted by the sponsor:

- 120-Day Safety Update for Nasonex 24HR Allergy NDA 215712
- Periodic Adverse Experience Report (PAER) submission for Nasonex NDA 20762 (Rx product) for the period October 2, 2019 through October 1, 2020

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved **172 reports**. After accounting for duplicate reports, **71 unique cases** were included for analysis. (See **Figure 1**).

Figure 1. FAERS Case Selection

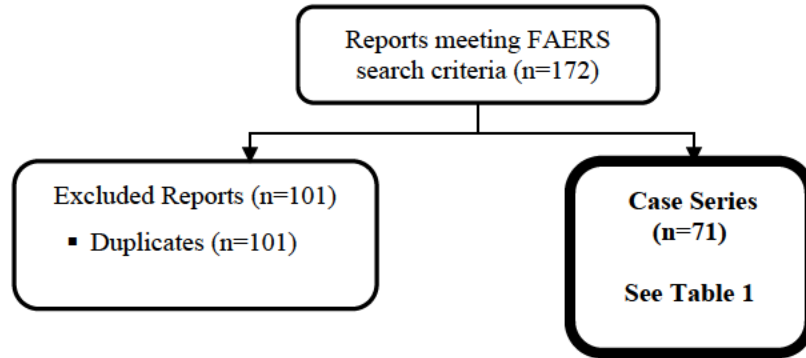


Table 1 summarizes the 71 FAERS cases reported with Nasonex for this case series.

Appendix C contains a line listing of the 71 cases in this case series.

Table 1. Descriptive Characteristics of FAERS Cases Reporting Adverse Events with Nasonex, Received by FDA From September 8, 2020 - March 31, 2021 (N=71)		
Age (years), n=50	Mean	57.1
	Median	59.1
	Range	2.6-91.3
Age Category, n=50	<18 years	2
	18 to <65 years	33
	≥65 years	15
Sex	Female	41
	Male	24
	Not reported	6
Country	USA	20
	Foreign	51
Report type	Direct	2
	Expedited	57
	Non-Expedited	12

Table 1. Descriptive Characteristics of FAERS Cases Reporting Adverse Events with Nasonex, Received by FDA From September 8, 2020 - March 31, 2021 (N=71)	
Initial FDA received year	
Sept 8 – Dec 31, 2020	43
Jan 1 – March 31, 2021	28
Serious Outcome?	
Yes	56
No	15
Serious outcome(s)*	
Hospitalization	15
Disability	3
Other	46
Confounded by concomitant medication	
Yes	51
No	20
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.	

Reviewer’s comments:

Overall, 56/71 (78.9%) cases reported a serious adverse event (SAE), though no deaths were reported. Six of the SAE cases were from the US, of which 4 were confounded by concomitant medications. Two SAE cases (both foreign) involved children <18 years (age 2.7 and 7 years); however, both cases lacked information (i.e., temporality, comorbidities). Elderly patients (≥ 65 years) represented 18% (10/56) of SAE cases. In addition, over 30% of SAE cases (17/56) were from a patient support program for Nucala (mepolizumab), which is a biologic used to treat severe asthma. These types of reports are uninformative for signal detection and represent confounded cases.

All 56 SAE cases were confounded by concomitant medications, comorbidities, or lacked information for assessment. A total of 45/56 (80.4%) SAE cases were confounded by multiple comorbidities and/or concomitant medications. A total of 11/56 (19.6%) SAE cases were not confounded by concomitant medications. However, all 11 SAE cases were confounded by comorbidities (i.e., macular degeneration), lacked information for assessment (i.e., temporality, concomitant medications), described Nasonex use for an off-label indication that contributed to the adverse event (i.e., fungal infection, adenoids, otosalpingitis), or described labeled adverse events (i.e., nosebleed). From our detailed review of these 11 SAE cases, we did not identify any new safety signal.

Table 2 summarizes the most frequently reported MedDRA PTs with Nasonex for this case series, for serious and nonserious cases.

Table 2. Most Frequently Reported MedDRA PTs with N≥4 Reported With Nasonex*, Received by FDA From September 8, 2020 - March 31, 2021, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of FAERS Reports	Labeled (Yes/No), Location or Other Category
Asthma	22	Yes, DFL Warning
Dyspnoea	21	Yes, DFL Warning
Wheezing	20	Yes, DFL Warning
Therapeutic product effect incomplete	18	U
Loss of personal independence in daily activities	15	U
Cough	13	No, DR/IR
Sleep disorder due to a general medical condition	13	U
Chest discomfort	10	No
Full blood count abnormal	9	No
Gastrooesophageal reflux disease	9	No
Productive cough	9	No, DR/IR
Drug ineffective	8	U
Headache	7	No, DR/IR
Hypertension	7	No
Abdominal pain upper	6	U
Lung disorder	6	U
Nasal polyps	6	No, DR/IR
Obstructive airways disorder	6	Yes, DFL Warning
Nasopharyngitis	5	No, DR/IR
Product dose omission issue	5	U
Anxiety	4	No
Diarrhoea	4	No
Dyspnoea exertional	4	No, DR/IR
Malaise	4	U
Nasal congestion	4	No, DR/IR
No adverse event	4	U
Oropharyngeal pain	4	No
Pneumonia	4	No, DR/IR
Pyrexia	4	U
Sleep apnoea syndrome	4	No, DR/IR
*Of note, we also reviewed PTs of interest reported in N<4 cases, related to the labeling of stinging after use in the proposed DFL. The PTs Nasal discomfort and Burning sensation were reported in 2 and 1 cases respectively. All 3 cases had alternative reasons for the nasal discomfort/burning sensation (i.e., deviated septum, fungal sinus infection, and burning was in relation to a headache).		

Reviewer's comments: The most frequently reported PTs are either labeled, generally uninformative for signal detection, or are indication- or disease-related. Many PTs are

generally recognized in patients with allergic rhinitis for which Nasonex is indicated, such as cough, productive cough, and headache.

The three most common PTs of Asthma, Dyspnoea, and Wheezing occurred frequently in patients using concomitant medications to treat chronic respiratory diseases like allergic rhinitis, asthma, and chronic obstructive pulmonary disease (COPD).

The most frequently reported PTs that are not labeled and not indication- or disease-related are addressed below:

- Chest discomfort (n=10): All are serious. All report multiple other concomitant medications and comorbidities that contribute to the adverse event or lack information for assessment.
- Full blood count abnormal (n=9): All are serious. All report multiple other concomitant medications and comorbidities that contribute to the adverse event or lack information for assessment.
- Gastroesophageal reflux disease (n=9): All are serious. All report multiple other concomitant medications and comorbidities that contribute to the adverse event or lack information for assessment. Some cases are lacking information to distinguish if the PT Gastroesophageal reflux disease is the adverse event or an underlying condition of the patient.
- Hypertension (n=7): All are serious. Six cases report multiple other concomitant medications and comorbidities that contribute to the adverse event or lack information for assessment. One case does not report confounding medications or disease states; however, it is unclear if the adverse events began prior to initiation of Nasonex.
- Anxiety (n=4): All are serious. All report multiple other concomitant medications and comorbidities that contribute to the adverse event or lack information for assessment.
- Diarrhoea (n=4): Three are serious, but all report multiple other concomitant medications and comorbidities that contribute to the adverse event or lack information for assessment. The non-serious case reports a patient who experienced stomachache and diarrhea after spraying Nasonex in his mouth 5 times by mistake. Oropharyngeal pain (n=4): All are serious. All report multiple other concomitant medications and comorbidities that contribute to the adverse event or lack information for assessment (2 cases are from a Nucala patient support program).

3.2 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Overall, 57/71 (80.3%) cases reported an AESI. **Table 3** describes the 57 AESI reported with Nasonex for this case series. These AESI were identified in the Nasonex NDA 215712 application because they were considered medically important/medically significant based on suggestions by the FDA during a Pre-NDA meeting.¹

Table 3. Adverse Events of Special Interest Reported with Nasonex, Received by FDA From September 8, 2020 - March 31, 2021	
Adverse Events of Special Interest	Case Count (%) N=71

Local nasal events	28 (39.4)
Mycotic/fungal infections including candidiasis	3 (4.2)
Ocular events including visual disturbances	8 (11.2)
Effects on the HPA Axis	1 (1.4)
Effects on growth and/or bone metabolism	9 (12.7)
Effects on glucose metabolism	4 (5.6)
Overdose events	1 (1.4)
Nonprescribed/nonmedical use exposure	3 (4.2)
No AEs of special interest	14 (19.7)

Reviewer's Comments: The majority of cases in this case series contained an AESI (57/71, 80.3%), which was similar to the sponsor's finding in their 120-Day Safety Update. In addition, the proportion of each AESI is also similar to the sponsor's FAERS search results. No new safety signals were identified from these reports of AESIs. Analysis was limited due to most cases with missing information (i.e., temporality) or cases with multiple concomitant medications and comorbidities.

3.3 SPONSOR'S DATA

3.3.1 120-Day Safety Update for Nasonex 24HR Allergy NDA 215712

- Within their FAERS analysis, the sponsor notes several PTs that were reported in unusual numbers and explains this to be due to a duplication of cases within FAERS data. Our assessment of each of these PTs is below:
 - Coma – Duplicate cases. After deduplication, one unique case (#18256240) contains the PT *Coma*. The case describes a 64-year-old female on over 10 concomitant medications including antithymocyte immunoglobulin, cellcept, nortriptyline, Lyrica, warfarin, and sulfatrim. No information on temporality or concomitant disease states is provided. The case is uninformative.
 - Gastroesophageal reflux disease – This PT was among the most frequently reported; however, this is due to concomitant medications and disease states that contribute to the adverse event. See *Reviewer's Comments* under **Table 2** for additional information.
 - Pneumonia aspiration – Duplicate cases. After deduplication, one unique case (#18253240) contains the PT *Pneumonia aspiration*. See details above as it is the same case with the PT *Coma*.
 - Somnolence – Duplicate cases. After deduplication, two unique case (#18253240, #18379291) contain the PT *Somnolence*. See details above as the first case is the same case with the PT *Coma*. The second case with the PT *Somnolence* describes off-label use of Nasonex in 32-month-old for adenoids.
 - Asthma, Cough, Dyspnea, Wheezing – These PTs were among the most frequently reported; however, this is due to common comorbidities with allergic rhinitis such as asthma and COPD. See *Reviewer's Comments* under **Table 2** for additional information.
 - Loss of personal independence of daily activities – This was one of the most frequently reported PTs (n=15), however it is uninformative for signal detection.

All of the cases reporting this PT were confounded by multiple concomitant medications or disease states.

- The sponsor notes larger than expected numbers of serious reports in FAERS (91%) with Nasonex. Our FAERS analysis identified that 78.8% (56/71) of our deduplicated cases were reported as serious. We agree with the sponsor's assessment that many of the serious adverse events were likely due to other events such as underlying medical conditions, concomitant medications, and surgical procedures. See *Reviewer's Comments* under **Table 1** for additional comment on serious FAERS cases.
- In addition to analyzing safety reports from FAERS, the sponsor found no new safety signals after reviewing postmarketing data including the MSD PV, Vigibase, and AAPCC/NPDS data.

3.3.2 Period Adverse Experience Report (PAER) submission for Nasonex NDA 20762 (Rx product) for the period October 2, 2019 through October 1, 2020

- The sponsor submitted 41 initial 15-day cases, two of which were domestic. No assessment was provided by the sponsor.
- The two domestic cases were submitted before the time period of this review (September 8, 2020 - March 31, 2021), therefore they are not represented in our FAERS analysis.
- One (case number 1912USA007963) of the two domestic cases includes PTs from the AESI Local Nasal Events (PTs *Nasal oedema, Paranasal sinus discomfort, Rhinorrhoea, Sinusitis aspergillus*); however, the case also reports PTs *Post procedural complication* and *Osteonecrosis of jaw* to indicate a possible post-surgery complication. Patient age, gender, comorbidities or case narrative is not provided.

4 CONCLUSION

Our review confirms that the sponsor's FAERS data reported in the 120-Day Safety Update is consistent with the adverse events reported in our FAERS searches. The most commonly reported PTs (*Asthma, Dyspnoea, Wheezing*) occurred in patients with allergic rhinitis, for which Nasonex is indicated. Even though we identified adverse events of special interest, analysis of the cases was limited due to missing information (i.e., temporality) or multiple concomitant medications and comorbidities. Furthermore, the low number of domestic serious adverse events, including adverse events of special interest reported with Nasonex indicate no increase in adverse events in FAERS. This data is consistent with the sponsor's data analysis.

5 REFERENCES

1. 120-Day Safety Update for Nasonex 24HR Allergy NDA 215712 (Mometasone Furoate Nasal Spray). Perrigo Company. Submitted on September 13, 2021.
2. Nasonex (mometasone furoate monohydrate spray, metered) [package insert] Merck Sharp & Dohme Corp. City. Whitehouse Station, NJ. September 2020.
3. Annotated Draft Labeling Text and Side-by-Side Comparison. Nasonex 24HR Allergy NDA 215712 (Mometasone Furoate Nasal Spray). Perrigo Company. Submitted on November 15, 2021.

6 APPENDICES

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

FDA Adverse Event Reporting System (FAERS)

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

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

6.2 APPENDIX B. PREFERRED TERMS FOR ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

See Integrated Summary of Safety (ISS) Statistical Analysis Plan, Addendum 1: 120-Day Safety Update, Appendices A1 through A8, Section 4.1 through Section 4.8 for preferred terms used for each designated adverse event of special interest.



ISS Statistical
Analysis Plan Adden

Exceptions are noted below:

- For the AESI ‘All Mycotic/Fungal Infections’, the PT Pulmonary mycosis listed by the sponsor is now an LLT under the PT Pneumonia Fungal, which is included in this search.
- For the AESI, ‘Ocular Events Including Visual Disturbances’,
 - The sponsor listed Contact lens user, for which there is no current PT or LLT, therefore this was not included in our search
 - The PT Eye burns listed by the sponsor is now an LLT, which maps up to the PT Thermal burns of the eye, which was not included in this search.
- For the AESI, ‘Effects on Growth and/or Bone Metabolism, the PTs Fractured ischium and Pubis fracture listed by the sponsor, are not LLTs under the PT Pelvic fracture, which is included in this search.

6.3 APPENDIX C. FAERS LINE LISTING OF NASONEX CASE SERIES (N=71)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	9/8/2020	18242476	1	CA-PFIZER INC-2020340565	Expedited (15-Day)	67.0	FEMALE	CAN	OT
2	9/10/2020	18253905	4	CA-JNJFOC-20200912057	Expedited (15-Day)	54.0	FEMALE	CAN	HO,OT
3	9/11/2020	18256240	1	CA-BAYER-2020-189546	Expedited (15-Day)	64.0	FEMALE	CAN	HO
4	9/15/2020	18266957	1	CA-ACCORD-200577	Expedited (15-Day)	78.0	FEMALE	CAN	HO,OT
5	9/15/2020	18267784	7	CA-PFIZER INC-2020353195	Expedited (15-Day)		FEMALE	CAN	HO,OT
6	9/16/2020	18272695	1	CA-COVIS PHARMA B.V.-2020COV00392	Expedited (15-Day)	54.0	MALE	CAN	OT
7	9/18/2020	18280889	3	CA-DRREDDYS-USA/CAN/20/0126946	Expedited (15-Day)	61.0	FEMALE	CAN	OT
8	9/21/2020	18290307	2	CA-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2020-BI-043983	Expedited (15-Day)	43.0	FEMALE	CAN	OT
9	9/23/2020	18303804	1	CA-BAUSCH-BL-2020-026600	Expedited (15-Day)		FEMALE	CAN	OT
10	9/24/2020	18304167	3	US-009507513-2009USA009180	Non-Expedited		FEMALE	USA	
11	9/24/2020	18304597	2	CA-BAUSCH-BL-2020-026755	Expedited (15-Day)		FEMALE	CAN	OT
12	9/24/2020	18308951	6	CA-APOTEX-2020AP018080	Expedited (15-Day)	51.0	FEMALE	CAN	OT
13	10/5/2020	18343135	2	US-009507513-2010USA000028	Non-Expedited		FEMALE	USA	
14	10/6/2020	18350325	1	CA-CIRCASSIA PHARMACEUTICALS INC-2020CA005813	Expedited (15-Day)	75.0	NULL	CAN	OT
15	10/7/2020	18358007	2	CA-ASTRAZENECA-2020SF26484	Expedited (15-Day)	53.0	FEMALE	CAN	OT

16	10/12/2020	18371164	2	CA-BAUSCH-BL-2019-025011	Expedited (15-Day)	56.0	MALE	CAN	HO,OT
17	10/13/2020	18379291	2	RU-009507513-2010RUS003504	Expedited (15-Day)	2.7	NULL	RUS	HO
18	10/13/2020	18379410	1	CA-ASTRAZENECA-2020SF30377	Expedited (15-Day)	61.0	MALE	CAN	OT
19	10/15/2020	18389465	3	CA-ASTRAZENECA-2020SF31233	Expedited (15-Day)	62.0	FEMALE	CAN	HO,OT
20	10/20/2020	18407378	2	AU-BAYER-2020-222872	Expedited (15-Day)	7.0	MALE	AUS	OT
21	10/21/2020	18411600	1	CA-JNJFOC-20201028838	Expedited (15-Day)	67.0	MALE	CAN	OT
22	11/2/2020	18453812	2	CA-GLAXOSMITHKLINE-CA2020AMR213717	Expedited (15-Day)		FEMALE	CAN	HO,OT
23	11/3/2020	18460184	1	US-009507513-2010USA012118	Expedited (15-Day)	54.0	FEMALE	USA	OT
24	11/4/2020	18462849	2	CA-GLAXOSMITHKLINE-CA2020AMR203823	Expedited (15-Day)		FEMALE	CAN	OT
25	11/17/2020	18509165	1	SE-009507513-2011SWE009247	Expedited (15-Day)	58.0	FEMALE	SWE	OT
26	11/23/2020	18538750	1	ES-009507513-2011ESP012003	Expedited (15-Day)	38.0	MALE	ESP	OT
27	11/24/2020	18540818	2	CA-GLAXOSMITHKLINE-CA2020AMR228465	Expedited (15-Day)		FEMALE	CAN	OT
28	11/27/2020	18554063	1	RU-009507513-2011RUS015506	Expedited (15-Day)		FEMALE	RUS	HO
29	11/27/2020	18554473	1	US-009507513-2011USA016111	Expedited (15-Day)	85.0	FEMALE	USA	OT
30	12/2/2020	18570161	1	CA-GLAXOSMITHKLINE-CA2018GSK115028	Expedited (15-Day)	45.0	MALE	CAN	OT
31	12/3/2020	18573882	1	CA-B.I. PHARMACEUTICALS, INC./RIDGEFIELD-2017-BI-052840	Expedited (15-Day)	64.0	NULL	CAN	OT

32	12/11/2020	18604578	1	DK-009507513-2012DNK004292	Expedited (15-Day)	46.0	MALE	DNK	HO
33	12/14/2020	18611590	1	CA-009507513-2012CAN005619	Expedited (15-Day)	48.0	FEMALE	CAN	OT
34	12/18/2020	18633424	1	SE-GLAXOSMITHKLI NE-SE2020246120	Expedited (15-Day)	47.0	MALE	SWE	DS
35	12/21/2020	18643316	1	US-009507513-2012USA005602	Expedited (15-Day)	18.0	MALE	USA	
36	12/21/2020	18643619	1	US-009507513-2012USA006402	Non-Expedited	51.4	NULL	USA	
37	12/22/2020	18649622	1	US-009507513-2012USA009148	Expedited (15-Day)	72.0	MALE	USA	OT
38	12/22/2020	18649881	1	AU-009507513-2012AUS009815	Expedited (15-Day)		NULL	AUS	OT
39	12/28/2020	18670632	1	FR-009507513-2012FRA002487	Expedited (15-Day)	91.3	MALE	FRA	DS,OT
40	12/29/2020	18672772	1	KR-009507513-2012KOR010769	Expedited (15-Day)		MALE	KOR	
41	12/29/2020	18677423	1	US-009507513-2012USA010007	Non-Expedited	71.0	FEMALE	USA	
42	12/31/2020	18686886	1	CA-ACCORD-212771	Expedited (15-Day)	69.0	MALE	CAN	HO
43	12/31/2020	18689135	1	US-009507513-2012USA013133	Non-Expedited		FEMALE	USA	
44	1/5/2021	18701513	2	US-009507513-2012USA013230	Non-Expedited	71.6	FEMALE	USA	
45	1/9/2021	18721356	1	CA-TEVA-2020-CA-1865841	Expedited (15-Day)	52.0	MALE	CAN	HO
46	1/18/2021	18751794	1	CA-GLAXOSMITHKLI NE-CA2019AMR133492	Expedited (15-Day)	58.0	FEMALE	CAN	OT
47	1/19/2021	18754419	1	US-009507513-2101USA006926	Non-Expedited		MALE	USA	
48	1/23/2021	18775990	2	CA-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2021-BI-077685	Expedited (15-Day)		FEMALE	CAN	OT
49	1/25/2021	18783583	2	CA-BAUSCH-BL-2021-001369	Expedited (15-Day)		FEMALE	CAN	HO,OT
50	1/27/2021	18795592	3	CA-GLAXOSMITHKLI	Expedited (15-Day)	28.0	MALE	CAN	OT

				NE- CA2021AMR013898					
51	1/29/2021	18811153	1		Direct		FEMALE	USA	OT
52	1/30/2021	18814894	1	US-009507513- 2101USA010946	Non- Expedited	29.0	MALE	USA	
53	2/1/2021	18833223	5	GB-009507513- 2102GBR000461	Expedited (15-Day)	46.0	FEMALE	GBR	OT
54	2/6/2021	18855181	1	US-009507513- 2101USA011651	Non- Expedited	87.0	FEMALE	USA	
55	2/10/2021	18869527	4	FR-B.I. PHARMACEUTICA LS,INC./RIDGEFIEL D-2021-BI-080834	Expedited (15-Day)	73.0	MALE	FRA	OT
56	2/12/2021	18888764	1	GB-009507513- 2102GBR003202	Expedited (15-Day)	61.0	FEMALE	GBR	OT
57	2/16/2021	18900986	1	AU-009507513- 2102AUS006046	Expedited (15-Day)		FEMALE	AUS	OT
58	2/17/2021	18902028	1	CA-AUROBINDO- AUR-APL-2021- 005916	Expedited (15-Day)	62.0	FEMALE	CAN	OT
59	2/19/2021	18916265	1	CA-AUROBINDO- AUR-APL-2021- 006238	Expedited (15-Day)	57.0	MALE	CAN	OT
60	2/19/2021	18916675	1	CA- GLAXOSMITHKLI NE- CA2021AMR045029	Expedited (15-Day)	44.0	MALE	CAN	OT
61	2/25/2021	18940226	1		Direct		FEMALE	USA	
62	3/9/2021	18986274	1	AU-ORGANON- O2103AUS000888	Expedited (15-Day)		NULL	AUS	OT
63	3/11/2021	18997947	2	US-ORGANON- O2103USA000349	Non- Expedited	85.0	FEMALE	USA	
64	3/16/2021	19011471	1	US-ORGANON- O2103USA001184	Non- Expedited		FEMALE	USA	
65	3/18/2021	19024433	1	CA-APOTEX- 2021AP006346	Expedited (15-Day)	64.0	MALE	CAN	OT
66	3/19/2021	19034016	1	US-PFIZER INC- 2021277846	Expedited (15-Day)	54.0	MALE	USA	HO
67	3/22/2021	19036516	1	CA-ORGANON- 1602CAN011168	Expedited (15-Day)	64.0	FEMALE	CAN	OT
68	3/23/2021	19047098	1	CA-ORGANON- 1609CAN014007	Expedited (15-Day)	72.0	FEMALE	CAN	DS
69	3/23/2021	19049212	1	NO-ORGANON- O2103NOR002317	Expedited (15-Day)		FEMALE	NOR	OT

70	3/24/2021	19054277	1	US- GLAXOSMITHKLI NE- USCH2021GSK0149 79	Expedited (15-Day)	60.1	MALE	USA	HO
71	3/26/2021	19064739	1	US-ORGANON- O2103USA000253	Non- Expedited	75.0	FEMALE	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome. Abbreviations: HO=hospitalization, DS= disability, OT=other medically significant

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