

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215712Orig1s000

INTEGRATED REVIEW

Division of Nonprescription Drugs**Integrated Review****Table 1. Administrative Application Information**

Category	Application Information
Application type	NDA
Application number(s)	215712
Priority or standard	Standard
Submit date(s)	5/17/2021
Received date(s)	5/17/2021
PDUFA goal date	3/17/2022
Division/office	Division of Non-Prescription Drugs I (DNPDI)
Review completion date	3/11/2022
Established/proper name	Mometasone furoate monohydrate
(Proposed) proprietary name	Nasonex 24HR Allergy
Pharmacologic class	Corticosteroid
Applicant	Perrigo Pharma International Designated Activity Company (PPI-DAC)
Dosage form(s)/formulation(s)	nasal spray
Dosing regimen	Adults and children (Ages ≥ 12 years): 2 sprays/nostril (50 mcg/spray) once daily while sniffing gently Children (Ages 2 to 11 years): 1 spray in each nostril once daily while sniffing gently
Applicant proposed indication(s)/ population(s)	Temporarily relieves these symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, and itchy nose
Proposed SNOMED indication	161614004 History of multiple allergies (situation)
Regulatory action	Approval
Approved dosage (if applicable)	Adults and children (Ages ≥ 12 years): 2 sprays/nostril (50 mcg/spray) once daily while sniffing gently Children (Ages 2 to 11 years): 1 spray in each nostril once daily while sniffing gently
Approved indication(s)/ population(s) (if applicable)	Treatment of Nasal Symptoms of Allergic Rhinitis in patients ≥ 2 years of age; Treatment of Nasal Congestion Associated with Seasonal Allergic Rhinitis in patients ≥ 2 years of age
Approved SNOMED term for indication (if applicable)	161614004 History of multiple allergies (situation)

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NDA 215712

Nasonex 24HR Allergy (mometasone furoate monohydrate) nasal spray, 50 mcg/spray

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Glossary

AAPCC	American Association of Poison Control Centers
AE	adverse event
AESI	adverse event of special interest
AET	antimicrobial effectiveness test
BID	twice daily
CFR	Code of Federal Regulations
CIL	Consumer Information Leaflet
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DFL	Drug Facts Label
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
HPA	hypothalamic-pituitary-adrenal
IDS	Interdisciplinary Scientist
INCS	intranasal corticosteroids
MFNS	mometasone furoate nasal spray
MSD	Merck Sharp & Dohme
NDA	new drug application
NPDS	National Poison Data System pharmacovigilance
OTC	over-the-counter
PAR	perennial allergic rhinitis
PDP	principal display panel
PK	pharmacokinetic
PT	preferred term
PV	pharmacovigilance
QD	once daily
Rx	prescription
SAE	serious adverse event
SAR	seasonal allergic rhinitis
SOI	statement of identity
TNSS	total nasal symptoms score
WHO	World Health Organization

I. Executive Summary

1. Summary of Regulatory Action

New drug application (NDA) 215712 was submitted as a partial prescription-to-over-the-counter (Rx-to-OTC) switch of Nasonex Nasal Spray (mometasone furoate monohydrate; throughout review may be used intermittently with mometasone furoate), 50 mcg by Perrigo Pharma International Designated Activity Company (PPI-DAC) (the Applicant) on May 16, 2021, and in accordance with section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. Nasonex NDA 20762 was originally sponsored and held by Schering-Plough Corporation, then transferred in a merger to Merck Sharp & Dohme (MSD) in 2009. The Applicant acquired right of reference to NDA 20762 from MSD, for the partial switch application. Subsequently, the Rx NDA was transferred to an MSD affiliate, Organon LLC.

Nasonex (NDA 20762) was originally approved on October 1, 1997, with a proprietary name of Nasonex Nasal Spray indicated for the prophylaxis and treatment of nasal symptoms associated with seasonal allergic rhinitis (SAR) and treatment of nasal symptoms associated with perennial allergic rhinitis [PAR]) in adults and children 12 years of age and older. Three subsequent supplemental NDAs led to labeling changes and the following Rx indications:

- Treatment of nasal symptoms of SAR and PAR in patients ≥ 2 years of age
- Treatment of nasal congestion associated with SAR in patients ≥ 2 years of age
- Treatment of nasal polyps in patients ≥ 18 years of age

The Applicant seeks an Rx-to-OTC switch for two Nasonex Rx indications (treatment of nasal symptoms of SAR and PAR and treatment of nasal congestion associated with SAR) conveyed on proposed labeling of the OTC product as provided below and consistent with well-established class labeling. The OTC product is intended for the same population as the Rx product of adults and children down to 2 years of age and has a proposed proprietary name of Nasonex 24HR Allergy.

The proposed OTC indication is:

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

- Nasal congestion
- Runny nose
- Sneezing
- Itchy nose

Review of this partial Rx-to-OTC switch application was based on trials previously reviewed under NDA 20762 along with safety data of previously conducted trials, but not reviewed for the Rx NDA. There were no new trials conducted for this Rx-to-OTC switch.

NDA 215712

Nasonex 24HR Allergy (mometasone furoate monohydrate) nasal spray, 50 mcg/spray

Pharmacovigilance data were submitted along with postmarketing safety data from external databases and the medical literature. No formula or container closure system changes were proposed. Proposed facilities for the drug product manufacturing and testing are in compliant status.

Based on the favorable benefit-risk assessment, the recommended regulatory action is approval. This partial Rx-to-OTC switch product will represent the fifth-in-class, intranasal corticosteroid (INCS) spray for SAR and PAR on the OTC market in the United States.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Allergic rhinitis, often called hay fever, is a common condition that causes symptoms such as sneezing, stuffy nose, runny nose, itchy nose, and itchy, watery eyes. - Allergic rhinitis can be seasonal or perennial. - Symptoms of seasonal allergic rhinitis (SAR) occur in spring, summer and/or early fall and usually caused by sensitivity to pollens from trees, grasses or weeds, or to airborne mold spores. - Symptoms of perennial allergic rhinitis (PAR) are year-round and generally caused by sensitivity to house dust mites, animal dander, cockroaches and/or mold spores. - Allergic rhinitis accounts for at least 2.5% of all clinician visits, 2 million lost school days, 6 million lost workdays, and 28 million restricted workdays per year (Vandenplas et al. 2018). - Allergic rhinitis is common, affecting 10 to 40% of children and adults in the United States and other industrialized countries (Settipane 2001; deShazo and Kemp 2022). - The Centers for Disease Control and Prevention (CDC) estimates that 19.2 million adults and 5.2 million children under 18 years of age were diagnosed with hay fever in the United States in 2018 (CDC 2018).	Allergic rhinitis negatively impacts sleep, quality of life, cognitive function, and school/workplace productivity (Meltzer et al. 2009). Economic loss is associated with impairment from symptoms of allergic rhinitis.
Current Treatment Options	- Allergen avoidance (not fully practical) - Over-the-counter (OTC) pharmacological treatments for allergic rhinitis include oral and nasal antihistamines, antihistamine/decongestant combination products, oral and nasal decongestants, cromolyn nasal spray, and intranasal corticosteroids.	Treatment is primarily pharmacologic (prescription [Rx] or OTC). Consumers often self-treat with OTC allergy products. The prevalence of allergic rhinitis highlights the importance of availability of safe and effective OTC allergy products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- OTC nasal treatments for allergic rhinitis/hay fever include: - Saline (spray: Simply Saline, Xlear, A&H, Ayr; irrigation: Nettipot, Neimed, Ayr) - Corticosteroid (Rhinocort Allergy, Flonase Allergy, Flonase Sensimist Allergy, Nasacort) - Mast cell stabilizer (Nasalcrom) - Decongestant (Afrin, Sinex, Dristan) - Antihistamine (Astepro) - Rx nasal treatments for allergic rhinitis/hay fever include: - Antihistamine (Patanase) - Corticosteroid (Nasonex, Q-Nasl, Beconase AQ, Omnaris, Zetonna, Flunisolide) - Combination antihistamine and steroid (Dymista, Ryaltris) - Anticholinergic (Atrovent)	
Benefit	- Nasonex 24HR Allergy is another choice for OTC treatment of allergic rhinitis - Product is dosed once a day - The number of adverse events (AEs) and serious adverse events (SAEs) are low	Nasonex provides relief of allergic rhinitis symptoms with once a day dosing convenience similar to other OTC intranasal corticosteroid (INCS) products. Product can be used chronically.
Risk and Risk Management	- Common AEs include: headache, viral infection, pharyngitis, epistaxis, coughing, upper respiratory tract infection, dysmenorrhea, musculoskeletal pain, and sinusitis. - SAEs include: cataracts, glaucoma, nasal septum perforation, hypersensitivity, candida infection and epistaxis - Adequacy of labeling/consumer understanding	The product has an established safety profile in the Rx environment which is generally consistent with the other four intranasal corticosteroids approved as OTC products for the same indication. AEs occur but are predominately nonserious with SAEs reported infrequently. The most common side effects are mild, reversible, local nasal events. A review of the postmarket safety databases did not raise new signals. Proposed OTC labeling includes essential warnings translated from the Rx label of Nasonex and consistent with class labeling for marketed OTC INCS products. Product considered safe for chronic intermittent use.

2.2. Conclusions Regarding Benefit-Risk

The partial switch from Rx to OTC of Nasonex (mometasone furoate monohydrate) nasal spray, 50 mcg for the temporary relief of symptoms of hay fever or other upper respiratory allergies (nasal congestion, runny nose, sneezing, and itchy nose) in adults and children 2 years of age and older is recommended. Nasonex will join many other INCS that can be used in a safe and effective manner by consumers without consulting a physician. Adverse events (AEs) associated with the use of the product seen during initial product development and in review of 10 years of postmarketing data are well known, addressed in Rx labeling, and conveyed in OTC labeling.

II. Interdisciplinary Assessment

3. Introduction

Nasonex Nasal Spray (mometasone furoate monohydrate), 50 mcg, is a second generation glucocorticoid that inhibits allergic inflammation in the nose through downregulation of inflammatory responses by binding to intracellular glucocorticoid receptors in the cytoplasm of inflammatory cells (deShazo and Kemp 2021). It was developed as an intranasal treatment for allergic rhinitis. The Rx NDA (20762) was approved in 1997 for prophylaxis and treatment of nasal symptoms associated with SAR and the treatment of nasal symptoms of PAR in adults and children 12 years of age and older. Five subsequent supplemental NDAs noted below led to labeling changes and approved Rx indications.

Supplemental NDAs:

- 11-hour onset of action added to the label (S-001, approved 1998)
- Treatment indication extended down to 3 years of age (S-004, approved 1999)
- Treatment indication extended down to 2 years of age based on a safety trial. No efficacy data were provided. (S-011, approved 2002)
- New indication added for nasal polyps (S-023, approved 2004)
- New indication added for nasal congestion associated with SAR for patients 2 years of age and older (S-038, approved 2010)

Approved Rx indications for Nasonex:

- Treatment of nasal symptoms of SAR and PAR in patients ≥ 2 years of age
- Treatment of nasal congestion associated with SAR in patients ≥ 2 years of age
- Prophylaxis of SAR in patients ≥ 12 years of age
- Treatment of nasal polyps in patients ≥ 18 years of age

Therapeutic Context

Analysis of Condition

Allergic rhinitis, also known as hay fever, is a common condition that causes symptoms such as sneezing, stuffy nose, runny nose, itchy nose, and itchy, watery eyes. Allergic rhinitis can be seasonal or perennial. Symptoms of SAR occur in spring, summer and/or early fall and are usually caused by sensitivity to pollens from trees, grasses, or weeds, or to airborne mold spores. Symptoms of PAR are year-round and generally caused by sensitivity to house dust mites, animal dander, cockroaches, and/or mold spores (CDC 2018; ACAAI 2022).

Allergic rhinitis affects approximately 10 to 40% of children and adults in the United States and other industrialized countries (Settipane 2001). According to the Centers for Disease Control and Prevention (CDC), 19.2 million adults and 5.2 million children under 18 years of age in the United States were diagnosed with hay fever in 2018. This condition is associated with

significant impairment and noted to account for at least 2.5% of all clinician visits, 2 million lost school days, 6 million lost work days, and 28 million restricted work days per year (Vandenplas et al. 2018). Nearly half of the direct medical costs of rhinitis is related to prescription medications (Soni ; Blaiss 2011).

Analysis of Current Treatment Options

Currently there are four other INCS products available OTC for treatment of allergic rhinitis. All four products underwent an Rx-to-OTC switch for this indication ([Table 3](#)).

Table 3. Approved OTC Intranasal Corticosteroid (INCS) Products

OTC Product Name	Established Name	Rx		OTC	
		NDA	Approval Date	NDA	Approval Date
Nasacort Allergy 24HR	Triamcinolone acetonide (55 mcg per spray)	20468	5/20/1996	Supplement 35 Full Rx-to-OTC switch	10/11/2013
Flonase Allergy Relief	Fluticasone propionate (50 mcg per spray)	20121	10/19/1994	205434 Partial Rx-to-OTC switch	7/23/2014
Rhinocort Allergy Spray	Budesonide (32 mcg per spray)	20746	10/1/1999	Supplement 32 Full Rx-to-OTC switch	3/23/2015
Flonase Sensimist Allergy Relief	Fluticasone furoate (27.5 mcg per spray)	22051	4/27/2007	Supplement 13 Full Rx-to-OTC switch	8/2/2016

Source: Reviewer Summary

Abbreviations: NDA, new drug application; OTC, over-the-counter; Rx, prescription.

Nasonex would be the fifth OTC INCS approved for treatment of allergic rhinitis. Other OTC products to treat symptoms associated with allergic rhinitis have been available for many years and include both oral and intranasal products such as first and second generation oral antihistamines, oral antihistamine/decongestant combination products, intranasal decongestants, and intranasal cromolyn. Antihistamine products marketed in combination with decongestants, include a “relief of nasal congestion” indication for these OTC oral antihistamines. In 2021, the first nasal antihistamine, Astepro (azelastine), was approved for OTC use in adults and children 6 years and older for allergic rhinitis.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Efficacy Well Established as a Prescription Product

Nasonex as a Rx product has extensive clinical trial data support establishing its efficacy as an INCS spray for treatment of allergic rhinitis. Switching Nasonex from Rx to OTC status will make this efficacious treatment with once a day convenience more accessible to consumers impacted by the nasal symptoms of allergic rhinitis.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Adverse Events Associated With Use of the Prescription Product

Nasonex has extensive clinical trial data and a 24-year history of Rx marketing with known adverse events (AEs) common to use of INCS spray. Risk will be evaluated by evidence of new safety signals of concern and adequacy of the label to convey safe and effective use of the product in accordance with the Rx label and OTC class labeling.

3.2. Approach to the Review

As this is the fifth Rx-to-OTC INCS proposed switch for treatment of allergic rhinitis the review will focus on assessing whether the benefit-risk is similar to previously switched INCSs for treatment of allergic rhinitis. Clinical trial data to support the dose selection and efficacy and safety of Nasonex for the management of nasal symptoms of SAR and PAR in adults and pediatric patients 2 years of age and older have already been reviewed in detail by the Agency and are summarized in the approved product label. Details of the individual trial designs are summarized in [Table 4](#) and efficacy data are summarized in [Section 6](#). A review of the safety data are presented in [Section 7](#). In addition to the Rx clinical trial database, the safety information for the application is supplemented by postmarketing data and medical literature.

Of note, the original records and review of the Rx NDA and subsequent supplements were difficult to obtain as the original NDA was approved 25 years ago. The Applicant, after acquiring the right of reference from the current Rx NDA holder, Merck Sharp & Dohme (MSD), relayed they were unable to locate many of the Rx Nasonex trial documents and databases from the original NDA Applicant which limited their ability to synthesize integrated reviews.

Table 4. Previously Reviewed Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations for Nasonex for Allergic Rhinitis

Protocol Number	Trial Title	Sample Size and Treatment Arms	Trial Duration
Original Rx NDA 20762 (19 Clinical Trials With Assessment of Efficacy and Safety)			
C92-011	Dose Ranging Study of the Safety and Efficacy of Mometasone Furoate in SAR	Efficacy n=474 (MFNS 50: n=94; MFNS 100: n=94; MFNS 200: n=96; MFNS 800: n=95; Placebo: n=95)	4 weeks
C93-184*	Onset of Action of Mometasone Furoate Nasal Spray 50 mcg/Spray vs. Placebo in SAR	Efficacy n=197 (MFNS: n=99; Placebo: n=98)	2 weeks

Protocol Number	Trial Title	Sample Size and Treatment Arms	Trial Duration
C93-193	Effect of Mometasone Furoate Nasal Spray on Early and Late Phase Inflammation During In-Vivo Ragweed Provocation in Patients With SAR	Efficacy evaluable population n=20 subjects total, with 11 subjects in the MFNS/placebo sequence group and 9 patients in the placebo/MFNS sequence group	2 weeks
C93-215	Prophylactic Treatment of SAR with Mometasone Furoate Aqueous Nasal Spray	Efficacy n=330 (MFNS: n=114; BDP: n=112; Placebo: n=104)	8 weeks
I93-133	Efficacy and Safety of Mometasone Furoate Aqueous Nasal Spray (MFNS) in the Prophylactic Treatment of SAR	Efficacy: n=500 (MFNS: n=164; Rhinocort: n=168; Placebo: n=168)	4 weeks
C94-145*	Safety and Efficacy of Mometasone Furoate Nasal Spray with the Addition of Loratadine Versus Placebo in the Treatment of SAR	Efficacy n=672 (MFNS+loratadine: n=166; MFNS: n=166; loratadine: n=175; Placebo: n=165)	2 weeks
I92-200	Efficacy and Safety of Mometasone Furoate Aqueous Nasal Spray in SAR	Efficacy n=477 (MFNS 100: n=122; MFNS 200: n=122; BDP: n=123; Placebo: n=110)	4 weeks
I94-001*	Efficacy and Safety of Mometasone Furoate Aqueous Nasal Spray vs. Placebo and Flonase® (Fluticasone Propionate) in SAR Patients	Efficacy n=311 (MFNS: n=104; FP: n=104; Placebo: n=103)	2 weeks
C92-280	Efficacy and Safety of Mometasone Furoate Nasal Spray 50 mcg/Spray vs. Vancenase® AQ (Beclomethasone Dipropionate) 42 mcg/Spray and Placebo in PAR	Efficacy n=477 (MFNS: n=160; BDP: n=157; Placebo: n=160)	12 weeks
C93-014	Long-Term Safety of Mometasone Furoate Nasal Spray 50 mcg/Spray in PAR	Efficacy n=293 (MFNS 200: n=100; MFNS 100-400: n=95; BDP: n=98)	52 weeks
C94-052	A Long-Term Safety Study of Mometasone Furoate Nasal Spray vs. Nasacort® in PAR	Efficacy n=351 (MFNS: n=175; Nasacort: n=176)	52 weeks
C94-092	Safety and Efficacy of Mometasone Furoate Nasal Spray vs. Placebo in the treatment of Elderly Patients with PAR	Efficacy n=314 (MFNS: n=162; Placebo: n=152)	12 weeks
I92-293	Efficacy and Safety of Mometasone Furoate Aqueous Nasal Spray vs. Beconase® AQ and Placebo in the Treatment of PAR	Efficacy n=387 (MFNS: n=129; BDP: n=134; Placebo: n=124)	12 weeks
I93-018	Long-Term Safety of Mometasone Furoate Aqueous Nasal Spray in PAR Patients	Efficacy n=228 (MFNS 200: n=77; MFNS 100-400: n=80; BDP: n=71)	52 weeks

Protocol Number	Trial Title	Sample Size and Treatment Arms	Trial Duration
I93-180	Assessment by Nasal Biopsy of Long-Term Safety of Mometasone Furoate Aqueous Nasal Spray vs. Fluticasone Propionate (Flixonase®) in PAR	Efficacy n=141 (MFNS: n=69; FP: n=72)	52 weeks
I93-221	Six Month Safety Study of Mometasone Furoate Aqueous Nasal Spray in PAR	Efficacy: n=331 MFNS: n=331	26 weeks
I94-079	Efficacy and Safety of Mometasone Furoate Aqueous Nasal Spray vs. Placebo and Fluticasone Propionate Aqueous Nasal Spray in the Treatment of Patients with PAR	Efficacy n=459 (MFNS: n=154; FP: n=157; Placebo: n=148)	12 weeks
C93-013*	Safety and Efficacy of Mometasone Furoate Nasal Spray 50 mcg/Spray vs. Vancenase® AQ 42 mcg/Spray and Placebo in SAR	Efficacy n=340 (MFNS: n=111; BDP: n=113; Placebo: n=116)	4 weeks
I94-139	A Pilot Study to Evaluate the Effect of Mometasone Furoate (MF) Nasal Spray on the Early and Late Phase Reactions Following Allergen-Specific Nasal Challenge in Patients with Pollen Allergy	Efficacy evaluable population n=42 (MFNS: n=24; Placebo: n=18)	2 weeks
12-Hour Onset sNDA 20762/S-001 (3 Clinical Trials With Assessment of Efficacy)			
P97-019	Onset of Action of Mometasone Furoate Nasal Spray vs. Placebo in SAR During an Acute Outdoor Exposure	Efficacy n=235 (MFNS: n=119; Placebo: n=116)	1 day
P97-020	Onset of Action of Mometasone Furoate Nasal Spray vs. Placebo in SAR During an Acute Outdoor Exposure	Efficacy n=196 (MFNS: n=99; Placebo: n=97)	1 day
I97-341	Onset of Action of Mometasone Furoate Aqueous Nasal Spray vs. Placebo in SAR Utilizing the Environmental Exposure Unit	Efficacy evaluable subset n=276 (MFNS: n=138; Placebo: n=138)	1 day
Pediatrics sNDA 20762/S-004 (4 Clinical Trials With Assessment of Efficacy)			
C95-161*	Dose-Ranging Study of Mometasone Furoate Nasal Spray in the Treatment of Children (Ages 6-11) with SAR	Efficacy n=602 (MFNS 25: n=120; MFNS 100: n=121; MFNS 200: n=116; BDP: n=125; Placebo: n=120)	4 weeks
I96-090	Four-week, Double-Blind Efficacy and Safety Study of Mometasone Furoate Aqueous Nasal Spray vs. Placebo, Followed by Six-Month, Open-Label Safety in Children with PAR.	Efficacy, n=360 (MFNS: n=179; Placebo: n=181)	4 weeks
C96-091	One-Year, Evaluator-Blind Safety Study of Mometasone Furoate Nasal Spray Versus Beclomethasone Dipropionate in Children (Ages 6-11) with PAR	Efficacy, n=251 (MFNS: n=166; BDP: n=85)	52 weeks
C96-094	One-Year, Double-Blind Study of the Effects of Mometasone Furoate Nasal Spray Versus Placebo on Growth of Children with PAR	Efficacy, n=98 (MFNS: n=49; Placebo: n=49)	52 weeks

Protocol Number	Trial Title	Sample Size and Treatment Arms	Trial Duration
Nasal Congestion sNDA 20762/S-038 (6 New Clinical Trials With Assessment of Efficacy)			
P04500	Efficacy and Safety of Concurrent Administration of Mometasone Furoate Nasal Spray and Oxymetazoline Nasal Spray Administered Once Daily vs. Oxymetazoline Twice Daily, Mometasone Furoate Daily, and Placebo in the Treatment of Subjects with SAR	All randomized n=707 (MFNS+OXY [1 spray]: n=146; MFNS+OXY [3 sprays]: n=139; MFNS: n=139; OXY: n=141; Placebo: n=142)	2 weeks
P05067	Placebo-Controlled Study of Mometasone Furoate Nasal Spray 200 mcg Daily in the Treatment of SAR	Efficacy n=422 (MFNS: n=209; Placebo: n=213)	2 weeks
P05106	Placebo-Controlled Study of Mometasone Furoate Nasal Spray 200 mcg Daily in the Treatment of SAR	Efficacy n=394 (MFNS: n=203; Placebo: n=191)	2 weeks
P05528	Placebo-Controlled Study of Mometasone Furoate Nasal Spray 200 mcg Daily in the Relief of Nasal Congestion Associated with SAR	Efficacy n=314 (MFNS: n=155; Placebo: n=159)	2 weeks
P05529	Placebo-Controlled Study of Mometasone Furoate Nasal Spray 200 mcg Daily in the Relief of Nasal Congestion Associated with SAR	Efficacy n=343 (MFNS: n=172; Placebo: n=171)	2 weeks
P05583	Placebo-Controlled Study of Mometasone Furoate Nasal Spray 200 mcg Daily in the Relief of Nasal Congestion Associated with SAR	Efficacy n=325 (MFNS: n=164; Placebo: n=161)	2 weeks
Allergic Rhinitis Down to 2 Years of Age sNDA 20762/S-011 (1 Safety Trial)			
P01225	Multiple-Dose Safety and Tolerance Study of Mometasone Furoate Nasal Suspension in Pediatric Patients (Aged 2-5 Years) with Allergic Rhinitis	MFNS n=28 Placebo n=28	6 weeks

Source: Applicant provided Integrated Summary of Efficacy and Integrated Summary of Safety; FDA review of sNDA 20762/S-011

* Efficacy data also included in Nasal Congestion sNDA 20762/S-038

Abbreviations: AQ, aqueous; BDP, beclomethasone dipropionate; BID, twice daily; FP, fluticasone propionate; MF, mometasone furoate; MFNS, mometasone furoate nasal spray; NDA, new drug application; OXY, oxymetazoline; PAR, perennial allergic rhinitis; QD, once daily; Rx, prescription; SAR, seasonal allergic rhinitis; sNDA, supplemental NDA; TAA, triamcinolone acetonide.

4. Patient Experience Data

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	See Section 6 .
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The Applicant acquired right of reference to NDA 20762 from MSD for a partial Rx-to-OTC switch of Nasonex and has not conducted any new clinical pharmacology studies. For general and critical pharmacology and pharmacokinetics information of Nasonex, refer to the approved label of NDA 20762 (FDA 2020).

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Corticosteroid
Mechanism of action	The precise mechanism of corticosteroid action on allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.
Active moieties	Mometasone furoate monohydrate
QT prolongation	Information not provided
General Information	
Bioanalysis	No new clinical pharmacology data provided, bioanalysis was not performed
Healthy subjects versus patients	N/A
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	N/A
Range of effective dosage(s) or exposure	N/A
Maximally tolerated dosage or exposure	N/A
Dosage proportionality	N/A
Accumulation	N/A
Time to achieve steady-state	N/A
Bridge between to-be-marketed and clinical trial formulations	N/A

Characteristic	Drug Information
	Absorption
Bioavailability	Refer to the approved drug label of NDA 20762, mometasone furoate monohydrate administered as a nasal spray suspension has very low bioavailability (<1%) in plasma using a sensitive assay with a lower quantitation limit (LOQ) of 0.25 pcg/mL.
T _{max}	N/A
Food effect (fed/fasted) Geometric least square mean and 90% CI	N/A
	Distribution
Volume of distribution	N/A
Plasma protein binding	Refer to the approved drug label of NDA 20762, the in vitro protein binding for mometasone furoate was reported to be 98% to 99% in concentration range of 5 to 500 ng/mL.
Drug as substrate of transporters	N/A
	Elimination
Mass balance results	N/A
Clearance	N/A
Half-life	Refer to the approved drug label of NDA 20762, the effective plasma elimination half-life of mometasone furoate is 5.8 hours.
Metabolic pathway(s)	Refer to the approved drug label of NDA 20762, studies have shown that any portion of a mometasone furoate dose which is swallowed and absorbed undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Upon in vitro incubation, one of the minor metabolites formed is 6β-hydroxymometasone furoate. In human liver microsomes, the formation of the metabolite is regulated by cytochrome P-450 3A4 (CYP3A4).
Primary excretion pathways (% dosage)	Refer to the approved drug label of NDA 20762, any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.
	Intrinsic Factors and Specific Populations
Body weight	N/A
Age	N/A
Renal impairment	Refer to the approved drug label of NDA 20762, the effects of renal impairment on mometasone furoate pharmacokinetics have not been adequately investigated.
Hepatic impairment	Refer to the approved drug label of NDA 20762, administration of a single inhaled dose of 400 mcg mometasone furoate to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50 to 105 pcg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment. However, the numbers of detectable levels were few.

Characteristic	Drug Information
	Drug Interaction Liability (drug as victim)
Inhibition/induction of metabolism	Refer to the approved drug label of NDA 20762, in a drug interaction study, an inhaled dose of mometasone furoate 400 mcg was given to 24 healthy subjects twice daily for 9 days and ketoconazole 200 mg (as well as placebo) were given twice daily concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/mL on Day 3 prior to coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 out of 12 subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/mL on Day 9 (211324 pcg/mL).
Inhibition/induction of transporter systems	N/A

Source:: NDA 20762 label (FDA 2020)

Abbreviations: CI, confidence interval; NDA, new drug application; T_{max}, time to maximum concentration.

5.1. Nonclinical Assessment of Potential Effectiveness

No original nonclinical data is included in this submission. Refer to original submissions and reviews under NDA 20762.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

Dose ranging trials of NDA 20762 (Trial C92-011 and Trial C95-161 in [Table 4](#)) were conducted to support the approved Rx dosing of 1 spray/nostril once daily in patients 2 to 11 years of age and 2 sprays/nostril once daily in patients ≥12 years of age for the treatment of nasal symptoms associated with allergic rhinitis and treatment of nasal congestion associated with SAR. As the proposed OTC dosing is the same as the Rx dosing, the dose ranging data will not be discussed in this review.

6.2. Clinical Trials Intended To Demonstrate Efficacy

6.2.1. Results of Analyses

The proposed OTC dosing and indication for Nasonex are consistent with dosing and indications of the approved Rx product. Efficacy data to support the OTC indication were reviewed as part of the Rx clinical development program and were not resubmitted to this NDA. Summaries of the clinical data used to support efficacy labeling of the OTC Drug Facts Label (DFL) along with summaries from the pivotal trials supporting the Rx approval are provided below. The review of clinical trials intended to demonstrate efficacy is organized by approved indications of the original Rx NDA 20762 and subsequent supplements.

6.2.1.1. Original Rx NDA 20762 (Allergic Rhinitis in Adolescents and Adults)

The efficacy and safety of Nasonex for the treatment of nasal symptoms of allergic rhinitis have been evaluated in 18 controlled trials and one uncontrolled clinical trial in approximately 3000 adults and adolescents (as outlined in [Table 4](#)). These trials included one dose-ranging trial (C92-011), seven SAR trials, nine PAR trials, and two additional trials assessing the effects of Nasonex on inflammatory response markers (C93-193 and I94-139). The allergic rhinitis trials evaluated total nasal symptom scores (TNSS) that included stuffiness, rhinorrhea, itching, and sneezing. Per the original NDA review, trial C93-013 was considered the pivotal trial to support efficacy in subjects with SAR and trial C92-280 was considered the pivotal trial to support efficacy in subjects with PAR. Nasonex 200 mcg daily had a statistically significant decrease in TNSS compared with placebo. The below summaries of the pivotal clinical trials were obtained from the clinical study report of the trials provided by the Applicant.

C93-013: Controlled, Pivotal Trial of Nasonex for the Treatment of SAR

This trial was a phase 3, randomized, multicenter, double-blind, active and placebo-controlled trial to determine the safety and efficacy of Nasonex (mometasone furoate) 200 mcg administered intranasally once daily (QD) versus the active control, beclomethasone dipropionate 168 mcg administered twice daily (BID) versus placebo for 28 days in the treatment of SAR. The trial enrolled 340 adults and adolescents 12 years of age and older with the diagnosis of SAR along with a positive response to an allergen skin prick. The primary endpoint was the average change from baseline in the TNSS (rhinorrhea, nasal congestion, sneezing, nasal itching, difficulty sleeping), over the initial 15-day study period (using averaged morning and evening scores). For the average change from baseline in TNSS over the day 1 to 15 interval, both active treatment groups- mometasone and beclomethasone, were significantly more effective than placebo ($p < 0.01$) ([Table 7](#)).

Table 7. Mean Change From Baseline in TNSS From Patient Diaries (Average of AM and PM Scores) for Trial C93-013

Scores/for Trial 055-019						
	Mometasone Furoate (A) n=111		Beclomethasone Dipropionate (B) n=113		Placebo (C) n=116	
	Mean %		Mean %		Mean %	
	Mean Improvement		Mean Improvement		Mean Improvement	
Baseline TNSS	7.6		7.3		7.6	
Change from baseline Days 1-15	-2.3 25%		-2.8 37%		-1.5 17%	
Pairwise Comparisons (P values) for Change						
	A vs. C		B vs. C		A vs. B	
P-value	<0.01		<0.01		0.06	

Source: CP93-013 Clinical Study Report

Abbreviations: TNSS, the total nasal symptoms score.

C92-280: Controlled, Pivotal Study of Nasonex for the Treatment of PAR

This trial was a phase 3, randomized, multicenter, double-blind, active and placebo-controlled trial to determine the safety and efficacy of Nasonex (mometasone furoate) 200 mcg administered intranasally QD versus the active control beclomethasone 168 mcg administered BID and versus placebo for a total of 12 weeks in the treatment of PAR. The trial enrolled 491 adults and adolescents 12 years of age and older with a history of perennial allergy documented by a positive response to allergen skin prick test. The primary endpoint was the mean change from baseline in the TNSS over the initial 15-day study period with Nasonex compared to placebo. Both active treatment groups were significantly more effective than placebo ($p \leq 0.01$) (Table 8). Mean percentage decrease in TNSS for patients receiving mometasone (200 mcg QD) was 21%, compared to a 23% decrease in patients receiving beclomethasone (168 mcg BID) and 13% in the patients receiving placebo.

Table 8. Mean Baseline TNSS From Patient Diaries and Mean Change From Baseline in Trial C92-280

	Mometasone Furoate (A) n=160		Beclomethasone Dipropionate (B) n=156		Placebo (C) n=160	
	Mean % Mean Improvement		Mean % Mean Improvement		Mean % Mean Improvement	
Baseline TNSS	6.6		6.7		6.9	
Change from baseline Days 1-15	-1.5	21%	-1.7	23%	-1.0	13%
Pairwise Comparisons (P values) for Change						
	A vs. C		B vs. C		A vs. B	
P-value	0.01		<0.01		0.53	

Source: CP92-280 Clinical Study Report

Abbreviations: TNSS, the total nasal symptoms score.

6.2.1.2. Onset of Action (S-001)

The Applicant proposes to include onset of action in OTC labeling ('you may start to feel relief within 12 hours and full effect after several days of regular, once-a-day use'). Support for onset of efficacy was previously reviewed under efficacy supplement S-001. This supplement included three clinical trials (P97-019, P97-020, I97-341) to define the time of onset of symptom relief after one dose of Nasonex 200 mcg versus placebo in subjects with SAR (Table 4). Trial P97-019 and P97-020 were conducted in an outdoor park and Trial I97-341 was conducted in an Environmental Exposure Unit). Trial P97-020 failed to show a difference compared to placebo and is not discussed further. Trial P97-019 established onset of action at 3 hours, but Trial I97-341 onset of action was 11 hours and there were no differences at 5 hours, therefore onset of action was determined as 11 hours, as summarized below.

P97-019: Onset of Action of Nasonex vs. Placebo in SAR During an Acute Outdoor Exposure

This trial demonstrated a decrease in TNSS in subjects treated with mometasone and placebo, with a greater and more sustained decrease in the mometasone group compared to placebo. The difference between the groups reached statistical significance at 3 hours after dosing for TNSS ($p=0.04$) and were maintained at all subsequent assessments ($p<0.01$) in TNSS.

I97-341: Onset of Action of Nasonex vs. Placebo in SAR Utilizing the Environmental Exposure Unit

Nasonex onset of action was 11 hours after dosing and was more effective than placebo in reducing TNSS at 11 and 12 hours post dose ($p < 0.05$). Both treatment groups had numerically similar decreases in TNSS for the first 5 hours post dose. After that, the placebo group began to worsen while the subjects in the mometasone group maintained their TNSS relative to baseline. Improvements in TNSS reported by the mometasone group were significantly different than those in the placebo group (11-hour mean change: -1.88 and -1.08, respectively, $p = 0.03$; 12 hour mean change: -1.75 and -1.02, respectively, $p = 0.05$). Time points after 12 hours were not assessed.

6.2.1.3. Allergic Rhinitis in Pediatrics (S-004, S-011)

The efficacy and safety of Nasonex in the treatment of SAR and PAR in pediatric patients 3 to 11 years of age were evaluated in four trials (a dose-ranging trial, a 4-week efficacy and safety trial (I96-090), a 1 year safety trial, and a 1 year safety assessing growth trial; [Table 4](#)). This included approximately 990 pediatric patients with SAR or PAR treated with mometasone furoate nasal spray ranging from 25 to 200 mcg/day. Pediatric patients treated with mometasone furoate (100 mcg total daily dose [1/spray per nostril], 374 patients) had a significant decrease in TNSS, compared to placebo-treated patients. No additional benefit was observed for the 200-mcg mometasone furoate total daily dose (2 sprays/nostril) in pediatric patients (ages 3 to 11 years). A summary of the main pediatric efficacy trial (I96-090) is provided below.

I96-090: Four-Week, Double-Blind Efficacy and Safety Study of Nasonex Versus Placebo, Followed by Six-Month, Open-Label Safety in Children 3 to 11 Years of Age With PAR

This was a randomized, double-blind, placebo-controlled trial assessing efficacy and safety at 4 weeks followed by an open-label, 6 month safety period. The trial enrolled subjects 3 to 11 years old who had at least a 1 year history of symptoms of PAR who required treatment within the previous year along with having a positive skin test to at least one clinically significant perennial allergen. The primary endpoint was physician evaluated change from baseline in TNSS at Day 15. A significantly greater reduction from baseline was observed in subjects treated with mometasone compared with subjects treated with placebo ($p = 0.02$; [Table 9](#)).

Table 9. Physician Evaluation of Change and Percentage Change From Baseline in TNSS for Trial I96-090

Study Visit	MFNS 100 µg			Placebo			p
	n	Mean Change	Mean % Change	n	Mean Change	Mean % Change	
Baseline TNSS	186	6.8		190	6.8		0.93
Change from baseline							
Day 8	186	-2.4	-32	189	-1.6	-22	<0.01
Day 15	185	-2.8	-39	188	-2.2	-32	0.02
Day 29	183	-3.4	-46	187	-2.5	-37	0.01
Endpoint	186	-3.3	-46	190	-2.5	-36	<0.01

Source: I96-090 Clinical Study Report

Abbreviations: MFNS, mometasone furoate; TNSS, the total nasal symptoms score.

The SAR and PAR indications were expanded down to 2 years of age based on a 42-day safety study conducted in children 2 to <6 years of age (P01225; [Table 4](#)).

6.2.1.4. Nasal Congestion Associated With SAR (S-038)

As nasal congestion is considered a symptom of SAR, the trials which supported this Rx indication are considered supportive of the SAR OTC indication and will not be reflected separately in OTC labeling.

The efficacy and safety of Nasonex for nasal congestion associated with SAR were evaluated in three randomized, placebo-controlled, double blind clinical trials of 15 days duration (P05528; P05529; P05583; [Table 4](#)). The other trials conducted for nasal congestion associated with SAR were considered supportive and were not used to support primary evidence of effectiveness as they either included other drug assessments (P04500) or they evaluated nasal congestion as part of the TNSS and not as a stand-alone primary endpoint (P05067; P05106). For the three pivotal trials, the primary efficacy endpoint was the change from baseline in average morning and evening reflective nasal congestion score over treatment day 1 to day 15 ([Table 10](#)). Two out of three studies demonstrated that treatment with Nasonex significantly reduced the nasal congestion symptom score ([Table 10](#)). TNSS over treatment day 1 to 15 was also significant decreased for Nasonex compared to placebo (data not shown). Support for expanding this indication down to patients 2 years of age was based on results in other allergic rhinitis studies with Nasonex in pediatric patients which demonstrated similar effects on nasal congestion associated with SAR in patients below 12 years of age.

Table 10. Effect of Nasonex on Two Randomized, Placebo-Controlled Trials on Nasal Congestion in Patients With SAR

Treatment (Patient Number)	Baseline ¹ LS Mean ²	Change From Baseline LS Mean ²	Difference From Placebo LS Mean ²	P-value for Nasonex 200 mcg Daily vs. Placebo
P05529				
Nasonex 200 mcg daily (N=176)	2.63	-0.64	-0.15	0.006
Placebo (N=175)	2.62	-0.49		
P05583				
Nasonex 200 mcg daily (N=168)	2.62	-0.71	-0.31	<0.001
Placebo (N=164)	2.60	-0.40		

Source: Prescribing information, revised March 2011

¹ Nasal congestion/obstruction was scored daily by the patient using a 0 to 3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms.

² LS mean and p-value were from an ANCOVA model with treatment, baseline value, and center effects.

Abbreviations: ANCOVA, analysis of covariance; LS, least squares.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Efficacy Well Established as a Prescription Product

Issue

Efficacy well established as a Rx product for chronic intermittent/chronic use.

Background

Nasonex is the fifth INCS proposed for an Rx-to-OTC switch for the treatment of nasal symptoms of allergic rhinitis. Nasonex, marketed since 1997, has well established efficacy in adults and children 2 years of age and older. Efficacy is established based on 32 clinical trials used for the development of the original NDA and subsequent supplements.

Assessment

Review of the trials used to approve the original Rx NDA along with the subsequent supplements demonstrated substantial evidence of effectiveness for treatment of nasal symptoms of allergic rhinitis in adults and children 2 years of age and older, as well as the onset of action of 'within 12 hours'. The Applicant also proposes to switch the treatment of nasal congestion associated with SAR. Trials to support this Rx indication are considered supportive of the SAR OTC indication and will not be reflected separately in OTC labeling.

Conclusion

Nasonex is efficacious for treatment of nasal symptoms of allergic rhinitis in adults and children 2 years of age and older.

Dissent

Not applicable.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No original nonclinical data are included in the current submission. Refer to original submissions and reviews under NDA 20762.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Similar to other INCS products, Rx labeling for Nasonex contains class specific Warning and Precautions statements regarding the potential risks of corticosteroid use. These risks include the following:

- Local nasal effects
- Increased risk of glaucoma and/or cataracts
- Hypersensitivity Reactions
- Immunosuppression
- Hypercorticism and adrenal suppression
- Reduction in growth velocity

Reviewer comment: The proposed OTC label adequately addressed the Warnings and Precautions.

7.3. Potential Risks or Safety Concerns Based on Postmarket Experience

The safety profile of Nasonex is well understood; established in clinical trials and supported by 24 years of marketing. Adverse events of special interest (AESI) for this drug class include those noted in Section [7.2](#). Additional aspects of safety considered in switching the drug to OTC use include potential for misuse or abuse and adequacy of OTC labeling to convey safe and effective use of the product in accordance with the Rx label and OTC class labeling. (Refer to Sections [7.8](#) and [21](#))

7.4. FDA Approach to the Safety Review

The safety of Nasonex for the OTC switch is based on the safety data provided in the Rx NDA along with review of the relevant data submitted by the Applicant. The safety data submitted in the original Rx NDA and supplements have been previously reviewed and supported the approval of the Rx NDA, with relevant safety findings described in the Rx product labeling. Given that original NDA reviews and supplemental reviews were unable to be located or provided minimal information, safety information from the Rx label is summarized for this review.

The safety review does not include assessment of trials not previously reviewed by the FDA in which datasets are not available. Postmarketing data was evaluated to determine if any new safety signals have emerged in the past 10 years of use.

The Applicant provided a safety summary for 89 Nasonex trials as outlined below. The Applicant relayed there were missing datasets when they obtained the rights to Nasonex from the original Applicant. Due to this, the safety data of Nasonex was not pooled into one large safety data set, but was broken down by the Applicant based on the following format:

- Trials previously reviewed by Food and Drug Administration (FDA) as part of NDA 20762 and supplements (52 trials)
- Trials not previously reviewed by FDA with partial database (16 trials)
- Trials not previously reviewed by FDA for which datasets are not available (21 trials)

The Applicant also provided 10-year (September 8, 2010 to September 7, 2020) and 120-day update (September 8, 2020 to May 17, 2021) safety data from four databases (outlined below) and safety findings from the medical literature. (Refer to Section [7.8](#))

- Postmarketing data
 - Merck Sharpe & Dohme (MSD) postmarketing pharmacovigilance (PV) (hereafter called MSD PV). Argus is the safety database used by MSD PV
 - FDA Adverse Event Reporting System (FAERS)
 - World Health Organization (WHO) global database of individual case safety reports (VigiBase)
 - American Association of Poison Control Centers (AAPCC)/National Poison Data System pharmacovigilance (NPDS)

7.5. Adequacy of the Clinical Safety Database

Safety for Nasonex is supported by 52 clinical trials conducted and previously reviewed for the Rx NDA of which, 33 were allergic rhinitis clinical trials ([Table 4](#)). The 33 allergic rhinitis clinical trials included approximately 5,399 patients over 2 years of age treated with mometasone furoate. Of these, there were 24 short term trials in which subjects received mometasone for at least 2 weeks and there were 6 long-term studies in which subjects received mometasone for at least 52 weeks. The Applicant also provided safety data summaries from 16 additional trials which were not previously reviewed (b) (4)

(b) (4) The clinical trial data is supported by 10-years of post-marketing safety data. Overall, the clinical safety database is adequate to support review of safety for this partial Rx-to-OTC switch.

7.6. Safety Findings and Concerns Based on Review of the Clinical Safety Database

7.6.1. Safety Findings and Concerns

7.6.1.1. Trials Previously Reviewed by FDA as Part of NDA 20762 and Supplements

Adults and Adolescents 12 Years of Age and Older

In controlled United States and international clinical studies, a total of 3210 adult and adolescent patients 12 years and older with allergic rhinitis received treatment with Nasonex at doses of 50 to 800 mcg/day. The majority of patients (n=2103) were treated with 200 mcg/day. A total of 350 adult and adolescent patients have been treated for one year or longer. Adverse reactions did not differ significantly based on age, sex, or race. Four percent or less of patients in clinical trials

discontinued treatment because of adverse events and the discontinuation rate was similar for the vehicle and active comparators. Adverse reactions reported by 5% or more of adult and adolescent patients aged 12 and older and that were more common with Nasonex than placebo include headache, viral infection, pharyngitis, epistaxis/blood-tinged mucus, coughing, upper respiratory tract infection, dysmenorrhea, musculoskeletal pain, sinusitis.

Reviewer comment: Epistaxis is included in the proposed OTC labeling.

Pediatric Patients <12 Years of Age

In controlled United States and international studies, a total of 990 pediatric patients (ages 3 to 11 years) with allergic rhinitis received treatment with Nasonex at doses of 25 to 200 mcg/day. The majority of pediatric patients (n=720) were treated with 100 mcg/day. A total of 163 pediatric patients have been treated for one year or longer. Two percent or less of patients in clinical trials who received Nasonex discontinued treatment because of adverse events and the discontinuation rate was similar for the placebo and active comparators.

Adverse events which occurred in $\geq 5\%$ of pediatric patients (ages 3 to 11 years) treated with Nasonex 100 mcg/day versus placebo and more frequently than in the placebo group included upper respiratory tract infection (5% in Nasonex group versus 4% in placebo) and vomiting (5% in Nasonex group versus 4% in placebo).

In a randomized, double-blind, placebo-controlled safety trial of Nasonex 100 mcg/day in 56 (1:1) subjects 2 to 5 years of age, the adverse reactions reported by 5% of patients and more commonly in Nasonex included: upper respiratory tract infection (7% versus 0%, respectively).

Controlled clinical studies have shown nasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with nasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with nasal corticosteroids has not been adequately studied.

A clinical study to assess the effect of Nasonex (100 mcg total daily dose) on growth velocity has been conducted in pediatric patients 3 to 9 years of age with allergic rhinitis. No statistically significant effect on growth velocity was observed for Nasonex compared to placebo following one year of treatment. No evidence of clinically relevant HPA axis suppression was observed following a 30-minute cosyntropin infusion. The potential of Nasonex to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

Nasal Congestion Associated With SAR

A total of 1008 patients aged 12 years and older received Nasonex 200 mcg/day (n=506) or placebo (n=502) for 15 days. Adverse reactions that occurred more frequently in patients treated with Nasonex compared to placebo included sinus headache (1.2% in Nasonex group versus 0.2% in placebo) and epistaxis (1% in Nasonex group versus 0.2% in placebo). The overall adverse reaction profile was similar to that observed in the other allergic rhinitis trials.

Nasal Polyps

In controlled clinical studies, the types of adverse reactions observed in patients with nasal polyps were similar to those observed in patients with allergic rhinitis. A total of 594 adult patients (ages 18 to 86 years) received Nasonex at doses of 200 mcg once or BID for up to 4 months for treatment of nasal polyps. The overall incidence of adverse reactions for patients treated with Nasonex was comparable to patients treated with the placebo except for epistaxis, which was 9% for 200 mcg QD, 13% for 200 mcg BID, and 5% for the placebo. Nasal ulcers and nasal and oral candidiasis were also reported in patients treated with Nasonex primarily in patients treated for longer than 4 weeks. No new safety signals were identified. Generally, the safety profile for use of Nasonex in patients with nasal polyps is similar to use of Nasonex in patients with allergic rhinitis.

Reviewer comment: (b) (4) is included in the proposed OTC label.

Acute Sinusitis

(b) (4)

The current Applicant summarized that the most frequently reported AEs in the mometasone groups included vaginitis, headache, diarrhea, epistaxis, pharyngitis, and nausea. The AE signals of diarrhea, nausea, and vaginitis are likely due to the use of antibiotics during the clinical trials. There were no deaths during the clinical development. There were no unexpected safety signals identified in this clinical program.

7.6.1.2. Trials Not Previously Reviewed by FDA With Partial Database

The Applicant relayed that there were 16 trials with Nasonex that had not been previously reviewed by FDA in which they had at least partial databases available. The Applicant divided this information into 6 pools based on FDA's input.

- Pool 1 (five trials): Short-term, double-blind, placebo-controlled trials in subjects with PAR
- Pool 2 (two trials): Short-term, open-label trials in subjects with SAR
- Pool 3 (three trials): Short-term, double-blind, placebo-controlled trials in other indications (acute rhinosinusitis, acute bacterial sinusitis)
- Pool 4 (two trials): Short-term, open-label trials in healthy subjects
- Pool 5 (two trials): Long-term, double-blind, placebo-controlled trials in subjects with upper respiratory allergic conditions
- Pool 6 (two trials): Long-term, open-label trials in subjects with PAR or adenoid hypertrophy

The safety review focused on Pool 1 (five trials) and Pool 5 (two trials) as these pools included controlled trials in SAR and PAR. Review of the safety summaries for Pools 2, 3, 4, and 6

provided by the Applicant did not identify new safety signals. No subject deaths occurred in any of the 16 trials.

Pool 1: Short-term (2 to 4 Weeks), Double-Blind, Placebo-Controlled Trials in PAR (925 Subjects, 633 Treated With Mometasone Furoate Nasal Spray, 292 With Placebo; Adults and Children ≥ 5 Years of Age)

Pool 1 consisted of trials which included 4 different mometasone furoate dose groups. A total of 220 subjects were treated with MFNS 100/200 mcg QD, 75 subjects were treated with mometasone furoate 100 mcg BID, 263 subjects were treated with mometasone furoate 200 mcg QD, and 75 subjects were treated with mometasone furoate 200 mcg BID.

Serious Adverse Events

Three subjects (0.3%) experienced at least one serious adverse event (SAE), with the incidence being similar between the total mometasone furoate group (N=633) and placebo group (N=292): 0.3% and 0.4%, respectively. The preferred terms (PTs) of SAEs consisted of platelet count decreased in one subject in the mometasone furoate 100 mcg BID dose group, fetal death in one subject in the mometasone furoate 200 mcg daily dose group, and testicular neoplasm in one subject in the placebo group.

Adverse Events

The incidence of AEs in the mometasone furoate group and placebo group were 30% and 37%, respectively. The most common ($\geq 2\%$ of subjects) PTs in the total mometasone furoate group were epistaxis (3% for total mometasone furoate and 4% for placebo), upper respiratory tract inflammation (2% and 3%, respectively), and headache (2% and 1%, respectively).

Adverse Events of Special Interest

Given the potential adverse events associated with intranasal corticosteroid use, AESIs assessing local nasal events, ocular events including visual disturbances, effects on growth and/or bone metabolism, and effects on glucose metabolism, and mycotic/fungal infections including candidiasis was assessed. The pooling of the adverse events showed that the risk difference for most of these events did not show a difference between treatment and placebo. For local nasal events, nasopharyngitis and epistaxis showed the greatest difference favoring placebo, but it was confounded based on large confidence interval.

Pool 5: Long-Term (12 to 16 weeks), Double-Blind Placebo-Controlled Trials (in Subjects ≥ 12 Years of Age With Upper Respiratory Allergic Indications)

This pool consisted of two trials, one in subjects with PAR the other in subjects with nasal polyps. Although nasal polyps is a different indication and therefore not directly applicable in the patient population for OTC, the population may be similar enough due to overlapping disease characteristics to leverage safety information. In this pool, 1092 subjects were exposed to mometasone furoate (546 subjects) or placebo (546 subjects). With respect to mometasone furoate dose, 171 subjects were treated with mometasone furoate 200 mcg daily (from PAR trial), and 375 subjects were treated with mometasone furoate 200 mcg BID (from nasal polyp trial). The dose being proposed for OTC is 200 mcg daily. A total of 1035 subjects (95%)

received treatment for at least 29 days, and 922 subjects (84%) received treatment for at least 85 days.

Adverse Events

The most common ($\geq 2\%$ of subjects) AEs in the total mometasone furoate group and greater than placebo were epistaxis (7% and 3%, respectively) and cough (4% and 3%, respectively). Otherwise, the other adverse events were comparable with respect to the incidences of most common PTs of AEs. The Applicant did not break down the adverse events based on mometasone furoate dose.

Serious Adverse Events

Ten subjects (1%) in Pool 5 experienced at least one SAE. The SAEs reported in the total mometasone furoate group consisted of asthma and nasal polypectomy in one subject (0.2%) each. No subject in the placebo group reported these SAEs. It is unclear if these SAEs occurred in the nasal polyp or allergic rhinitis trial or both, but it is known that allergic rhinitis, nasal polyps and asthma are common comorbidities.

Adverse Events of Special Interest

Subjects in Pool 5 reported AESIs in the categories of local nasal events, all mycotic/fungal infections including candidiasis, ocular events including visual disturbances, effects on growth and/or bone metabolism, and effects on glucose metabolism. For nasal events, there was greater risk of epistaxis in the mometasone furoate treated group, which is a known common AE and already labeled in the Warning and Precautions section of the Rx label. Otherwise the other AESI appears to have similar risk between treatment and placebo group.

7.7. Key Review Issue(s) Relevant to Evaluation of Risk

7.7.1. Adverse Events Associated With Use of the Prescription Product

Issue

Consistency of the safety profile at Rx level with a product that is safe for OTC use.

Background

Nasonex is the fifth INCS proposed for an Rx-to-OTC for the treatment of nasal symptoms of allergic rhinitis. Nasonex has been on the market since 1997 and has a well-established safety profile. As with the other four approved OTC INCSs, support for OTC use is based on the safety previously established by the Rx NDA, review of trials previously conducted but not reviewed for the Rx NDA, and postmarketing safety data.

Assessment

Common adverse events associated with Nasonex for those 12 years of age and older as described in the current Rx label include headache, viral infection, pharyngitis, epistaxis, coughing, upper respiratory tract infection, dysmenorrhea, musculoskeletal pain, and sinusitis. In pediatric patients 2 to 11 years of age, common adverse reactions reported by $\geq 5\%$ of patients and more frequently than in the placebo group include upper respiratory tract infection and vomiting. The safety profile is similar to other products switched from Rx to OTC for treatment of nasal symptoms of allergic rhinitis in similar age groups

No new safety signals were detected in the review of previously conducted trials. The risk differences of the adverse events of special interest (local nasal events, ocular events, increase in infection, hypercorticism, growth reduction) for INCSs remain low when compared to placebo. These potential issues are mitigated by information provided in the OTC label.

Review of the trials used to approve the original Rx NDA along with the subsequent supplements, review of trials previously conducted but not reviewed for the Rx NDA, and postmarketing safety data demonstrated sufficient safety for OTC use.

Conclusion

The benefit of Nasonex outweighs the potential risks associated with the intended use. NDA 215712 Nasonex 24HR Allergy (mometasone furoate), 50 mcg is appropriate for a partial Rx-to-OTC switch.

Dissent

Not applicable.

7.8. Safety Findings and Concerns Based on Review of the Postmarketing Safety Databases and Medical Literature

7.8.1. Adverse Events Identified in Postmarket Experiences

There have been approximately (b) (4) bottles of Rx Nasonex distributed globally, with an estimated (b) (4) patient-years of exposure based on annual distribution dating to 1997. Following the initial marketing of Nasonex in 1997, no unexpected serious safety concerns have been identified from clinical trials or pharmacovigilance monitoring that affect the overall safety profile of Rx Nasonex.

Limitations of postmarket reporting precludes estimating frequency of events reported however, reported events are consistent with those seen in the clinical trials. No new potential safety concerns for Nasonex were identified in the submitted data covering 10 years of postmarket experience for the Rx product. Overdose events and potential misuse/abuse events were few. Refer to Section [21](#) for discussion of OTC product labeling.

7.8.1.1. Postmarketing Data

To support the partial Rx-to-OTC switch of Nasonex, the Applicant obtained and analyzed data on cases with Nasonex exposure from four databases listed below for the 10-year time period of September 8, 2010 to September 7, 2020 and the 120-Day safety update encompassing an 8-month time span (September 8, 2020 to May 17, 2021) due to time elapsed between the Applicant's completion of the 10-year data assessment and submission of the NDA.

Postmarketing databases searched include:

- Merck Sharpe & Dohme (MSD) postmarketing pharmacovigilance (PV)
- Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)
- World Health Organization (WHO) global database of individual case safety reports (VigiBase)
- American Association of Poison Control Centers (AAPCC)/National Poison Data System pharmacovigilance (NPDS)

In addition, relevant medical literature was identified through searches of the Embase® and PubMed® databases and reviewed for safety information.

[Table 11](#) provides an overview of AEs identified in the MSD PV, FAERS, and VigiBase databases occurring in at least 2% of patients. AEs reported in at least 2% of patients across three of the databases included hypersensitivity and nasal discomfort. Additional AE data to include AESI are provided in topic and database respective subsections. Due to the extent of missing information for age-related, dose and treatment duration AEs, no conclusions could be derived for these parameters of Nasonex use.

Table 11. MSD PV, FAERS, and VigiBase: Preferred Terms of Adverse Events by System Organ Class Reported in at Least 2% of Patients (9/8/2010 to 9/7/2020)

System Organ Class Preferred Term	MSD PV N=3191 n (%)	FAERS N=3334 n (%)	VigiBase N=3679 n (%)
Gastrointestinal disorders	173 (5.4)	424 (12.7)	274 (7.4)
Gastroesophageal reflux disease	13 (0.4)	229 (6.9)	13 (0.4)
Immune system disorders	127 (4.0)	203 (6.1)	136 (3.7)
Hypersensitivity	73 (2.3)	82 (2.5)	68 (1.8)
Injury, poisoning and procedural complications	1889 (59.2)	1614 (48.4)	1677 (45.6)
Overdose	21 (0.7)	19 (0.6)	104 (2.8)
Nervous system disorders	395 (12.4)	614 (18.4)	600 (16.3)
Coma	9 (0.3)	187 (5.6)	10 (0.3)
Dizziness	53 (1.7)	51 (1.5)	79 (2.1)
Headache	156 (4.9)	156 (4.7)	215 (5.8)
Somnolence	21 (0.7)	203 (6.1)	44 (1.2)

System Organ Class	MSD PV	FAERS	VigiBase
Preferred Term	N=3191	N=3334	N=3679
	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders	814 (25.5)	1047 (31.4)	890 (24.2)
Asthma	42 (1.3)	96 (2.9)	35 (1.0)
Cough	99 (3.1)	151 (4.5)	94 (2.6)
Dyspnea	122 (3.8)	178 (5.3)	129 (3.5)
Epistaxis	149 (4.7)	129 (3.9)	206 (5.6)
Nasal congestion	143 (4.5)	127 (3.8)	133 (3.6)
Nasal discomfort	71 (2.2)	63 (1.9)	74 (2.0)
Pneumonia aspiration	8 (0.3)	184 (5.5)	8 (0.2)
Rhinorrhea	89 (2.8)	89 (2.7)	72 (2.0)
Wheezing	22 (0.7)	80 (2.4)	16 (0.4)

Source: NDA 215712 Applicant Table 1, Module 5.3.6, Section 2.6.2, page 27

System organ class and preferred term are based on version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

Patients experiencing more than one event within a single SOC are only counted once in the bolded summary count for the given system organ class. Similarly, patients experiencing more than one event within a single PT are only counted once in the summary count for the given preferred term.

Abbreviations: FAERS, FDA Adverse Event Reporting System; MSD, Merck Sharp & Dohme; PV, postmarketing pharmacovigilance; VigiBase, WHO global database of individual case safety reports, WHO, World Health Organization.

Overall, no new safety findings were identified and analyses support the established safety profile of Nasonex.

7.8.1.1.1. Merck Sharp & Dohme Postmarketing Pharmacovigilance

The Applicant acquired right of reference to NDA 20762 held by Merck Sharp & Dohme (MSD), analyzed and submitted MSD PV safety data. Argus, the safety database used by MSD PV, collects safety reports communicated to MSD from various sources, including healthcare professionals, patients, parents, manufacturers, and government agencies. MSD also gathers safety information from ongoing clinical trials, patient support programs, and the medical literature.

Cumulatively from September 8, 2010 until September 7, 2020, a total of 3191 postmarketing case reports were received for Nasonex. The majority of cases were nonserious (n=2571; 80.6%), there were 620 (19.4%) serious cases. Of the total cases, 10 (0.3%) patients were <2 years of age, 82 (2.6%) were ≥2 to <12 years of age, 344 (10.8%) were ≥12 to <65 years of age, 159 (5.0%) were ≥65 years of age, and the majority of cases 2596 (81.4%) did not report the age. 1709 patients were female (53.6%), 963 were male (30.2%), and 519 (16.3%) of the cases did not identify the sex.

[Table 12](#) provides a summary of AESI including additional safety concerns of overdose and potential misuse/abuse events. The Applicant states that reported events show no clinically meaningful change in safety trends across this postmarketing timeframe.

Adverse Events of Special Interest

A summary of AESI identified in MSD PV data are provided in [Table 12](#). There were reports across all AESI categories however, the majority of patients reported no AESIs (n=2132; 66.8%), there were 1059 (33.2%) patients reporting at least one. Cases assessed as overdose and potential misuse cases are identified in subsequent tables ([Table 13](#) and [Table 14](#)).

The Applicant analyzed AEs associated with underlying medical conditions (asthma/bronchospasm, cataract, glaucoma, hepatic disorders, hyperglycemia/diabetes, immunosuppression, acute renal failure, chronic kidney disease, pregnancy/nursing mothers) and concomitant medications (nasal preparations, systemic antihistamine or corticosteroid, Cytochrome P450 [CYP3A4] inhibitors) that may result in increased AEs by widespread use inherent to OTC availability. Conclusions based on the incidence of most AEs were confounded by the low number of patients in each of the categories as well as the low numbers of specific AEs however, results of this analysis were consistent with the safety profile of Nasonex and align with Rx and OTC labeling.

Table 12. Summary of Adverse Events of Special Interest (AESI) in MSD PV

AESI Reported	N=3191
Characteristic of Special Interest	n (%)
Any AESI reported	1059 (33.2)
Local nasal events	697 (21.8)
All mycotic/fungal infections including candidiasis	31 (1.0)
Ocular events including visual disturbances	239 (7.5)
Hypothalamic pituitary adrenal (HPA) axis events	15 (0.5)
Growth and/or bone metabolism events	51 (1.6)
Glucose metabolism events	23 (0.7)
Overdose events	44 (1.4)
Nonprescribed/nonmedical use exposure events	110 (3.4)
No AESI reported	2132 (66.8)

Source: NDA 215712, Module 5.3.6, Section 2.12.1.1, MSD PV, Table 2.1.3, pg 147/558

Abbreviations: MSD, Merck Sharp & Dohme; NDA, new drug application; PV, postmarketing pharmacovigilance.

Table 13. Summary of Overdose Events

System Organ Class	Total Cases
Preferred Term	N=3191
	n (%)
Injury, poisoning and procedural complications	44 (1.4)
Accidental overdose	3 (<0.1)
Extra dose administered	3 (<0.1)
Intentional overdose	2 (<0.1)
Overdose	21 (0.7)
Prescribed overdose	11 (0.3)
Product administered to patient of inappropriate age*	4 (0.1)

Source: NDA 215712, Module 5.3.6, Section 2.12.1.1, MSD PV, Table 2.1.3, pg 159/558

* The event "Product administered to patient of inappropriate age" is only summarized for patients under two years old.

System organ class and preferred term are based on version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA)

Abbreviations: MSD, Merck Sharp & Dohme; NDA, new drug application; PV, postmarketing pharmacovigilance.

Table 14. Summary of Nonprescribed/Nonmedical Use Exposure Events

System Organ Class Preferred Term	N=3191 n (%)
Injury, poisoning and procedural complications	109 (3.4)
Accidental exposure to product	75 (2.4)
Accidental exposure to product by child	1 (<0.1)
Exposure via direct contact	1 (<0.1)
Exposure via skin contact	4 (0.1)
Fetal exposure during pregnancy	9 (0.3)
Incorrect route of product administration	13 (0.4)
Intentional product misuse	7 (0.2)
Social circumstances	1 (<0.1)
Drug abuser	1 (<0.1)

Source: NDA 215712, Module 5.3.6, Section 2.12.1.1, MSD PV, Table 2.1.3.8, pg 163/558

Abbreviations: MSD, Merck Sharp & Dohme; NDA, new drug application; PV, postmarketing pharmacovigilance.

Serious Adverse Events

SAEs included 26 deaths (0.8%), 18 life-threatening (0.6%), 161 hospitalizations – initial or prolonged (5.0%), 49 disabling/incapacitating (1.5%), 10 congenital anomaly/birth defect (0.3%), and 479 other serious (15.0%).

Cases reporting death included:

- Only reported event of death (10)
- Events associated with death (5)
 - Adverse event and sepsis
 - Pneumonia and septic shock
 - Malignant neoplasm (multiple other events)
 - Gastrointestinal bleed, cardiac arrest, and epistaxis
 - Cardiac disorder (valve surgery)
- Fetal death (4)
 - Death (at 27 weeks), exposure during pregnancy, and Trisomy 21
 - Exposure during pregnancy and Trisomy 22
 - Abortion induced and limb reduction defect
 - Fetal exposure during pregnancy and diaphragmatic hernia
- Potentially misclassified (3)

In summary, AE reports of the MSD PV postmarketing data are generally consistent with clinical trial safety data, noted in the Rx label, and conveyed in the OTC label. Overdose events and potential misuse/abuse events were few.

7.8.1.1.2. FDA Adverse Event Reporting System

The FDA Adverse Event Reporting System (FAERS) database contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA by manufacturers, healthcare professionals, and consumers. Most of the data are submitted directly to FDA by the manufacturers through Periodic Safety Reports. Healthcare professionals and consumers voluntarily submit reports of AEs. The primary value of this

database is in identifying unexpected, unusual, or serious events not previously recognized for the drug.

During the time period of 8 Sep 2010 to 7 Sep 2020, a total of 3334 cases were reported in the FAERS database. The majority of cases were nonserious (n=2129; 63.9%), there were 1205 (36.1%) assessed as serious. Of the total cases, 17 (0.5%) patients were <2 years of age, 114 (3.4%) were ≥2 to <12 years of age, 925 (27.7%) were ≥12 to <65 years of age, 370 (11.1%) were ≥65 years of age, and 1908 (57.2%) of the cases did not report age. 1782 patients were female (53.4%), 1008 were male (30.2%), and 544 (16.3%) of the cases did not identify sex of the patient.

Adverse Events of Special Interest

A summary of AESI identified in FAERS data is provided in [Table 15](#). There were reports across all AESI categories however, the majority of patients reported no AESIs (n=2192; 65.7%), there were 1142 (34.3%) patients reporting at least one. Cases assessed as overdose and potential misuse cases are identified in subsequent tables ([Table 16](#) and [Table 17](#)).

Table 15. Summary of Adverse Events of Special Interest (AESI) in FAERS

AESI Reported	N=3334
Characteristic of Special Interest	n (%)
Any AESI reported	1142 (34.3)
Local nasal events	701 (21.0)
All mycotic/fungal infections including candidiasis	54 (1.6)
Ocular events including visual disturbances	294 (8.8)
Hypothalamic pituitary adrenal (HPA) axis events	24 (0.7)
Growth and/or bone metabolism events	104 (3.1)
Glucose metabolism events	28 (0.8)
Overdose events	35 (1.0)
Nonprescribed/nonmedical use exposure events	115 (3.4)
No AESIs reported	2192 (65.7)

Source: NDA 215712, Module 5.3.6, Table 9, pg 79/138

Abbreviations: AESI, adverse event of special interest; FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; NDA, new drug application.

Table 16. Summary of Overdose Events

System Organ Class	Total Cases
Preferred Term	N=3334
	n (%)
Injury, poisoning and procedural complications	35 (1.0)
Accidental overdose	3 (<0.1)
Extra dose administered	3 (<0.1)
Intentional overdose	19 (0.6)
Prescribed overdose	6 (0.2)
Product administered to patient of inappropriate age	4 (0.1)

Source: NDA 215712, Module 5.3.6, Section 2.12.2, FAERS, Table 2.1.3.7, pg 280/12151

Abbreviations: FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; NDA, new drug application.

Table 17. Summary of Nonprescribed/Nonmedical Use Exposure Events

System Organ Class	Total Cases
Preferred Term	N=3334
	n (%)
Injury, poisoning and procedural complications	114 (3.4)
Accidental exposure to product	40 (1.2)
Accidental exposure to product by child	1 (<0.1)
Exposure via direct contact	3 (<0.1)
Exposure via eye contact	1 (<0.1)
Exposure via skin contact	2 (<0.1)
Fetal exposure during pregnancy	17 (0.5)
Incorrect route of product administration	42 (1.3)
Intentional product misuse	9 (0.3)
Maternal drugs affecting foetus	3 (<0.1)
Prescription drug used without a prescription	1 (<0.1)
Social circumstances	1 (<0.1)
Drug abuser	1 (<0.1)

Source: NDA 215712, Module 5.3.6, Section 2.12.2, FAERS, Table 2.1.3.8, pg 281/12151

Abbreviations: FAERS, FDA Adverse Event Reporting System; FDA, Food and Drug Administration; NDA, new drug application.

Serious Adverse Events

Serious adverse events included 33 deaths (1.0%), 41 life-threatening (1.2%), 450 hospitalizations – initial or prolonged (13.5%), 82 disabling/incapacitating (2.5%), 20 congenital anomaly/birth defect (0.6%), and 893 other serious event (26.8%). Most of the 33 cases reporting death reflect cases reported in MSD PV data, some are likely duplicates within FAERS.

Events reported by year showed four AEs reported in unusual numbers (at least 2% of cases) that included coma, gastroesophageal reflux disease, pneumonia aspiration, and somnolence. These appear to be from duplicate reporting of cases in the FAERS database. AEs of asthma, cough, dyspnea, and wheezing increased in 2019 and 2020. The majority of cases reported no dose nor data on duration of treatment (n=2902; 87%) though the most commonly reported duration was at least 29 days (n=216; 6.5%).

120-Day Safety Update

A Division of Pharmacovigilance (DPV) review confirms that the Applicant's FAERS data reported in the 120-Day Safety Update (September 8, 2020 to May 17, 2021) is consistent with the AEs reported in FDA FAERS searches. The most commonly reported PTs (asthma, dyspnea, wheezing) occurred in patients with allergic rhinitis, for which Nasonex is indicated.

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 U.S., of which four 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 a biologic used to treat severe asthma. These types of reports were 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, otosalingitis), or described labeled adverse events (i.e., nosebleed). From detailed review of these 11 SAE cases, we did not identify any new safety signal.

The Applicant noted several PTs that were reported in unusual numbers and explains this to be due to a duplication of cases within FAERS data. The DPV assessment of each of these PTs follows.

- Coma – Duplicate cases. After deduplication, one unique case (#18256240) 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.
- 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 cases (#18253240, #18379291) contain the PT *Somnolence*. See details above as the first case is the same case with the PT *Coma*. The second case describes off-label use of Nasonex in a 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 chronic obstructive pulmonary disease.
- 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.

Even though AESIs were identified, analysis of the cases was limited due to missing information (i.e., temporality). Many of the SAEs were likely due to other events such as underlying medical conditions, concomitant medications, and surgical procedures. Overall, the low number of domestic SAEs, including AESI reported with Nasonex indicate no increase in AEs in FAERS.

7.8.1.1.3. World Health Organization Vigibase

Vigibase is the World Health Organization (WHO) global database of individual case safety reports (ICSR) related to medication use and collected from over 130 member countries as part of the WHO's Program for International Drug Monitoring (PIDM). Vigibase is primarily used for postmarketing safety surveillance. The ICSRs come from a variety of sources (healthcare providers, required and voluntary patient reports), are qualitative and include the suspected drug, events related to the drug, patient demographics, and other information deemed relevant to the event, such as time to onset and outcome.

The report of this database search included data on mometasone-based products for the 10-year period from September 8, 2010 through September 7, 2020. In total, 3,679 cases identified Nasonex as suspected of contributing to the event, directly or through interaction with another product. The majority of cases were nonserious (n=2943; 80.0%), there were 610 (16.6%) were serious. Of the total cases, 18 (0.5%) patients were <2 years of age, 185 (5.0%) were ≥2 to <12 years of age, 1113 (30.3%) were ≥12 to <65 years of age, 446 (12.1%) were ≥65 years of age, and 1917 (52.1%) of the cases did not report age. 1980 patients were female (53.4%), 1191 were male (32.4%), and 508 (13.8%) of the cases did not identify sex.

Adverse Events of Special Interest

A summary of AESI identified in FAERS data is provided in [Table 18](#). There were AE reports across all AESI categories however, the majority of patients reported no AESIs (n=2370; 64.4%), there were 1309 (35.6%) patients reporting at least one AESI. Cases assessed as overdose and potential misuse cases are identified in subsequent tables ([Table 19](#) and [Table 20](#)).

Table 18. Summary of Adverse Events of Special Interest (AESI) in VigiBase

AESI Reported	N=3679
Characteristic of Special Interest	n (%)
Any AESI reported	1309 (35.6)
Local nasal events	806 (21.9)
All mycotic/fungal infections including candidiasis	33 (0.9)
Ocular events including visual disturbances	318 (8.6)
Hypothalamic pituitary adrenal (HPA) axis events	20 (0.5)
Growth and/or bone metabolism events	56 (1.5)
Glucose metabolism events	23 (0.6)
Overdose Events	115 (3.1)
Nonprescribed/nonmedical use exposure events	78 (2.1)
No AESIs reported	2370 (64.4)

Source: NDA 215712, Module 5.3.6, Table 10, pg 82/138

Abbreviations: AESI, adverse event of special interest; NDA, new drug application; VigiBase, WHO global database of individual case safety reports, WHO, World Health Organization.

Table 19. Summary of Overdose Events

System Organ Class	Total Cases
Preferred Term	N=3679
	n (%)
Injury, poisoning and procedural complications	115 (3.1)
Accidental overdose	3 (<0.1)
Extra dose administered	2 (<0.1)
Overdose	104 (2.8)
Prescribed overdose	2 (<0.1)
Product administered to patient of inappropriate age	4 (0.1)

Source: NDA 215712, Module 5.3.6, Section 2.12.3, VigiBase, Table 2.1.3.7, pg 253/825

Abbreviations: NDA, new drug application; VigiBase, WHO global database of individual case safety reports, WHO, World Health Organization.

Table 20. Summary of Nonprescribed/Nonmedical Use Exposure Events

System Organ Class	N=3679
Preferred Term	n (%)
Injury, poisoning and procedural complications	78 (2.1)
Accidental exposure to product	37 (1)
Accidental exposure to product by child	1 (<0.1)
Exposure via breast milk	1 (<0.1)
Exposure via direct contact	3 (<0.1)
Exposure via eye contact	1 (<0.1)
Exposure via skin contact	5 (0.1)
Fetal exposure during pregnancy	4 (0.1)
Incorrect route of product administration	16 (0.4)
Intentional product misuse	9 (0.2)
Prescription drug used without a prescription	4 (0.1)

Source: NDA 215712, Module 5.3.6, Section 2.12.3.8, VigiBase, Table 2.1.3.7, pg 254/825

Abbreviations: NDA, new drug application; VigiBase, WHO global database of individual case safety reports, WHO, World Health Organization.

Serious Adverse Events (SAE)

Serious cases included 19 deaths (0.5%), 26 life-threatening (0.7%), 146 hospitalizations – initial or prolonged (4.0%), 65 disabling/incapacitating (1.8%), 7 congenital anomaly/birth defect (0.2%), 430 other serious (11.7%), 11 cases assessed as serious but without criteria (0.3%), 126 cases without seriousness reported. Most of the 19 reported deaths reflect cases reported in FAERS.

7.8.1.1.4. American Association of Poison Control Centers / National Poison Data System

The American Association of Poison Control Centers (AAPCC)/National Poison Data System pharmacovigilance (NPDS) is a data warehouse for the nation's 55 poison control centers. De-identified case data is submitted by the poison control centers to NPDS after providing poison exposure management and information services to callers. Exposures do not necessarily represent a poisoning or overdose and AAPCC is not able to completely verify the accuracy of every report.

For the 10-year period September 8, 2010 to September 7, 2020, there were a total of 1277 reports of exposure to Nasonex. 1082 cases (84.7%) involved exposure to Nasonex alone and 1164 of the 1277 cases were unintentional exposures. The primary routes of reported exposures were ocular 433 (38.8%), inhalation/nasal 357 (32%), and ingestion 280 (26.1%) ([Table 21](#)). Misuse accounted for 83 (6.5%) of the exposures. Regardless of demographic, the majority of cases (n=1164; 97.7%) were managed at the caller's residence. Outcomes of those <2 years of age were no follow up or no effect in 89.1%. All 11 (0.9%) cases resulting in hospital admission were in patients ≥12 and <65 years of age and included exposure to Nasonex plus one or more additional drug product(s). A single report of death occurred in a 68 year old and included Nasonex with four additional drugs, none of which were considered causal.

Table 21. Route of Exposure, All Ages

Route of Exposure	N	% of All Routes	% of All Cases N=1082
Ocular	433	38.8	40.0
Inhalation/nasal	357	32.0	33.0
Ingestion	280	25.1	25.9
Dermal	17	1.5	1.6
Other	13	1.2	1.2
Optic	11	1.0	1.0
Aspiration (with ingestion)	2	0.2	0.2
Unknown	2	0.2	0.2
Total	1115	100	103

Source: NDA 215712, Module 5.3.6, Report 2, AAPCC/NPDS, Table 1.8.1, pg 61/610

Abbreviations: AAPCC, American Association of Poison Control Centers; NDA, new drug application; NPDS, National Poison Data System pharmacovigilance.

7.8.1.2. Medical Literature

Applicant searches of Embase and PubMed (MEDLINE) databases for the 10-year reporting period identified 739 articles specifically mentioning Nasonex. Fifty were considered relevant to Nasonex safety and OTC indications ([Table 22](#)). The clinical safety information reported in the literature is consistent with safety information presented for the reference NDA 20762 and in the partial Rx-to-OTC switch application. Eight unlisted AEs noted in the review that have not been reported to the MSD PV are similar to events already reported (e.g., nasal stinging similar to nasal discomfort), likely relate to underlying conditions, or not related to Nasonex. No new clinically relevant safety findings were identified in this literature review.

Table 22. Types of Literature Retrieved

Type of Article	Number	References for Articles With OTC Indications
Clinical trial	11 for OTC indication 9 for non-OTC conditions	(Salapatek et al. 2010; Fokkens et al. 2012; Makihara et al. 2012; Berger et al. 2013; Meltzer et al. 2013a; Meltzer et al. 2013b; Emanuel et al. 2014; Kuna et al. 2014; Shah et al. 2015; Antila et al. 2016; Yonezaki et al. 2016)
Case report	8 for OTC indication 1 for non-OTC conditions	(Ebrahimi et al. 2013; Esteves et al. 2014; Hanna and Mack 2014; Taefi et al. 2014; Ricketti et al. 2015; Forbush and Banks 2016; Duman and Fulco 2017; Kopsidas et al. 2019)
Meta-analysis	4 for OTC indication	(Meltzer et al. 2011; Seresirikachorn et al. 2018; Wu et al. 2019a; Wu et al. 2019b)
Review	16 for OTC indication	(Berlucchi and Barbara 2010; Sankovic Babic and Rade 2010; Wolthers 2010; Blaiss 2011; Meltzer 2011; Lightman and Scadding 2012; Sastre and Mosges 2012; Nyenhuis and Mathur 2013; Saberi et al. 2013; AhmadiAfshar and AhmadiAfshar 2014; Gupta and Fonacier 2016; Jang and Kim 2016; Passali et al. 2016; Pali-Scholl et al. 2017; Alhussien et al. 2018; Seth and Kamat 2019)
White paper	1 for OTC indication	(Luskin et al. 2011)

Source: NDA 512712, Module 5.3.6, Report 3: Medical Literature

Abbreviations: NDA, new drug application; OTC, over-the-counter.

8. Therapeutic Individualization

8.1. Intrinsic Factors

The following information is from Section 12.3 of the approved label of Nasonex (mometasone furoate monohydrate) Nasal Spray (revised Sep 2020) (FDA 2020).

- Patients with hepatic impairment: Administration of a single inhaled dose of 400 mcg mometasone furoate to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only one or two subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50 to 105 pcg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels were few.
- Patients with renal impairment: The effects of renal impairment on mometasone furoate pharmacokinetics have not been adequately investigated.
- Pediatric patients: Mometasone furoate pharmacokinetics have not been investigated in the pediatric population.
- Male and female patients: The effects of gender on mometasone furoate pharmacokinetics have not been adequately investigated.
- Racial or ethnic groups: The effects of race on mometasone furoate pharmacokinetics have not been adequately investigated.

The following information is from Section 8 of the approved label of Nasonex (mometasone furoate monohydrate) Nasal Spray (revised Sep 2020) (FDA 2020).

- Section 8.5 Geriatric Use: A total of 280 patients above 64 years of age with allergic rhinitis or nasal polyps (age range 64 to 86 years) have been treated with Nasonex for up to 3 or 4 months, respectively. The adverse reactions reported in this population were similar in type and incidence to those reported by younger patients.
- Section 8.6 Hepatic Impairment: Concentrations of mometasone furoate appear to increase with severity of hepatic impairment

Reviewer comment: The clinical meaning of “having detectable peak plasma concentrations of mometasone furoate” in several subjects with hepatic impairment is unclear. In addition, the Rx label does not include specific dosing modifications for patients with hepatic or renal impairment or based up gender or race. The Rx label includes specific dosing recommendations for pediatric patients based upon clinical trial data. The OTC label will reflect this.

8.2. Drug Interactions

The following information is from the approved label of Nasonex (mometasone furoate monohydrate) Nasal Spray (revised Sep 2020) (FDA 2020).

- Section 12.3 Inhibitors of Cytochrome P4503A4: In a drug interaction study, an inhaled dose of mometasone furoate 400 mcg was given to 24 healthy subjects BID for 9 days and ketoconazole 200 mg (as well as placebo) were given BID concomitantly on Days 4 to 9. Mometasone furoate plasma concentrations were <150 pcg/mL on Day 3 prior to

coadministration of ketoconazole or placebo. Following concomitant administration of ketoconazole, 4 out of 12 subjects in the ketoconazole treatment group (n=12) had peak plasma concentrations of mometasone furoate >200 pcg/mL on Day 9 (211-324 pcg/mL).

- Section 7 Inhibitors of Cytochrome P450 3A4: Studies have shown that mometasone furoate is primarily and extensively metabolized in the liver of all species investigated and undergoes extensive metabolism to multiple metabolites. In vitro studies have confirmed the primary role of cytochrome CYP3A4 in the metabolism of this compound.

Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of, and increase the systemic exposure to, mometasone furoate and potentially increase the risk for systemic corticosteroid side effects. Caution should be exercised when considering the coadministration of Nasonex with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, cobicistat-containing products, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) (see Clinical Pharmacology [12.3]). Consider the benefit of coadministration versus the potential risk of systemic corticosteroid effects, in which case patients should be monitored for systemic corticosteroid side effects.

Reviewer comment: The Rx label includes drug-drug interaction information regarding effects of ketoconazole on mometasone furoate PK. Mometasone furoate is metabolized by cytochrome P-4503A4 (CYP3A4) and ketoconazole is a strong CYP3A4 inhibitor, which implies a strong DDI potential. The OTC label will reflect this.

8.3. Plans for Pediatric Drug Development

Not applicable. The drug is approved for children down to 2 years of age.

8.4. Pregnancy and Lactation

The following information is from the approved label of Nasonex (mometasone furoate monohydrate) Nasal Spray (revised September 2020) (FDA 2020).

- Pregnancy: There are no adequate and well-controlled clinical studies of Nasonex in pregnant women. In animal reproduction studies with pregnant mice, rats, or rabbits, mometasone furoate caused increased fetal malformations and decreased fetal survival and growth following administration of doses that produced exposures approximately 1/3 to 8 times the maximum recommended human dose (MRHD) on a mcg/m² or area under the concentration-time curve (AUC) basis (see Data). However, experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

- Lactation: There are no available data on the presence of Nasonex in human milk, the effects on the breastfed child, or the effects on milk production. Other corticosteroids are excreted in human milk. The developmental and health benefits of breastfeeding should be considered

along with the mother's clinical need for Nasonex and any potential adverse effects on the breastfed infant from Nasonex or from the underlying maternal condition.

9. Product Quality

Recommendation and Conclusion on Approvability

Regarding quality aspects of the submitted application the drug substance, drug product, biopharmaceutics, microbiology, process, and facility sections are reviewed and found adequate to support the approval of the application. The drug product is granted a 24-month shelf life when stored at controlled room temperature.

Summary of Quality Assessment

Information on biowaiver request submitted by the Applicant under 21 CFR 320.22(d)(2) is reviewed by the Biopharmaceutics reviewer (see biopharmaceutics review dated June 28, 2021). Since the formulation, manufacturing process, and container (i.e., spray bottles, pumps, actuators) remain the same as the Rx drug product approved under NDA 20762, it was concluded that the bioequivalence between this proposed product and the approved Rx is self-evident and that bridging of formulations is not necessary.

The Applicant did not perform in-use stability studies for the finished product and a discard date is not proposed following opening the bottle. It was a quality concern since the OTC products are often used intermittently and theoretically in-use period are open-ended. The mometasone furoate nasal spray, 50 mcg/spray, 120 spray configurations contain sufficient volume for (b) (4) sprays, or (b) (4) days of dosing based on a daily dose of 2 sprays in each nostril. In addition, it is known that the products (b) (4)

(u) (4). Thus, micro reviewer asked for an extended AET for at least (b) (4) days to support the proposed in-use period and recommended to include a discard date for the in-use period. The Applicant provided extended AET data and include updated labeling statement "discard 75 days after first use of the product" (see details in micro review dated January 13, 2022).

Description/Commercial Image

Mometasone furoate nasal spray formulation is white to off-white opaque nonsterile suspension having a pH between 4.3 and 4.9. The Applicant's OTC mometasone furoate nasal spray, 50 mcg/spray is supplied in a white, high density polyethylene bottle fitted with a white metered-dose, manual spray pump, and blue cap. The drug product is supplied in fill volumes of 7.5 mL, 10 mL and 17 mL. Each metered spray delivers a mean volume of 0.10 mL containing 50 mcg of mometasone furoate. Same formulation is used in NDA 20762. The only difference between the approved Rx NDA 20762 formula and the Applicant's OTC formula will be (b) (4)

(b) (4) All excipients used for the manufacture of the drug product are of United States Pharmacopeia/National Formulary (USP/NF) grade. Inactive ingredients are same as approved in NDA (b) (4). The direction of use is the same as in the referenced NDA (b) (4). The pump should be primed before initial use by actuations until a fine mist appears and reprimed after storage unused for 1 week or more. The recommended dosage

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for adults and children ≥ 12 years of age is 2 sprays per nostril QD. The recommended dosage for children 2 to 11 years of age is 1 spray in each nostril QD.

The proposed shelf-life of the product is 24 months when stored at controlled room temperature, 20°C to 25°C and is (see drug product review).

Summary of Product Design

The proposed NDA application for the commercial OTC formulation will have the same container closure system as currently approved for Rx Nasonex (mometasone furoate monohydrate) Nasal Spray, 50 mcg (NDA 20762). The proposed product OTC Nasonex Nasal Spray, 50 mcg/spray is packaged into 19 mL or 13 mL oval high density polyethylene (HDPE) white bottles. The bottles have a blue, (b) (4) cap, and a white (b) (4) actuator, and (b) (4) pump. (b) (4)

Process Selection

All the facilities proposed for the drug product manufacturing and testing are in compliant status. Based on the low manufacturing risk of this drug product, past device experience from the drug product manufacturing firm, recent inspection history and current compliant status the facilities are recommended for approval.

Expiration Date and Storage Conditions

The drug product is granted a 24-month shelf life when stored at controlled room temperature, 20°C to 25°C (68°F to 77°F). The storage statement will be written as “Store between 20°C – 25°C (68°F – 77°F).”

Table 23. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Nasonex 24HR Allergy
Nonproprietary name of the drug product	Mometasone furoate 0.05% (w/v nasal spray)
Nonproprietary name of the drug substance	Mometasone furoate
Proposed indication(s) including intended patient population	Temporary relief of symptoms associated with hay fever or other respiratory allergies, including: nasal congestion, runny nose, sneezing, and itchy nose.
Duration of treatment	(b) (4)
Maximum daily dose	0.20 mg
Alternative methods of administration	None

9.1. Device or Combination Product Considerations

Nasonex Nasal Spray is a drug/device combination product. The actuator is a standard nasal spray actuator consistent with other nasal spray actuators that are available OTC.

The Applicant submitted use-related risk analysis (URRA) and comparative analysis in October 2019, which were reviewed under IND 142446. The Division of Medical Errors and Prevention and Analysis (DMEPA) 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 human factor validation study results were not needed to support the NDA, Rx-to-OTC switch.

10. Human Subjects Protections / Clinical Site and Other Good Clinical Practice Inspections / Financial Disclosure

No new clinical trials were conducted to support this NDA. Refer to original submissions and reviews under NDA 20762.

11. Advisory Committee Summary

There was no Advisory Committee meeting for this fifth in class Rx-to-OTC switch application.

III. Additional Analyses and Information

12. Summary of Regulatory History

Table 24. Summary of Regulatory History

Date	Activity	Outcome
Oct 10, 1996	Reference listed drug, NDA 20762 Nasonex (mometasone furoate) nasal spray, 0.05 mg/spray, submitted for approval	Approved (Oct 1, 1997)
Dec 27, 2018	Type B, pre-NDA meeting request submitted under Pre-IND 142446	Teleconference held on Mar 14, 2019, to discuss overall information requirements and 505(b)(1) submission strategy for partial Rx-to-OTC switch.
Jun 4, 2019	Proprietary name review for <i>Nasonex 24HR Allergy</i>	Conditionally acceptable on Nov 20, 2019
Sep 27, 2019	Type C, Chemistry meeting submitted under Pre-IND 142446	Meeting, WRO granted and responded on Dec 6, 2019. Discussion confirmed mirror of NDA 020762 acceptance criteria for a partial Rx-to-OTC switch under 505(b)(1) of FD&C Act.
Oct 26, 2019	Human Factors/Use-Related Risk Analysis submitted	Mar 17, 2020 – DMEPA review agrees that results of human factors validation study does not need to be submitted as part of marketing application.
Nov 21, 2019	Type C meeting request to discuss the requested potency table and labeling	WRO issued Feb 4, 2020 that addressed relative potency information for corticosteroids and labeling.
May 4, 2020	Type C, Chemistry meeting submitted under Pre-IND 142446	Meeting, WRO granted and responded on Jul 17, 2020 – FDA confirmed acceptance of supplier pump/actuator manufacturer approvals and bracketed stability program.
Oct 27, 2020	Type C, Guidance meeting submitted under Pre-IND 142446 to discuss potency table justification and labeling comments on the Drug Facts label and consumer information leaflet (see discussion below).	This meeting request was withdrawn on May 24, 2021 after NDA 215712 Nasonex 24HR Allergy (mometasone) nasal spray, 50 mcg/spray, was submitted.
May 24, 2021	NDA 215712 Nasonex 24HR Allergy (mometasone) nasal spray, 50 mcg/spray, was submitted to propose a partial prescription to over-the-counter switch.	Proposal to change marketing status of 2 of 4 prescription indications to nonprescription leaving <i>Prophylaxis of SAR in patients ≥12 years of age</i> and <i>Treatment of Nasal Polyps in patients ≥18 years of age</i> as prescription indications.
Sep 8, 2021	Proprietary name granted for <i>Nasonex 24HR Allergy</i> under NDA 215712	Approved

Abbreviations: DMEPA, Division of Medication Error Prevention and Analysis; IND, investigational new drug; NDA, new drug application; OTC, over-the-counter; Rx, prescription; SAR, seasonal allergic rhinitis; WRO, written response only.

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On October 27, 2020, the Applicant's response noted that drug facts labeling had been revised to include medicine for HIV infection (e.g., ritonavir), steroids for asthma, allergies or skin rash, and ketoconazole pills to the list of medications that the consumer should tell their healthcare provider about before use.

Direct comparisons between agents cannot be made without head-to-head trials. However, based on Applicant information, mometasone furoate appears to be within the range of existing OTC INCSs. Labeling includes warnings as discussed with the Applicant in pre-NDA communications.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted Under the IND

There were no original nonclinical data included in the current submission. Refer to original submissions and reviews under NDA 20762.

13.2. Individual Reviews of Studies Submitted to the NDA

No original nonclinical data included in current submission. Refer to original submissions and reviews under NDA 20762.

14. Clinical Pharmacology

The Applicant has not conducted any new clinical pharmacology studies under this submission. The Applicant has submitted reports for 16 clinical studies which either were not included under NDA 20762 original submission or have only partial databases available under NDA 20762. All the general and critical clinical pharmacology information of Nasonex were presented in the original NDA 20762 and subsequent supplements. No additional clinical pharmacologically meaningful pharmacokinetic (PK) information for Nasonex is provided in this partial Rx-to-OTC switch NDA.

14.1. In Vitro Studies

No new in vitro information submitted in this NDA.

14.2. In Vivo Studies

Among 16 clinical studies, only two studies contained PK data:

(b) (4)

The clinical pharmacology review team did not review these two clinical studies for the following reasons:

- Both studies were relative bioavailability studies for comparing the performance (including PK) of Nasonex Nasal Spray with other mometasone furoate nasal spray devices which are irrelevant to the current submission where the Applicant is proposing to do a switch from prescription (Rx) to OTC product.
- No bioanalytical studies or method validation are submitted for the two studies.

14.3. Waiver of In Vivo Bioavailability or Bioequivalence Studies Requirement

The Applicant proposed not conducting additional bioequivalence studies or characterization testing of the bottles, pumps, actuators, or bottle/pump/actuator combinations to support approval of their product since it has exact same qualitative/quantitative formula, manufacturing process, and bottles/pumps/actuators approved by Food and Drug Administration (FDA) for use in the Rx NDA 20762 held by the listed drug. The 19 mL bottle and related pump/actuator approved in the listed drug will be used for the OTC 120 spray count and the OTC 60 spray count. (b) (4)

(b) (4). Further, the Applicant proposed that finished product release testing data, which includes spray pattern, droplet size distribution, and particle size measurement data to support the waiver requests.

Information on biowaiver request submitted by the Applicant under 21 CFR 320.22(d)(2) is reviewed by the biopharmaceutics reviewer.

15. Trial Design

Not applicable.

16. Efficacy

Not applicable.

17. Clinical Safety

Not applicable.

18. Mechanism of Action / Drug Resistance

Not applicable.

19. Other Drug Development Considerations

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Not applicable.

21. Labeling Summary of Considerations and Key Additional Information

21.1. Approach to the Labeling Review

The Interdisciplinary Scientist (IDS) review team in the Division of Nonprescription Drugs 1 (DNPD1) has assessed NDA 215712 partial Rx-to-OTC switch with respect to specific review issues that affect important labeling aspects of switching the intranasal glucocorticoid Rx drug product Nasonex 24HR Allergy (mometasone furoate), 50 mcg/spray, to OTC use. During the process of identifying and addressing key labeling review issues across all submitted nonprescription labeling components of the proposed nonprescription drug product (refer to [Table 26](#)), the following approved Full Prescribing Information (Rx label) sections were considered: prescription labeling indication(s), limitation(s) of use, recommended dosage, directions, risk information (e.g., contraindications, warnings and precautions, or boxed warnings), or other relevant components of the Rx labeling. For this review, the proposed draft Nasonex 24HR Allergy OTC labeling was assessed as to whether (and how adequately) the important and most critical information from the Rx label, for safe and effective use of this product by consumers, was carried over from the Rx label to the proposed OTC Drug Facts Label (DFL) and OTC labeling² (see Labeling Review in Document Archiving, Reporting, and Regulatory Tracking System [DARRTS]). In addition, this labeling review also considers whether additional critical labeling statements are necessary, and whether (and how adequately)

² The regulations for constructing an OTC drug label (for reference) are primarily found in the following sections of the Code of Federal Regulations (21 CFR) Part 201:

- Subpart A- General Labeling Provisions, Subpart C – Labeling Requirements for OTC drugs, which provides the labeling for packaging (PDP at §201.60 and Statement of Identity (SOI) at §201.61, etc.) and content and format of the DFL at §201.66 (c) and (d), Subpart G - Packaging and Labeling Control which provides the labeling for the tamper-evident packages at §211.132

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the proposed OTC labeling aligns to current labeling for other OTC intranasal glucocorticoid allergy symptom reliever drug products³.

Table 26. Proposed Draft Labeling

Proposed Draft Labeling	Date(s) 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

Source: Reviewer Summary based on Labeling Review in DARRTS

21.2. Review Issue(s)

The following risk/risk management issue was identified by the team at the start of the review clock of NDA 215712 as the only issue directly related to labeling and where the DNPDP1 IDS review team could provide input:

- Does the proposed OTC labeling (including the DFL, immediate and secondary containers, and package insert) adequately convey safe and effective use of the product in accordance with the prescription label and minimize misuse?
 - Do the directions on the DFL adequately instruct consumers (in particular adults and children 12 years of age and over) how long they may safely use the product before consulting a doctor?
 - Do the directions on the immediate container label provide sufficient information for safe and effective use for consumers (in particular adults and children 12 years of age and over)?
 - Is the disposal information adequately addressed in the labeling and is it supported by the in-use stability data?
 - Is there any other key information that should be included or emphasized (for instance, reiterated on the package insert) in the labeling?

³ Current approved OTC intranasal glucocorticoid drug products include:

- Flonase Sensimist Allergy Relief (fluticasone furoate 27.5 mcg per spray; NDA 22051)
- Flonase Allergy Relief (fluticasone propionate 50 mcg per spray; NDA 205434)
- Nasacort Allergy 24HR (triamcinolone acetonide 55 mcg per spray; NDA 20468)
- Rhinocort Allergy Spray (budesonide 32 mcg per spray; NDA 20746)

The IDS review team in DNPD1 has assessed NDA 215712 with respect to this broad review issue (see Labeling Review in DARRTS), however additional responses to this review issue may be reflected in the Integrated Review sections by other disciplines and incorporated into Section [7.7](#) discussing all the other key review issues.

21.3. Assessment

A. Drug Facts Label

The importance of the DFL for OTC drug products is that it conveys the most critical information from the Full Prescribing Information for safe and effective use of the product by consumers, to a written “consumer-friendly” standardized format and content in accordance with 21 CFR 201.66(c) & (d). The only substantive changes to what the Applicant proposed in their original DFL label was the addition of the warning “stinging may occur for a few seconds right after use” to the subheading “When using this product” in the DFL and the addition of the disposal or discard information to the “Other information” section. Under the “Other information” heading, the following statement “Discard 75 days after first use of the product” was added as the last bullet and is reiterated on the consumer information leaflet based on the extended antimicrobial effectiveness test (AET) study deemed acceptable by the chemistry, manufacturing, and controls (CMC) team.

We conclude that regarding the content of the DFL ([Table 27](#)), the Applicant has demonstrated that the product is labeled such that it can be used safely and effectively. The DFL adequately instructs consumers to stop use if symptoms do not improve within 7 days. Based on input from the Division of Pulmonology, Allergy, and Critical Care (DPACC) review team during team meetings (July 8, 2021 and September 22, 2021), a limitation of use for adults and children 12 years of age and older is not necessary and consistent with clinical practice. In addition, the directions for children 2 to 11 years of age instruct consumers (in bold) that children should use for the shortest amount of time and that they should talk to their doctor if their child needs to use it for 2 months a year. The proposed Nasonex 24HR Allergy DFL communicates the important information from the Rx label for safe and effective use of this product and is aligned with labeling for other OTC INCS drug products.

Table 27. Proposed Nasonex 24HR Allergy Drug Facts Label

(b) (4)

B. Principal Display Panel

The importance of the principal display panel (PDP) is that it, according to 21 CFR 201.60, is the part of the label most likely to be displayed, presented, shown or examined under customary conditions of display for retail sale. We conclude that consumers are given appropriate information on the PDP towards making a decision whether to self-select this product.

The PDP components of the OTC proposed label that required substantive changes to what the Applicant proposed included increasing the size and prominence of the statement of identity (SOI) and associated asterisked statement, which are now acceptable. In addition, we recommended revision of the SOI to “Mometasone furoate, 50 mcg/spray allergy symptom reliever (glucocorticoid)* nasal spray” so that the dosage form would be at the end. There is currently no United States Pharmacopeia (USP) monograph for mometasone furoate nasal spray. However, the Applicant declined to revise. The SOI language originally proposed “Mometasone furoate nasal spray, 50 mcg/spray allergy symptom reliever (glucocorticoid)*” is consistent with the SOI labeling for other intranasal glucocorticoid drug products in this product class. Therefore, this is acceptable.

C. Other Labeling Outside DFL and PDP (May Include Side or Top Carton Panels, Consumer Information Leaflet, Website, or Coupons if Applicable)

The only substantive changes to what the Applicant proposed in their original consumer information leaflet (CIL) was the addition of the discard information (“Discard 75 days after first use of the product”) to match language under the “Other information” heading of the DFL. The discard date of 75 days was deemed acceptable by the chemistry, manufacturing, and controls (CMC) review team based on the Microbiology review of the extended AET study. This is acceptable. Another substantive change was the addition of the statement “NOTE: There is enough medicine in the bottle to allow for priming sprays plus the number of sprays labeled on the bottle” to the consumer information leaflet under the heading “Prime.” The review team determined at the wrap up meeting that this information should be emphasized because INCS products in this category notify consumers that there is enough medication in the bottle to allow for priming sprays. This is acceptable. The Applicant initially included (b) (4)

(b) (4). This is acceptable.

21.4. Medication Error Prevention

The Division of Medication Error Prevention and Analysis 2 (DMEPA 2) reviewed the proposed Nasonex 24HR Allergy container labels, carton labeling, and CIL for areas of vulnerability that may lead to medication errors.

The proposed Nasonex 24HR Allergy (b) (4) container labels, carton labeling, and CIL are consistent with the information contained in the prescription Prescribing Information and Instructions for Use 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

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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 the Applicant submitted and OPQ confirmed.

21.5. Outstanding Items To Be Addressed During Label Negotiations

If there are any minor format requirements regarding the proposed OTC labels which still need to be addressed with the Applicant to determine whether all the proposed labeling meets all applicable labeling regulations, these may not be finalized until close to the end of the review cycle. The Labeling Review will be filed in DARRTS and any Addendum reviews will be completed when labeling negotiations are finalized.

22. Postmarketing Requirements and Commitments

None.

23. Financial Disclosure

No financial disclosures were made for this partial Rx-to-OTC switch, as no new studies were performed.

24. References

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25. Review Team

Table 28. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Sherry Stewart, PharmD, Office of Regulatory Operations/Division of Regulatory Operations for Nonprescription Drugs Phong Pham, PharmD, MBA Office of Regulatory Operations/Division of Regulatory Operations for Nonprescription Drugs
Chief, Project Management Staff	CAPT Dan Brum, PharmD, MBA, RAC, Office of Regulatory Operations/Division of Regulatory Operations for Nonprescription Drugs
Nonclinical Reviewer	Donald Charles Thompson, RPh, PhD, Office of Nonprescription Drugs
Nonclinical Team Leader	Jane J. Sohn, PhD, Office of Nonprescription Drugs
Office of Clinical Pharmacology Reviewer(s)	Suneet Shukla, PhD, Office of Clinical Pharmacology
Office of Clinical Pharmacology Team Leader(s)	Yunzhao Ren, MD, PhD, Office of Clinical Pharmacology
DPACC Clinical Reviewer	Jennifer Lan, MD, Division of Pulmonology, Allergy and Critical Care Products
DPACC Clinical Team Leader	Miya Paterniti, MD, Division of Pulmonology, Allergy and Critical Care Products
DPACC Division Director	Sally Seymour, MD, Division of Pulmonology, Allergy and Critical Care Products
Interdisciplinary Scientist (IDS)	Teegan Dellibovi-Ragheb, PhD, Division of Nonprescription Drugs I
IDS Team Leader	Sergio Coelho, PhD, Division of Nonprescription Drugs I
Medical Editor Lead	Mei-Hsun Lu
Cross-Disciplinary Team Leader	Martha Lenhart, MD, Division of Nonprescription Drugs I
Division Director (pharm/tox)	N/A
Division Director (OCP)	N/A
Division Director (OB)	N/A
Division Director (clinical)	Nushin Todd, MD, PhD, Division of Nonprescription Drugs I
Office Director (or designated signatory authority)	N/A

Abbreviations: DPACC, Division of Pulmonology, Allergy, and Critical Care; OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 29. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Swapan De, PhD, Quality Assessment Lead, Office of Pharmaceutical Quality (OPQ), Office of New Drug Products, Division of New Drug Products II, Branch VI
OPQ Regulatory Business Process Manager	CDR Teshara Bouie, MSA, OTR/L, RAC, PMP Senior Regulatory Business Process Manager Office of Program and Regulatory Operations Office of Pharmaceutical Quality
Microbiology Primary Rev.	Yan Zheng, Ph.D., Senior Pharmaceutical Quality Assessor, Office of Pharmaceutical Quality, Division of Microbiology Assessment II, Branch 4
Microbiology Secondary Rev.	Jesse Wells, Ph.D., Senior Pharmaceutical Quality Assessor, Office of Pharmaceutical Quality, Division of Microbiology Assessment II, Branch 4
OPMA Reviewer	Wenchun Feng, Ph.D., Staff Fellow, Office of Pharmaceutical Quality (OPQ), Office of Pharmaceutical Manufacturing Assessment (OPMA)
OPMA Team Leader	Sudipan Karmakar, Ph.D., Senior Pharmaceutical Quality Assessor (SPQA), Office of Pharmaceutical Quality (OPQ), Office of Pharmaceutical Manufacturing Assessment (OPMA)/ Division of Pharmaceutical Manufacturing Assessment III (DPMA-III)/PMB-9
Biopharmaceutics Primary Rev.	Rebecca Moody, Ph.D., Staff Fellow, Office of Pharmaceutical Quality (OPQ), Office of New Drug Products, Division of Biopharmaceutics – Branch III
Biopharmaceutics Secondary Rev.	Kimberly Raines, Ph.D., Branch Chief, Office of Pharmaceutical Quality (OPQ), Office of New Drug Products, Division of Biopharmaceutics – Branch III
OSE/Regulatory Business Project Manager	LCDR Abiola Olagundoye-Alawode, PharmD, MS, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE) Project Management Staff
OSE/Regulatory Business Project Manager Team Leader	Ameet Joshi, PharmD, Team Lead, Office of Surveillance and Epidemiology (OSE) Project Management Staff
OSE/DMEPA	Grace Jones, PharmD, Safety Evaluator, Office of Surveillance and Epidemiology, Office of Medication Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
OSE/DMEPA Team Leader	Janine Stewart, PharmD, Safety Evaluator Team Leader, Office of Surveillance and Epidemiology, Office of Medication Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
OSE/DPV	Allison Lardieri, PharmD, BCPPS, Safety Evaluator, Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigilance
OSE/DPV Team Leader	Lynda McCulley, PharmD, BCPS, Safety Evaluator, Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigilance

Abbreviations: OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis

Table 30. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Signatory Authority	Signature: {See appended electronic signature page}		
Clinical	Nushin Todd	OND/ONPD/DNPD I	Section I (1), ☐ Authored ☐ Contributed ☒ Approved

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Martha Lenhart	OND/ONPD/DNPD I	Sections I (1, 2), II (3, 4, 6, 7, 8, 10, 11), III (12, 21.5) ☒ Authored ☒ Contributed ☐ Approved
Cross-Disciplinary Team Lead	Signature: {See appended electronic signature page}		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Regulatory Project Mangement	Sherry Stewart	ORO/DRO-NPD	Section III (12) ☐ Authored ☐ Contributed ☒ Approved
Regulatory Project Manager	Signature: Sherry A. Stewart -S Digitally signed by Sherry A. Stewart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000591369, cn=Sherry A. Stewart -S Date: 2022.03.16 11:41:20 -04'00'		
Regulatory Project Management	Phong Pham	ORO/DRO-NPD	Section III (12) ☒ Authored ☐ Contributed ☐ Approved
Regulatory Project Manager	Signature: Phong T. Pham -S Digitally signed by Phong T. Pham -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Phong T. Pham -S, 0.9.2342.19200300.100.1.1=2003169485 Date: 2022.03.03 11:28:00 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Regulatory Project Management	Dan Brum	ORO/DRO-NPD	Section III (12) ☐ Authored ☐ Contributed ☒ Approved
Chief, Project Management Staff	Signature: Daniel Brum Digitally signed by Daniel Brum DN: cn=Daniel Brum, o=Office of New Drugs, ou=Division of Nonprescription Drug Products, email=dan.brum@fda.hhs.gov, c=US Date: 2022.03.14 15:34:17 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Donald Charles Thompson	OND/ONPD	Sections II (5,7,8), III (13) ☒ Authored ☒ Contributed ☒ Approved
Reviewer	Signature: D Charles Thompson -S Digitally signed by D Charles Thompson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300161935, cn=D Charles Thompson -S Date: 2022.03.14 11:49:42 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Jane Sohn	OND/ONPD	Sections II (5,7,8), III (13) ☒ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Jane J. Sohn -S Digitally signed by Jane J. Sohn -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jane J. Sohn -S, 0.9.2342.19200300.100.1.1=0012161667 Date: 2022.03.14 13:09:26 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Suneet Shukla	OND/OCP	Sections II (5, 8, 14) ☒ Authored ☒ Contributed ☒ Approved
Reviewer	Signature: Suneet Shukla -S Digitally signed by Suneet Shukla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suneet Shukla -S, 0.9.2342.19200300.100.1.1=0011353819 Date: 2022.03.14 14:05:12 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Yunzhao Ren	OND/OCP	Sections II (5, 8, 14) ☒ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Yunzhao Ren -S Digitally signed by Yunzhao Ren -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yunzhao Ren -S, 0.9.2342.19200300.100.1.1=2000971048 Date: 2022.03.14 14:15:48 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Jennifer Lan	OND/DPACC	Section II (2, 3, 4, 6, 7, 8) ☒ Authored ☐ Contributed ☐ Approved
Reviewer	Signature: Jennifer P. Lan -S Digitally signed by Jennifer P. Lan - Date: 2022.03.14 15:17:27 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Miya Paterniti	OND/DPACC	Section II (2, 3, 4, 6, 7, 8) ☐ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Miya Paterniti -S Digitally signed by Miya Paterniti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Miya Paterniti -S, 0.9.2342.19200300.100.1.1=0010923598 Date: 2022.03.15 09:33:06 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Sally Seymour	OND/DPACC	Section II (2, 3, 4, 6, 7, 8) ☐ Authored ☐ Contributed ☒ Approved
Division Director	Signature: Sally M. Seymour -S Digitally signed by Sally M. Seymour -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222097, cn=Sally M. Seymour - S Date: 2022.03.04 08:35:04 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Interdisciplinary Scientist	Teegan Dellibovi-Ragheb	OND/ONPD/DNPD I	Section III (21) ☐ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Teegan A. Dellibovi-ragheb -S Digitally signed by Teegan A. Dellibovi-ragheb -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001529238, cn=Teegan A. Dellibovi- ragheb -S Date: 2022.03.03 13:26:08 -05'00'		

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Nasonex 24HR Allergy (mometasone furoate monohydrate) nasal spray, 50 mcg/spray

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Interdisciplinary Scientist	Sergio Coelho	OND/ONPD/DNPD I	Section III (21) ☒ Authored ☐ Contributed ☒ Approved
Team Leader	Digitally signed by Sergio G. Coelho -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0012323503, cn=Sergio G. Coelho - S Date: 2022.03.15 10:24:00 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Product Quality	Swapan De	OPQ/ONDP/DNDP II, Branch VI	Section II (9), III (14) ☒ Authored ☐ Contributed ☒ Approved
Assessment Lead	Digitally signed by Swapan K. De -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Swapan K. De -S, 0.9.2342.19200300.100.1.1=1300132497 Date: 2022.03.15 10:38:18 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Product Quality	Teshara Bouie	OPQ/ONDP/DNDP II, Branch VI	Section II (9) ☐ Authored ☐ Contributed ☒ Approved
Regulatory Project Manager	Digitally signed by Teshara G. Bouie -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300229648, cn=Teshara G. Bouie -S Date: 2022.03.15 11:09:28 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Microbiology	Yan Zheng	OPQ/OPMA/DMA II, Branch 4	Section II (9) ☐ Authored ☒ Contributed ☒ Approved
Primary Reviewer	Digitally signed by Yan Zheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yan Zheng -S, 0.9.2342.19200300.100.1.1=2001873749 Date: 2022.03.16 09:48:52 -04'00'		

NDA 215712

Nasonex 24HR Allergy (mometasone furoate monohydrate) nasal spray, 50 mcg/spray

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Microbiology	Jesse Wells	OPQ/OPMA/DMA II, Branch 4	Section II (9) ☐ Authored ☐ Contributed ☒ Approved
Secondary Reviewer	Signature: Jesse Wells -S Digitally signed by Jesse Wells -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jesse Wells -S, 0.9.2342.19200300.100.1.1=0012236983 Date: 2022.03.15 13:50:18 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
OPMA	Wenchun Feng	OPQ/OPMA/DPM3	Section II (9) ☐ Authored ☒ Contributed ☒ Approved
Primary Reviewer	Signature: Wenchun Feng -S Digitally signed by Wenchun Feng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wenchun Feng -S, 0.9.2342.19200300.100.1.1=2002424534 Date: 2022.03.15 12:16:02 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
OPMA	Sudipan Karmakar	OPQ/OPMA/DPM3/PMB- 9	Section II (9) ☐ Authored ☒ Contributed ☒ Approved
Secondary Reviewer	Signature: Sudipan Karmakar -S Digitally signed by Sudipan Karmakar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000576474, cn=Sudipan Karmakar -S Date: 2022.03.16 10:47:13 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Biopharmaceutics	Rebecca Moody	OPQ/ONDP/DB	Section II (9), III (14) ☐ Authored ☒ Contributed ☒ Approved
Primary Reviewer	Signature: Rebecca R. Moody -S Digitally signed by Rebecca R. Moody -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003162748, cn=Rebecca R. Moody -S Date: 2022.03.16 08:08:43 -04'00'		

NDA 215712

Nasonex 24HR Allergy (mometasone furoate monohydrate) nasal spray, 50 mcg/spray

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Biopharmaceutics	Kim Raines	OPQ/ONDP/DB	Section II (9), III (14) ☐ Authored ☒ Contributed ☒ Approved
Branch Chief	Signature: Kimberly Raines -S Digitally signed by Kimberly Raines -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000629012, cn=Kimberly Raines -S Date: 2022.03.16 09:02:59 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
OSE	Abiola Olagundoye	OSE/PMS	Section II (7.6, 9) ☐ Authored ☐ Contributed ☒ Approved
Regulatory Project Manager	Signature: Abiola Olagundoye-alawode -S Digitally signed by Abiola Olagundoye-alawode -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000631675, cn=Abiola Olagundoye-alawode -S Date: 2022.03.16 10:38:27 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
OSE	Ameet Joshi	OSE/PMS	Section II (7.6, 9) ☐ Authored ☐ Contributed ☒ Approved
Team Leader	Signature: Ameet C. Joshi -S Digitally signed by Ameet C. Joshi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ameet C. Joshi -S, 0.9.2342.19200300.100.1.1=2002104886 Date: 2022.03.16 10:04:04 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
OSE/DMEPA 2	Grace Jones	OSE/OMEPRM/DMEPA	Section III (21.5) ☐ Authored ☒ Contributed ☒ Approved
Reviewer	Signature: Grace P. Jones -S Digitally signed by Grace P. Jones -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Grace P. Jones -S, 0.9.2342.19200300.100.1.1=2001398923 Date: 2022.03.14 14:34:42 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
OSE/DMEPA 2	Janine Stewart	OSE/OMEPRM/DMEPA	Section III (21.5) ☐ Authored ☐ Contributed ☒ Approved
Team Leader	Signature: Grace P. Jones -S Digitally signed by Grace P. Jones -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Grace P. Jones -S, 0.9.2342.19200300.100.1.1=2001398923 Date: 2022.03.14 14:35:37 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
OSE/DPV	Allison Lardieri	OSE/OPE/DPV	Section II (7.6) ☐ Authored ☒ Contributed ☒ Approved
Reviewer	Signature: Allison B. Lardieri -S Digitally signed by Allison B. Lardieri -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002382370, cn=Allison B. Lardieri -S Date: 2022.03.14 12:25:19 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
OSE/DPV	Lynda McCulley	OSE/OPE/DPV	Section II (7.6) ☐ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Lynda V. Mcculley -S Digitally signed by Lynda V. Mcculley -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001302577, cn=Lynda V. Mcculley -S Date: 2022.03.14 21:35:19 -04'00'		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/

PHONG T PHAM
03/17/2022 11:26:58 AM

MARTHA K LENHART
03/17/2022 11:47:11 AM

NUSHIN F TODD
03/17/2022 11:48:54 AM