CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202813Orig1s000

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: NDA 202,813 (Qnasl [Beclomethasone Propionate HFA 134a] Nasal Spray)
Submissions dated May 24, 2011 and October 27, 2011, respectively

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
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Division of Pulmonary, Allergy, and Rheumatology Products

DATE: February 17, 2012

I concur with the conclusions and recommendations of Dr. Luqi Pei's Review dated February 2, 2012. The review recommends approval of the application from the nonclinical perspective.

The sponsor has proposed to register Beclomethasone Propionate HFA 134a nasal spray as a therapy for seasonal and perennial allergic rhinitis in patients 12 years of age and older. This will be the second HFA-based nasal spray. Beclomethasone Propionate HFA 134a nasal spray uses exactly the same formulation and canisters as QVAR Inhalation Aerosol although the spray caps differ slightly.

The formulation of the to-be-marketed product contains (b) (4) beclomethasone dipropionate (BDP), (b) (4) dehydrated ethanol, and (b) (4) HFA134a. The drug product is formulated to deliver per actuation, 80 mcg (ex-actuator) or 100 mcg (ex-valve) of BDP. The total daily dose of BDP is 320 µg. The sponsor also conducted nonclinical studies in support of the formulation (i.e., 90-day nose-only inhalation toxicity study in rats, Study number #0792SR0390; BDP in (b) (4) Ethanol and (b) (4) 1,1,1,2-tetrafluoroethane). There was no evidence of local toxicity in the nasal cavity. Ethanol and HFA134a were also used at comparable concentrations in Ciclesonide HFA nasal spray (NDA 202,129) although total daily exposures were different. See Dr. Pei's Review for further details.

There were no issues for impurities, extractables, and leachables given that the formulation is identical to QVAR Inhalation Aerosol.

Dr. Pei's Review makes recommendations for changes in the product labeling in Sections 8.1, 10, and 13.1.

There are no outstanding PharmTox issues.

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/s/

TIMOTHY W ROBISON
02/17/2012

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 202,813
Supporting document/s:	Sequences 0000 and 0010
Applicant's letter date:	May 17, 2011 (original submission) and October 27, 2011 (the latest proposed labeling)
CDER stamp date:	May 18 and October 27, 2011
Product:	Qnasl (Beclomethasone Propionate HFA 134a) Nasal Spray
Indication:	Rhinitis (Seasonal and Perennial Allergic)
Applicant:	Teva Pharmaceuticals
Review Division:	Pulmonary, Allergy and Rheumatology
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.,
Project Manager:	Carol Hill

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

Teva filed NDA 202,813 under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. NDA 202,813 proposes to market beclomethasone dipropionate (BDP) nasal spray (a HFA 134a formulation) for seasonal and perennial allergic rhinitis in patients 12 years of age and older. The application is referencing NDA 20-911 (Qvar Inhalation Aerosol) for its nonclinical support. NDAs 202,813 and 20-911 use exactly the same formulation and canisters, although the spray caps differ slightly in mechanics. Teva is the owner of both NDAs. NDA 20-911 was also a 505(b)(2) application that relied on other NDAs for its approval. See Section 2.7 Regulatory Background for the additional information on these NDAs.

The current submission contained no new nonclinical data. The submission contained all nonclinical data of BDP that had been submitted previously in NDA 20-911. Dr. Timothy McGovern completed review of these studies in the original NDA review and the labeling review of Qvar on May 6, 1999 and September 12, 2000 in NDA 20-911, respectively. There is no need to review the previously reviewed study reports. The main task of the nonclinical review of the current application is a review of the appropriate labeling sections.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted in the current application. The following summary is based on the nonclinical review completed by Dr. Timothy McGovern on May 6, 1999 in NDA 20-911 (Qvar Inhalation aerosol) and the Qvar label approved on August 18, 2008.

Pharmacology: Beclomethasone dipropionate is a corticosteroid. The precise mechanisms of corticosteroid action in rhinitis are unknown. Inflammation is recognized as an important component in the pathogenesis of allergic rhinitis. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the allergic inflammation.

Pharmacokinetic and Toxicokinetics: Oral bioavailability of BDP was generally low. BDP undergoes rapid and extensive conversion to beclomethasone-17-monopropionate (17-BMP) during absorption when given by inhalation. About 15% of the inhaled dose was present in the respiratory tract in dogs. BDP is metabolized by P450 enzymes to beclomethasone-17-monopropionate (17-BMP) and beclomethasone. Lung slices metabolize BDP rapidly to 17-BMP and more slowly to alcohol beclomethasone. 17-BMP is the most active metabolite. The principle route of excretion is the feces for all routes of administration. Plasma protein binding ranged from 87% - 96% in animals and humans.

Toxicology: BDP possesses a toxicological profile typical of corticosteroids. Major toxicity observed in animal studies include immunosuppression, decreases in body

weights, liver glycogen depression, increases in liver serum functional enzyme levels, thymus involution, adrenal atrophy, and serum potassium elevation. BDP is non-genotoxic and non-carcinogenic but teratogenic and may adversely affect fertility.

Genetic toxicity: Beclomethasone dipropionate did not induce gene mutation in the bacterial cells or mammalian Chinese Hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

Carcinogenicity: BDP is non-carcinogenic in rats. The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of carcinogenicity in this study at the highest dose.

Impairment on Fertility: In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day. Impairment of fertility, as evidence by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day. No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg.

Teratogenic Effects: BDP is teratogenic and embryocidal in the mouse and rabbits when given by subcutaneous injection at doses of 0.1 and 0.025 mg/kg/day in mice and rabbits, respectively. No teratogenicity or embryocidal effects were seen in rats when exposed to an inhalation dose of 15 mg/kg/day.

1.3 Recommendations

1.3.1 Approvability

Approval of the application is recommended from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The following text is recommended for Sections 8.1, 10 and 13.1 of the Qnasl product label. See the Labeling Review section (p10 – 16) for discussions about the labeling recommendations.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women treated with QNASL Nasal Aerosol. BDP was teratogenic and embryocidal in the mouse and rabbit although these effects were not observed in rats. QNASL Nasal Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in

pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

(b) (4) (subcutaneous) BDP was teratogenic and embryocidal in the mouse and rabbit at doses approximately twice the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mg/m^2 basis at maternal doses of 0.1 and 0.025 mg/kg/day in mice and rabbits, respectively). No teratogenicity or embryocidal effects were seen in rats at approximately 460 times the MRHDID in adults (on a mg/m^2 basis at a maternal inhalation dose of 15 mg/kg/day).

Non-teratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism *[see **Warnings and Precautions (5.3)**]*. There are no data available on the effects of acute or chronic overdosage with QNASL Nasal Aerosol.

12.1 Mechanism of Action

BDP is a prodrug that is (b) (4) 17 monopropionate (b) (4) The precise mechanism through which BDP affects rhinitis symptoms is unknown. Corticosteroids have been shown to have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and the release of inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines).

Beclomethasone 17 monopropionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of BDP. The clinical significance of these findings is unknown.

13 NONCLINCIAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenicity of BDP was evaluated in rats that were exposed for a total of 95 weeks: 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. In this trial, there was no evidence of carcinogenicity at the highest dose: approximately 70 times the maximum recommended human daily intranasal dose (MRHDID) in adults on a mg/m^2 basis.

BDP did not induce gene mutation in bacterial cells or mammalian Chinese Hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

In rats, BDP caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 490 times the MRHDID in adults on a mg/m^2 basis). There was no significant effect of BDP on fertility in rats at oral dose of 1.6 mg/kg/day (approximately 50 times the MRHDID in adults on a mg/m^2 basis). Inhibition of the estrus cycles in dogs was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 50 times the MRHDID in adults on a mg/m^2 basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure at an estimated inhalation dose of 0.33 mg/kg/day (approximately 35 times the MRHDID in adults on a mg/m^2 basis).

2 Drug Information

2.1 Drug

CAS Registry Number: 5534-09-8

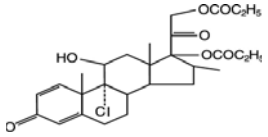
Generic Name: Beclomethasone dipropionate nasal spray

Code Name: FDA code: 5B307S63B2; ATC codes: A07EA07, D07AC15, R01AD01, and R03BA01

Chemical Name: 9-chloro-11ß,17, 21-trihydroxy-16ßmethylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Molecular Formula/Molecular Weight: $C_{38}H_{37}ClO_7$, 521.1

Structure or Biochemical Description:



Pharmacologic Class: Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDAs 17-573, 18-153, 18-521, 18-584, 19-389, 19-589, 20-469, 20-286 and 20-911. See Table 1 for information on drug name, indication and approval dates.

IND 101,639, (b) (4), (b) (4), (b) (4)

DMF (b) (4)

2.3 Drug Formulation

This nasal spray formulation consists of (b) (4) beclomethasone dipropionate, (b) (4) dehydrated ethanol, and (b) (4) HFA134a. Each actuation releases 100 and 80 μg of BDP from the valve and the mouth piece, respectively.

2.4 Comments on Novel Excipients

None. The formulation uses alcohol (b) (4) and HFA 134a as the excipient. Both ingredients at the same concentrations have been approved for intranasal use in NDA 202,129. The sponsor also conducted nonclinical studies in support of the formulation.

2.5 Comments on Impurities/Degradants of Concern

None. This drug product will use the same formulation as Qvar Inhalation Aerosol (NDA 20-911, approved on). Qvar is a currently marketed product. Any impurities present in the to-be-marketed products have been considered acceptable previously in the Qvar application.

2.6 Proposed Clinical Population and Dosing Regimen

(Qnasl) Beclomethasone Dipropionate Nasal Aerosol will be indicated for the treatment of (b) (4) seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The recommended dose of BDP dose is 320 μg/day (80 mcg/actuation, 2 actuations/nostril).

2.7 Regulatory Background

Teva filed a new drug application (NDA 202,813) for beclomethasone dipropionate nasal spray under the 505(b)(2) provision of the Federal Food, Drug, and Cosmetic Act. NDA 202,813 proposed to market this nasal spray for seasonal and perennial allergic rhinitis in patients 12 years and older. NDA 202,813 listed NDA 20-911 (Qvar inhalation aerosol) as its reference. Teva is the owner of both the current (NDA 202,813) and the reference (Qvar, NDA 20-911) applications.

NDA 20-911 (Qvar) was also a 505(b)(2) application that relied on other applications for the nonclinical support. Table 1 lists BDP products that Qvar used as its references, according to the nonclinical review completed by Dr. Timothy McGovern on May 6, 1999 in NDA 20-911. The current marketing status was based on the search results from the Agency's two electronic databases (i.e., DARRTS and Drugs@FDA) in November 2011.

Table 1: Currently Marketed and Discontinued NDAs of beclomethasone

NDA	Product	Indication	Date of Approval	Current Marketing Status
17-573	Vanceril	Asthma	3/17/1979	Discontinued
18-153	Beclovent	Asthma	9/10/1985	Discontinued
18-521	Vancenase	Rhinitis	11/02/1985	Discontinued
18-584	Beconase	Rhinitis	9/30/1981	Discontinued
19-389	Beconase AQ	Rhinitis	7/27/1987	On the market
19-589	Vancenase AQ	Rhinitis	6/16/2006	Discontinued
20-469	Vancenase AQ	Rhinitis	6/16/2006	Discontinued
20-486	Vanceril DS	Asthma	12/24/1996	Discontinued
20-911	Qvar Inh. Aeros.	Asthma	9/15/2000	On the market

Beclomethasone dipropionate (BDP) is the active pharmaceutical ingredient of nine approved products indicated for respiratory diseases. The first drugs indicated for asthma (Vanceril) and rhinitis (Beclonase) were approved in 1979 and 1981, respectively. However, only two products (Beconase AQ and Qvar) remain on the market; the remaining seven have been discontinued. Beconase AQ (NDA 19-389) Qvar (NDA 20-911) are indicated for rhinitis and asthma, respectively.

The BDP nasal spray of NDA 202,813 was developed under IND 101,639. Teva and DPARP had two meetings that discussed the nonclinical requirements for the BDP nasal spray program under the IND. The meetings include a pre-IND meeting held on April 2, 2008 and a pre-NDA meeting held on October 18, 2010, respectively. DPARP and Teva agreed in these meetings that no additional nonclinical studies would be needed for the BDP nasal spray program. See the minutes of the pre-IND and pre-NDA meetings for additional information.

3 Studies Submitted

3.1 Studies Reviewed

None. All nonclinical studies submitted to NDA 202,813 were previously reviewed under NDA 20-911 and other relevant NDAs.

3.2 Studies Not Reviewed

All nonclinical studies submitted to NDA 202,813. None of the nonclinical studies submitted to the NDA was reviewed because each study had been reviewed previously under NDA 20-911 and other relevant NDAs. See Previous Reviews Referenced for the reviews.

3.3 Previous Reviews Referenced

This review references to nonclinical reviews completed by Dr. Timothy McGovern on May 6, 1999 and September 12, 2000, respectively

4 Pharmacology

Not applicable because no new data were submitted.

5 Pharmacokinetics and Toxicokinetics

Not applicable because no significant, new data were submitted.

6 General Toxicology

Not applicable because no data were submitted.

7 Genetic Toxicology

Not applicable because no data were submitted.

8 Carcinogenicity

Not applicable because no data were submitted.

9 Reproductive and Developmental Toxicology

Not applicable because no data were submitted.

10 Special Toxicology Studies

None

11 Integrated Summary and Safety Evaluation

Teva has submitted adequate nonclinical information to support the safety of beclomethasone dipropionate (BDP) nasal spray (NDA 202,813). This applicant has proposed to register BDP nasal spray as a therapy for allergic rhinitis under the 505(b)(2) provision of the Food, Drug and Cosmetic Act. The Agency has approved higher BDP doses for the proposed indication in reference NDAs. The Agency has also approved the proposed formulation (HFA 134a) for asthma indication previously. The nonclinical safety of the proposed product has been established in the reference NDAs. Approval of the application is recommended from the nonclinical perspective.

Teva has proposed to market BDP HFA nasal spray for seasonal and perennial allergic rhinitis in patients 12 years and older. The maximum recommended BDP dose will be 320 μg/day (80 μg/actuation, 2 actuations/nostril/day).

NDA 202,813 references NDA 20-911 (Qvar inhalation aerosol) for the nonclinical support. Approved on September 15, 2000, NDA 20-911 was also a 505(b)(2) application. NDA 20-911 cites several other NDAs for references according to the nonclinical original NDA review completed by Dr. Timothy McGovern on May 6, 1999. See the regulatory background section (Table 1, page 6) for a list of these NDAs.

The nonclinical safety of BDP for intranasal use has been established in previous NDAs. Table 2 presents BDP doses for the current application (NDA 202,813) and the currently marketed products. The proposed BDP dose is 320 μg/day in patients 12 years of age and older. The proposed dose is smaller than what the Agency has approved for intranasal (336 μg/day) and inhalation (640 μg/day) routes of administration in reference products in the same patients populations. Because the proposed BDP dose is smaller than the approved doses in reference applications, the nonclinical safety of the proposed BDP use has been established.

Table 2: Major Characteristics of Proposed and Marketed BDP Products

NDA No.	19-389		20-911		202,813
Product Name	Beconase AQ		Qvar Inhalation Aerosol		BDP Nasal spray
Formulation	Aqueous		HFA 134a [a]		HFA 134a [a]
Approval status	Approved		Approved		Proposed
Indication	Rhinitis		Asthma		Rhinitis
Patient age (year)	5 – 11 yrs	≥ 12 yrs	5 - 11 yrs	≥ 12 yrs	≥ 12 years
MRHDD (μg/day) [b]	336	336	320	640	320

a. The vehicle consists of HFA134a and ethano (b) (4)
b. MRHD, the maximum recommended human daily doses.

The nonclinical safety of the to-be-marketed formulation has also been established. The to-be-marketed formulation consists of BDP, HFA 134a and ethanol. This formulation is identical to that of Qvar inhalation aerosol which is currently on the market. Also, the formulation was tested in a 90-day nose-only inhalation toxicity study in rats (#0792SR0390). No significant local findings were observed in the nasal cavity, according to the nonclinical review completed by Dr. Timothy McGovern on May 6, 1999 in NDA 20-911. The review states that the BDP NOAEL of the study was 4.8 μg/kg/day (pulmonary deposit). This dose corresponds to an intranasal NOAEL for ethanol of 450 μg/kg/day.[1] Furthermore, the same vehicle was used in an approved and currently marketed product (Zetonna™ Nasal Spray, NDA 202,129). The available data has established the nonclinical safety of the proposed formulation.

The above discussions indicate that the nonclinical safety of the proposed product has been established previously in the reference NDAs. Approval of the application is recommended from the nonclinical perspective, pending labeling review.

LABELING REVIEW

Edits to nonclinical sections (Sections are 8.1, 10 and 13) of the proposed label for beclomethasone dipropionate nasal spray submitted on October 27, 2011 are recommended. These edits are made to ensure that the label for the to-be-marketed product is consistent with the Division's most current practice. The edits were primarily made in two areas: dose ratios and text.

Dose Ratios: The review calculated new dose ratios between animals and humans in sections 8.1 and 13.1. The calculations were prompted by the Division policy change in body weight for adults. The Division recently decided to use a 60-kg body weight (vs. the previous 50-kg) for the adult population. The applicant used a 50-kg body weight in adults to calculate the dose ratios as the Division did previously. The review recommends revising

1 (b) (4)

dose ratios using the 60-kg body weight. Table 3 (next page) presents dose ratios to be used for the labeling of the to-be-marketed product and parameters used to derive the dose ratios.

(b) (4)

Text: Edits to the text of the proposed label were recommended. The most prominent edits were deletion of the (b) (4). Other edits included addition of a boilerplate sentence to Section 8.1 and some minor edits.

Approved labels of beclomethasone products are available. These labels, however, are not in compliance with the current product labeling rules. The currently marketed BDP products include Beconase AQ Nasal Spray (NDA 19-389, indicated for rhinitis) and Qvar inhalation Aerosols (NDA 20-911, included for asthma). Texts of the labels for Beconase AQ and Qvar vary slightly although the contents are essentially the same. See Table 4 in the Pregnancy section for the approved labels for Beconase AQ and Qvar for an example. The label for the to-be-marketed product should be compliant with the PLR format. This review uses the recently completed label for ciclesonide nasal spray (NDA 202-129) as a template.

Contents of the proposed labeling for BDP nasal spray were adapted from the Qvar (NDA 20-911) label approved on August 18, 2008. Nonclinical section of the Qvar labeling was based on Dr. Timothy McGovern's recommendations in reviews completed on September 12 and 14, 1999, respectively, in NDA 20-911. See these reviews for additional information. The following sections discuss details of edits and rationale for the recommended edits. The highlights indicate additions and strikeouts indicate deletions.

PREGNANCY

Edits were made to the proposed text of Section 8.1 Pregnancy. Briefly, dose ratios were revised; an acronym MRHDID was introduced to shorten sentences; a statement about the species difference in teratogenic effects of corticosteroid between rodents and humans was added; and the order of the text describing clinical data and the nonclinical data was rearranged. The last two points were to ensure label consistency among the recently approved corticosteroid products. The review used the recently approved Zetonna (ciclesonide) nasal spray labeling (NDA 202,129, approved on January 20, 2012) as a

template.[2] Table 4 presents the text of the pregnancy section of the currently marketed beclomethasone products.

Table 4: Pregnancy Section Marketed BDP Product Labels

Beconase AQ (NDA 19-389) Indicated for Rhinitis Approved on October 27, 2005	Qvar (NDA 20-911) Indicated for Asthma Approved on August 18, 2008
Teratogenic Effects: Pregnancy Category C Like other corticosteroids, beclomethasone dipropionate was teratogenic and embryocidal in the mouse and rabbit at a subcutaneous dose of 0.1 mg/kg in mice or 0.025 mg/kg in rabbits (approximately equal to the maximum recommended daily intranasal dose in adults on a mg/m2 basis). No teratogenicity or embryocidal effects were seen in rats when exposed to an inhalation dose of 0.1 mg/kg plus oral doses of up to 10 mg/kg per day for a combined dose of 10.1 mg/kg (approximately 240 times the maximum recommended daily intranasal dose in adults on a mg/m2 basis).	Teratogenic Effects: *Pregnancy Category C* Like other corticosteroids, parenteral (subcutaneous) beclomethasone dipropionate was teratogenic and embryocidal in the mouse and rabbit when given at a dose of 0.1 mg/kg/day in mice or at a dose of 0.025 mg/kg/day in rabbits. These doses in mice and rabbits were approximately one-half the maximum recommended daily inhalation dose in adults on a mg/m^2 basis. No teratogenicity or embryocidal effects were seen in rats when exposed to an inhalation dose of 15 mg/kg/day (approximately 190 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).
There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	There are no adequate and well controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.	**Non-teratogenic Effects:** Findings of drug-related adrenal toxicity in fetuses following administration of beclomethasone dipropionate to rats suggest that infants born of mothers receiving substantial doses of QVAR during pregnancy should be observed for adrenal suppression.

[2] Section 8.1 of the label for Zetonna (ciclesonide) nasal spray (202,129, as approved on 20-Jan-2012) reads:

"8.1 Pregnancy Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. Zetonna Nasal Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Oral administration of ciclesonide in rats at approximately 120 times the maximum recommended human daily intranasal dose (MRHDID) in adults (on mcg/m^2 basis at a maternal dose of 900 mcg/kg/day) produced no teratogenicity or other fetal effects. However, subcutaneous administration of ciclesonide in rabbits at similar to MRHDID (on a mcg/m^2 basis at a maternal dose of 5 mcg/kg/day) produced fetal toxicity. This included fetal loss, reduced fetal weight, cleft palate, skeletal abnormalities including incomplete ossifications, and skin effects. No toxicity was observed at ¼ of the MRHDID in adults (on a mcg/m^2 basis at a maternal dose of 1 mcg/kg/day).

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored."

The proposed text of Section 8.1 for the label of the to-be-marketed product is in general in agreement with the Qvar label, but based on the ciclesonide precedence (NDA 202,129). The review recommends adding the following sentences "BDP was teratogenic and embryocidal in the mouse and rabbit although these effects were not observed in rats. (b) (4) to the paragraph describing clinical experience of the BDP. Below is the text recommended for Section 8.1 Pregnancy:

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women treated with QNASL Nasal Aerosol. BDP was teratogenic and embryocidal in the mouse and rabbit although these effects were not observed in rats. QNASL Nasal Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

(b) (4) (subcutaneous) BDP was teratogenic and embryocidal in the mouse and rabbit at doses approximately twice the maximum recommended human daily intranasal dose (MRHDID) in adults (on a mg/m^2 basis at maternal doses of 0.1 and 0.025 mg/kg/day in mice and rabbits, respectively). No teratogenicity or embryocidal effects were seen in rats at approximately 460 times the MRHDID in adults (on a mg/m^2 basis at a maternal inhalation dose of 15 mg/kg/day).

(b) (4)

Non-teratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

OVERDOSAGE

Descriptions of the [redacted] in this section were removed per current policy. The clinical team recommended removing the sentence that states: [redacted] Below is the recommended text for Section 10 Overdosage:

10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism *[see **Warnings and Precautions (5.3)**]*. There are no data available on the effects of acute or chronic overdosage with QNASL Nasal Aerosol. [redacted]

MECHANISM OF ACTION

The proposed text for Section 12.1 is acceptable from the nonclinical perspective although it differs from the Beconase AQ label. Table 5 (next page) presents the text of labels for both Beconase AQ and Qvar. Beconase AQ is provided because it is a reference drug for the rhinitis indication. Qvar is presented because it another Teva-owned BDP product although it has a different indication. Below is the proposed text for Section 12.1 of the to-be-marketed product.

12.1 Mechanism of Action

BDP is a prodrug [redacted], 17 monopropionate [redacted] The precise mechanism through which BDP affects rhinitis symptoms is unknown. Corticosteroids have been shown to have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and the release of inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines).

Beclomethasone 17 monopropionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of BDP. The clinical significance of these findings is unknown.

Table 5: Mechanism of Action Section of BDP Product Labels

Beconase AQ (NDA 19-389) Indicated for Rhinitis Approved on October 27, 2005	Qvar (NDA 20-911) Indicated for Asthma Approved on August 18, 2008
Following topical administration, beclomethasone dipropionate produces anti-inflammatory and vasoconstrictor effects. The mechanisms responsible for the anti-inflammatory action of beclomethasone dipropionate are unknown. 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. The direct relationship of these findings to the effects of beclomethasone dipropionate on allergic rhinitis symptoms is not known. Biopsies of nasal mucosa obtained during clinical studies showed no histopathologic changes when beclomethasone dipropionate was administered intranasally. Beclomethasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is hydrolyzed via esterase enzymes to its active metabolite beclomethasone-17-monopropionate (B-17-MP), which has high topical anti-inflammatory activity.	Airway inflammation is known to be an important component in the pathogenesis of asthma. Inflammation occurs in both large and small airways. Corticosteroids have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and release of inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines). These anti-inflammatory actions of corticosteroids such as beclomethasone dipropionate contribute to their efficacy in asthma. Beclomethasone dipropionate is a prodrug that is rapidly activated by hydrolysis to the active monoester, 17 monopropionate (17-BMP). Beclomethasone 17 monopropionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of beclomethasone dipropionate. The clinical significance of these findings is unknown. Studies in patients with asthma have shown a favorable ratio between topical antiinflammatory activity and systemic corticosteroid effects with recommended doses of QVAR.

NONCLINICAL TOXICOLOGY

Minor edits to Section 13.1 of the proposed label were recommended. The edit include revision of dose ratios, use of MRHDID to replace the phrase maximum recommended human inhalation dose. Use of MRHDID shortens the paragraph. See below for the recommended edits.

13 NONCLINCIAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenicity of BDP was evaluated in rats that were exposed for a total of a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. In this trial, there was no evidence of carcinogenicity at the highest dose: approximately 70 times the

maximum recommended human daily intranasal dose (MRHDID) in adults on a mg/m2 basis.

BDP did not induce gene mutation in bacterial cells or mammalian Chinese Hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

In rats, BDP caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 490 times the MRHDID in adults on a mg/m^2 basis). There was no significant effect of BDP on fertility in rats at oral dose of 1.6 m/kg/day (approximately 50 times the MRHDID in adults on a mg/m^2 basis). Inhibition of the estrus cycles in dogs was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 50 times the MRHDID in adults on a mg/m^2 basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure at an estimated inhalation dose of 0.33 mg/kg/day (approximately 35 times the MRHDID in adults on a mg/m^2 basis).

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/s/

LUQI PEI
02/02/2012

TIMOTHY W ROBISON
02/02/2012
I concur

DIVISION OF PULMONARY, ALLERGY & RHEUMATOLOGY PRODUCTS

PHARMACOLOGY AND TOXICOLOGY CONSULTATION

Date:	November 10, 2011
To:	Craig Bertha, Ph.D., Senior Chemist Office of New Drug Quality Assurance /DPA I, CDER
From:	Luqi Pei, Ph.D., Senior Pharmacologist Division of Pulmonary and Allergy Products, CDER
Through:	Timothy Robison, Ph.D., Pharmacology Team Leader Division of Pulmonary and Allergy Products, CDER
Subject:	Safety Evaluations of Particulate Matter in Qnasl (NDA 202,813)

General Information

NDA/IND#:	NDA 202,813 Chemistry Consultation Review No. 1
Sponsor:	Boehringer Ingelheim, Inc.
Drug Product:	Qnasl (beclomethasone diproprionate nasal Aerosol)

Evaluation: There is no nonclinical safety concern about the proposed specifications of particulate matter (PM) in Qnasl. The PM contents of this drug product are identical to that of Qvar Inhalation Aerosol (NDA 20-911), an approved and currently marketed product. No additional nonclinical safety evaluation is needed.

Dr. Craig Bertha requested a nonclinical safety evaluation of the PM in Qnasl on November 7, 2011. Qnasl and Qvar had the same formulation and canister contents. The only difference between the two products is their aerosol generating device. This difference does not affect the PM profile because the canisters are the PM sources. Thus, the PM contents of Qnasl and Qvar were identical.

Qvar was approved on September 15, 2000 and remains on the market. The Agency determined previously that the PM specification in Qvar was acceptable. There is no need to conduct another safety evaluation of the PM in Qnasl.

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/s/

LUQI PEI
11/10/2011

TIMOTHY W ROBISON
11/10/2011
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202,813 **Applicant:** Teva **Stamp Date:** May 18, 2011

Drug Name: Beclomethasone dipropionate nasal spray **NDA/BLA Type:** Original NDA

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		Yes. The applicant resubmitted all nonclinical studies previously submitted in NDAs 20-911. There is no need to review the previously submitted and reviewed studies.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Yes but no review is needed. See comments in Item 1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. See comments in Item 1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. No additional nonclinical studies are required for the current NDA. See minutes of the 02-APR-2008 pre-IND meeting and the 18-OCT-2010 pre-NDA meeting in IND 101,639.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		x	The to-be-marketed product (beclomethasone dipropionate nasal aerosol) uses a currently marketed formulation. Qvar Inhalation Aerosol (NDA 20-911) and the to-be-marketed product use the same canister/formulation. The Agency has determined that Qvar Inhalation Aerosol is safe. No additional testing is needed.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable. See comments in Item 5.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. See comments in Items 1 and 5.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable. No studies were requested in pre-IND or pre-NDA meetings.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		The proposal labeling is in the PLR format. Its content was generally the same as that of Qvar (approved on 08-AUG-2008, NDA 20-911). Edits are needed and will be handled during the labeling review.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?	x		The drug is approved and currently marketed for the same route of the administration and same patient demographics. No abuse potential has been identified.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. There is currently no OTC nasal spays of corticosteroids.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES._____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Luqi Pei, Ph.D.	July 1, 2011
Reviewing Pharmacologist	Date
Timothy Robison, Ph.D.	July 1, 2011
Team Leader	Date

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/s/

LUQI PEI
07/01/2011

TIMOTHY W ROBISON
07/01/2011