CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202813Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 8, 2012
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 202-813
Applicant	Teva Pharmaceuticals
Date of Submission	May 24, 2011
PDUFA Goal Date	March 24, 2012
Proprietary Name / **Established (USAN) names**	QNASL Nasal Aerosol Beclomethasone dipropionate nasal aerosol
Dosage forms / Strength	Metered dose canister, 80/mcg beclomethasone dipropionate/ex-actuator (100 mcg ex-valve) per actuation
Proposed Indication(s)	(b) (4)
Recommended Action:	*Approval*

1. Introduction

Teva Pharmaceuticals submitted this 505(b)(2) new drug application for use of QNASL Nasal Aerosol [budesonide dipropionate nasal aerosol (BDP), HFA propelled] on May 24, 2011. The BDP-containing products Beconase AQ (NDA 19-389) and Vanceril Inhalation Aerosol (NDA 20-486) are listed as reference products. Vanceril has been withdrawn from the market as a result of the phase-out of CFC-propelled inhaler products and not for reasons of safety or efficacy. Teva is also cross-referencing their own product, QVAR Inhalation Aerosol (NDA 20-911), which was also approved via the 505(b)2 pathway and referenced Vanceril. The proposed indication is (b) (4) The proposed dose is 2 actuations in each nostril once daily (50 mcg ex actuator per actuation). The drug product is the same as that of a marketed BDP oral inhalation product (QVAR) indicated for the treatment of patients with asthma with the exception that a nasal actuator replaces the oral inhalation actuator on the drug canister. The application is based on clinical efficacy and safety studies in patients with SAR and PAR. This review will provide an overview of the application, with a focus on the clinical efficacy and safety studies used to support the proposed indication. The PDUFA date for this application is March 24, 2012.

2. Background

There are many drug products approved to treat patients with allergic rhinitis. These include systemic and oral antihistamines, the oral leukotriene antagonist montelukast, and intranasal corticosteroids. Table 1 lists the various nasal corticosteroid products marketed for the treatment of allergic rhinitis in the United States.

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Table 1: Corticosteroid nasal sprays approved for allergic rhinitis

Drug	Trade name	Formulation	Indication; age (year)
Budesonide	Rhinocort Aqua	Microcrystalline aqueous suspension in manual pump	SAR and PAR; ≥6
Beclomethasone	Beconase AQ	Microcrystalline aqueous suspension in manual pump	SAR, PAR, and vasomotor rhinitis; ≥6
Triamcinolone	Nasacort AQ	Microcrystalline aqueous suspension in manual pump	SAR and PAR; ≥2
Flunisolide	Nasarel	Aqueous solution in metered dose manual pump	SAR and PAR; ≥6
Fluticasone propionate	Flonase	Microfine aqueous suspension in metering atomizing spray pump	SAR and PAR; ≥4
Fluticasone furoate	Veramyst	Microcrystalline aqueous suspension in metering atomizing spray pump	SAR and PAR; ≥2
Ciclesonide	Omnaris Zetonna	Microcrystalline aqueous suspension in manual pump Nasal Aerosol solution	SAR ≥6; PAR ≥12 SAR and PAR; ≥12
Mometasone	Nasonex	Aqueous suspension in manual pump	SAR and PAR; ≥2

Budesonide dipropionate is currently marketed in the United States as an aqueous suspension for intranasal administration (Beconase AQ) and as an HFA-propelled inhalation aerosol solution delivered via a metered dose inhaler for the treatment of asthma (QVAR). The proposed QNASL Nasal Aerosol utilizes the same drug substance and canister as the QVAR asthma product coupled with a nasal actuator to allow for nasal administration. Budesonide dipropionate was previously available as a CFC-based nasal aerosol intranasal product but is no longer marketed due to the phase-out of CFC-based propellants. Currently, one other HFA-propelled nasal aerosol corticosteroid in solution is approved for use in the United States, Zetonna Nasal Aerosol (ciclesonide).

QNASL Nasal Aerosol was developed under IND# 101,639 which was opened on January 20, 2009. Milestone meetings included Pre-IND, End-of-Phase 2, and Pre-NDA meetings during which the following discussion/agreements transpired:

- No additional nonclinical toxicology studies were required.
- Comment by the Division that the efficacy measures in the long term safety study are primarily for compliance monitoring.
- The Division voiced concern that since BDP (QVAR) is dosed twice daily for the asthma indication that once daily dosing for AR may not be the most appropriate dosing interval.
- Agreement that a long term safety study of 52 weeks' duration will include a subset of approximately 250 patients assessed for ocular safety Including LOCS III and IOP evaluation.
- Statement that HPA-axis study should include about 40 patients 12 years of age and older per arm.
- Agreement that information from QVAR, NDA 20-911, may be cross referenced.
- At a Pre-NDA meeting Teva proposed the indication for BDP Nasal Aerosol as (b) (4) [redacted] of nasal symptoms (b) (4) seasonal (b) (4) and perennial allergic rhinitis in adult/adolescent patients 12 years of age and older." The Division stated that "the general outline of your program is reasonable to support an indication for allergic rhinitis. Whether the data from your clinical program is adequate to support this indication is a review issue."

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3. CMC/Device

The drug substance beclomethasone dipropionate is a well-known glucocorticoid compound that has been previously been used as the active ingredient for several marketed nasal and orally administered spray and aerosol products for use in patients with allergic rhinitis and asthma. The drug product QNASL (beclomethasone dipropionate) is a nonsterile solution nasal aerosol propelled with HFA-134a propellant and includes (b) (4) ethanol (b) (4) for the beclomethasone dipropionate (BDP). It is essentially the same product as the currently marketed BDP product for asthma, QVAR (NDA 20911), with the exception that the QVAR oral actuator is replaced with a smaller nasal actuator with a (b) (4) exit orifice. It is designed to deliver 120 actuations and has a target fill of (b) (4) Each actuation delivers 80 mcg ex actuator (100 mcg ex-valve) of drug in 59 mg of formulation. The nasal actuator incorporates a counter which counts down from 120 to 0 after four priming actuations (initial counter reading 124). The drug product filled canisters are manufactured using the same formulation, manufacturing process, and at the same facility, with the same canister and valve as for QVAR.

The design of the actuator device was changed twice during development, (b) (4) Adequate bridging data have been supplied to support the changes in actuator design. Actuator robustness was also tested and was judged as acceptable as excessive and dropping had no effect on in vitro dose delivery.

The drug substance is manufactured by Teva Parenteral Medicines, Inc. (previously Sicor). Manufacture of the bulk filled canisters and microbiological testing is performed by 3M Drug Delivery Systems, Northridge, CA. Assembly of the drug product, labeling, and packaging are done by Teva Pharmaceuticals, Waterford, Ireland. All manufacturing and testing facilities associated with this application have acceptable EER status.

The proposed (b) (4) expiry period is supported by stability data.

4. Nonclinical Pharmacology/Toxicology

A full toxicology assessment for BDP was submitted previously and reviewed under the NDA for QVAR Inhalation Aerosol (# 20911) and was found to be acceptable. QVAR was also a 505(b)2 submission and referenced several other BDP products of which 2 (Beconase AQ and QVAR) continue to be marketed. QVAR and QNASL use exactly the same formulation and canisters, although the spray caps differ slightly. In studies conducted previously to support the formulation and nasal route of administration (90-day nose-only inhalation toxicity study in rats with BDP in (b) (4) Ethanol and (b) (4) 1,1,1,2- tetrafluoroethane) there was no evidence of local toxicity in the nasal cavity.

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5. Clinical Pharmacology/Biopharmaceutics

The general clinical pharmacology and biopharmaceutical considerations for BDP were addressed in the original NDA for QVAR Inhalation Aerosol. Beclomethasone dipropionate (BDP) is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. It is a pro-drug that is rapidly activated by in vivo hydrolysis to the active monoester, 17 BMP monopropionate (17-BMP) which binds to the human glucocorticoid receptor (GR). The Applicant reports that the binding affinity of 17-BMP for the human GR is approximately 25 times that of BDP, 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, and 1.5 times that of budesonide.

To support of the QNASL Nasal Aerosol NDA, data from two clinical pharmacology studies were submitted. The goals of the 2 clinical pharmacology studies was to compare the relative bioavailability of the proposed QNASL Nasal Aerosol product following intranasal administration to that for QVAR inhalation Aerosol following oral inhalation and to characterize the effects of intranasal administration of the QNASL on hypothalamic-pituitary-adrenal (HPA)-axis function.

The relative bioavailability study was a single-dose randomized, open-label, 3-period crossover PK study in male or female healthy volunteers who received intranasal administration of QNASL at doses of 80 mcg and 320 mcg and BDP HFA 320 mcg (QVAR) by oral inhalation. The study was designed to assess whether the systemic exposure of intranasally administered BDP would be less as compared to that of approved orally inhaled BDP (QVAR) thus bridging the systemic safety of QVAR to the proposed QNASL Nasal Aerosol product. Both BDP and the active metabolite, 17-BMP, levels were measured. The results demonstrated that systemic exposure of BDP and 17-BMP for intranasally delivered BDP (QNASL) was approximately 25% that of the systemic exposure when administered by oral inhalation (QVAR).

Teva conducted a conducted a 6-week HPA axis assessment study in patients 12-45 years of age with PAR. The study arms included a QNASL Nasal Aerosol dose of 320 mcg, placebo, and a 10 mg oral prednisone treatment (for the last 7 days) arm as a positive control. The difference from placebo for change from baseline in geometric mean serum cortisol weighted mean values at end of treatment were -0.86 mcg/dL, -0.44 mcg/dL, and -5.02 mcg/dL, for QNASL Nasal Aerosol 320 mcg, placebo, and prednisone treatment arms, respectively, indicating that QNASL 320 mcg had little effect on change in mean cortisol levels in subjects 12 years of age and older.

6. Clinical Microbiology

As a nasally administered product, QNASL Nasal Aerosol is not required to be sterile. Manufacturing specifications regarding possible microbiological contamination are adequate.

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7. Clinical/Statistical- Efficacy

Overview of the Clinical Program

The clinical program submitted by Teva to support this application was relatively small but typical of programs used to support an allergic rhinitis program. The "core" program included a dose-ranging study and single studies in patients with SAR and PAR. It is acceptable that demonstrating efficacy in single studies, one in each type of allergic rhinitis, is sufficient to support an indication for both SAR and PAR. These core studies were further supported by a 52-week long-term safety study in patients with PAR and an HPA axis study, also in patients with PAR. The basic design characteristics of relevant clinical studies submitted to support the application are outlined below in Table 2. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions.

Table 2: Relevant Clinical Studies for the QNASL Program

Study Year Begun	**Study type**	**Study Duration**	**Patient Age, yrs**	**Treatment Groups***	**N (ITT)**	**Primary efficacy variable**	**Countries**
201 2009	Dose-ranging in SAR	2 weeks	12 - 78	BDP HFA 80 mcg BDP HFA 160 mcg BDP HFA 320 mcg Placebo	118 123 122 123	Reflective total nasal symptom score over 2 wks	USA (various states)
301 2009	Efficacy and Safety in SAR	2 weeks	12 - 73	BDP HFA 320 mcg Placebo	167 171	Reflective total nasal symptom score over 2 wks	USA (TX)
302 2010	Efficacy and Safety in PAR	6 weeks	12 - 82	BDP HFA 320 mcg Placebo	232 234	Reflective total nasal symptom score over 6 wks	USA (various states)
303 2009	Safety in PAR	30/52 weeks	12 - 74	BDP HFA 320 mcg Placebo	414 110	Reflective total nasal symptom score over 30 wks	USA (various states)
304 2010	Safety HPA Axis in PAR	6 weeks	12 - 45	BDP HFA 320 mcg Placebo Prednisone 10 mg oral (last 7 d)	49 41 09	Reflective total nasal symptom score over 6 wks	USA (TX, MA)

* BDP HFA = budesonide dipropionate nasal aerosol administered in each nostril ((b) (4) actuation)
Note: All doses are ex-actuator

Design and Conduct of the Studies

All efficacy and safety studies (201, 301, and 302) were randomized, double-blind, placebo-controlled, parallel-group design study conducted in patients 12 years of age and older with SAR or PAR. For the SAR study 201, no single allergen was specified while for SAR study 301, the allergen was specified as Texas Mountain Cedar. The studies had a 7-21 day single-blind placebo run-in period followed by a double-blind treatment period of 2 weeks for SAR studies 201 and 301, and 6 weeks for PAR study 302 (Table 2). The primary efficacy endpoint for all studies was the change from baseline in average morning and evening reflective total nasal symptom scores (rTNSS: sum of runny nose, sneezing, itchy nose, and nasal congestion; each scored on 0-3 scale) collected daily averaged over 2 weeks of treatment for SAR studies or 6 weeks of treatment for the PAR study. Key secondary efficacy variables included:

- Instantaneous recording of the same four symptoms (iTNSS) for all studies,

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- Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) for both SAR studies (201 and 301) and PAR study 302 in patients with impaired quality of life defined as RQLQ score >3 during the run-in period. The RQLQ is a disease-specific quality of life questionnaire developed to measure the functional problems troublesome to adults with allergies. The adult version of the RQLQ has 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Subjects were asked to recall their experiences during the previous week and to give their responses on a 7-point scale (0 = Least severe to 6 = Extremely severe). The applicant-proposed RQLQ population was a subset of the ITT population that included only those subjects with an impaired quality of life at baseline as defined by a RQLQ score at the randomization visit of 3.0 or greater, were aged 18 years or more and who understood English. The minimally clinical significance of the difference in the RQLQ score is considered to be 0.5.
- Reflective total ocular symptom score (rTOSS): sum of ocular itching, tearing, and redness; each scored on 0-3 scale) for SAR studies 201 and 301 in symptomatic patients defined as TOSS of ≥4 during the run-in period. Safety assessments included recording of adverse events, vital signs, physical examinations including ENT examinations, and clinical laboratory measurements.

Study 303 was a randomized, double-blind, placebo-controlled, parallel group 52-week study conducted primarily to support the long-term safety of QNASL Nasal Aerosol but also assessed efficacy at the 30 and 52-week time points, primarily as an indicator of patient compliance. The primary efficacy endpoint was change from baseline in weekly averages of 24-hour rTNSS over the first 30 weeks of treatment. Of note, the TNSS was recorded once daily in the morning prior to administration of study medication or starting any activity; this is different from how it was recorded in Studies 301 and 302 (i.e., recorded twice daily every 12 hours). The secondary efficacy endpoints for Study 303 were the iTNSS over the first 30 weeks of the treatment period, 24-hour rTNSS over 52 weeks, iTNSS over 52 weeks, and the RQLQ at 30 weeks and 52 at weeks. Safety assessments included recording of adverse events, vital signs, physical examinations including ENT examinations, and clinical laboratory measurements.

The design and conduct of efficacy and safety studies were generally typical of allergic rhinitis programs with two caveats. First, there was a single efficacy trial for SAR in which the allergen was specified as Texas Mountain Cedar. While exposure to many different allergens can result SAR, because the underlying pathophysiology of SAR is similar across allergens, demonstration of efficacy for a single allergen in an SAR program can support efficacy in other allergen sensitive patient groups in SAR. Second, for the key secondary efficacy variables of RQLQ and TOSS only patients with high baseline scores were included. This is not acceptable because such analyses do not represent the whole SAR population and conclusions from such analyses cannot be generalized (b) (4) In this review, results from only the whole group (ITT population) will be shown.

Efficacy Findings and Conclusions
The submitted studies support the efficacy of QNASL Nasal Aerosol at a dose of 320 mcg (two, 80 mcg actuations in each nostril) administered once daily for the treatment of nasal

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symptoms associated with SAR and PAR in adult and adolescent patients 12 years of age and older. The findings of study data submitted are inadequate to support the efficacy of QNASL Nasal Aerosol (b) (4)

In the dose ranging study (201), the 320 mcg dose was the only treatment to demonstrate a significant improvement in rTNSS and iTNSS over placebo (Table 3). Of note is that the treatment effect for the 320 mcg dose (-0.63) was relatively small which prompted the Division to comment at the end-of-phase-2 meeting that a single dose of 320 mcg daily may not be the most effective dose for your Phase 3 studies. Nevertheless, Teva proceeded with the 320 mcg once daily dose in the subsequent SAR and PAR clinical trials. In studies 301 and 302, QNASL Nasal Aerosol administered as 320 mcg once daily demonstrated statistically significant differences from placebo in the change from baseline rTNSS and iTNSS (Table 3).

Table 3: Change from baseline in nasal symptoms scores rTNSS and iTNSS *

	Treatments †	n	Baseline LS mean	Change from baseline	Difference from placebo LS mean	95% CI	P value
SAR Trial 201							
rTNSS*	BDP HFA 80 mcg QD	118	9.33	-1.88	-0.29	-0.80, 0.21	0.255
	BDP HFA 160 mcg QD	123	9.24	-1.87	-0.29	-0.78, 0.21	0.257
	BDP HFA 320 mcg QD	122	9.17	-2.22	-0.63	-1.13, 0.13	0.013
	Placebo	123	8.98	-1.59			
iTNSS	BDP HFA 80 mcg QD	153	8.36	-1.77	-0.27	-0.77, 0.22	0.278
	BDP HFA 160 mcg QD	158	8.28	-1.71	-0.22	-0.70, 0.27	0.385
	BDP HFA 320 mcg QD	153	8.32	-2.10	-0.60	-1.09, -0.11	0.016
	Placebo	153	8.01	-1.50			
SAR Trial 301							
rTNSS	BDP HFA 320 mcg QD	167	9.6	-2.0	0.91	-1.3, -0.5	<0.001
	Placebo	171	9.5	-1.0			
iTNSS	BDP HFA 320 mcg QD	167	9.0	-1.70	0.92	-1.3, -0.5	<0.001
	Placebo	171	8.7	-0.80			
PAR Trial 302							
rTNSS	BDP HFA 320 mcg QD	232	8.9	-2.5	-0.84	-1.2, -0.5	<0.001
	Placebo	234	9.0	-1.6			
iTNSS	BDP HFA 320 mcg QD	232	8.1	-2.1	-0.78	-1.1, -0.4	<0.001
	Placebo	234	8.3	-1.4			

* Subject-rated rated AM and PM reflective or instantaneous total nasal symptom scores (rTNSS or iTNSS) (maximum score = 24) averaged over the 2-week treatment period in SAR and the 6-week treatment period in PAR studies.
† BDP = budesonide HFA nasal aerosol administered in each nostril (b) (4) actuation; ex-actuator dose)

(b) (4)

The treatment differences crossed 0.5, considered to be the minimally important difference only in the single PAR study 302. This finding was not supported in any other study including study 303, the long-term safety study in which RQLQ was also assessed. Ocular symptoms were assessed in the dose-ranging and the confirmatory SAR study (301). While study 301 demonstrated a statistically significant improvement in rTOSS over placebo, this finding was again, not confirmed in any other study.

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Table 4: Change from baseline in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Reflective Ocular Symptom Scores (rTOSS) in Confirmatory SAR and PAR Studies (ITT Population)

	Treatments †	n	Baseline LS mean	Change from baseline	Difference from placebo LS mean	95% CI	P value
SAR Trial 301							
RQLQ	BDP HFA 320 mcg QD	152	4.0	-1.1	-0.4	-0.7, -0.1	0.008
	Placebo	157	3.9	-0.7			
rTOSS	BDP HFA 320 mcg QD	167	6.7	-1.3	-0.56	-0.9, -0.2	0.002
	Placebo	171	6.6	-0.7			
PAR Trial 302							
RQLQ	BDP HFA 320 mcg QD	205	3.4	-1.2	-0.56	-0.8, -0.3	<0.001
	Placebo	214	3.4	-0.6			

† BDP = budesonide HFA nasal aerosol administered in each nostril (50 mcg/actuation; ex-actuator dose)

As detailed above, Study 303 was conducted primarily to assess long-term safety but efficacy was assessed at the 30 and 52 week time points, albeit in a different manner than was assessed in the short-term efficacy trials (rTNSS was assessed once daily and the primary endpoint was change from baseline in weekly averages of 24-hour rTNSS). Given these differences, the results are supportive of the efficacy of QNASL Nasal Aerosol for treatment of nasal symptoms of PAR; there was a statistically significant treatment effect of -0.97 and -1.09 in the rTNSS at the 30 and 52 week time points, respectively. The RQLQ quality of life measurement failed to demonstrate a meaningful or statistically significant difference from placebo. For the ITT population the LS mean treatment difference between QNASL Nasal Aerosol and placebo at 30 weeks was -0.24 (95% CI: -0.5, 0.0; p=0.100) and at 52 weeks was -0.27 (95% CI: -0.7, 0.1; p=0.198).

Onset of Action

For the QNASL Nasal Aerosol clinical development program Teva did not conduct dedicated studies such as an “allergen chamber” study or “day-in-the-park” study that is designed specifically to evaluate onset of action. Instead, an estimate of the onset of action for QNASL Nasal Aerosol was evaluated by assessment of the rTNSS for each individual day for which it was collected in the confirmatory (pivotal) studies in patients with SAR and PAR. For regulatory purposes, onset of action is defined as the first time point, replicated in two studies, where the difference between the active treatment and placebo in the efficacy measure is statistically significant and the difference persists consistently after that time point. It is also expected that the difference would be clinically meaningful. The pivotal SAR and PAR studies provide more clinically meaningful onset of action information than the pharmacodynamic “allergen chamber” and “day-in-the-park” type studies. The data submitted are an estimate of an onset of action of approximately 48-72 hours for QNASL Nasal Aerosol.

8. Safety

Safety database

The safety assessment of QNASL Nasal Aerosol is based primarily on two SAR studies of 2 weeks duration, one PAR study of 6 weeks duration, a year-long study in PAR and a 6 week HPA axis study in patients with PAR (Table 2). In these studies over 1,200 patients with SAR or PAR received BDP HFA at doses ranging from 80 to 320 mcg once daily with approximately 984 patients receiving the indicated dose of 320 mcg once daily for up to one

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year. Beclomethasone is a well-characterized corticosteroid that has previously been the active drug substance for several nasally administered products used to treat SAR and PAR. Considering this wealth of clinical experience, the size of the database is adequate.

Safety Findings and Conclusion
The submitted data support the safety of QNASL Nasal Aerosol in patients 12 years of age and older. No new safety concerns were raised and the frequencies of adverse reactions that are known to be associated with nasally-administered corticosteroid use were generally consistent with the frequencies observed in marketed nasal corticosteroid products.

There were no deaths in the clinical program.

Serious adverse events were uncommon and most that did occur were not likely to be related to a nasally-administered corticosteroid such as BDP nor did they suggest a new safety signal. There was one SAE of angioedema reported for a patient enrolled in the dose-ranging study who received the BDP HFA 160 mcg once daily dose that deserves further comment. The patient was a 27-years old female patient with SAR and PAR and a skin prick test positive for mixed tree pollen who discontinued the study due to moderate angioedema after having received BDP Nasal Aerosol 160 mcg once daily for 10 days due. The angioedema did not occur acutely but over a course of days. She was initially treated with the antihistamine, Claritin, without benefit and subsequently was seen in an emergency department and treated with Benadryl (another H1 blocking antihistamine), Pepcid, an H2 blocker, and systemic corticosteroids. Of note is that the patient was also receiving linisopril, a drug known to be associated with angioedema, which was then changed to amlodipine.

Local adverse reactions such as nasal discomfort, epistaxis, nasal ulcerations, and nasal septal perforations are known class effects of nasally administered corticosteroid products. Nasal discomfort and epistaxis occur relatively frequently while the more serious adverse reaction, nasal ulcerations, are much less common and septal perforations even more so and rarely observed in NDA studies. There were no nasal septal perforations observed in the QNASL Nasal Aerosol clinical development program. In the short-term 2-6-week studies, nasal ulcerations occurred in one patient treated with QNASL Nasal Aerosol and two patients who received placebo. In the long-term (one year) safety study, nasal ulceration was reported in one patient treated with QNASL Nasal Aerosol and in no patients who received placebo. Four patients receiving QNASL Nasal Aerosol were noted to have nasal erosions (a possible precursor to ulceration) compared to none in the placebo patients.

Study discontinuations due to adverse reactions were very uncommon in the short-term, 2-6-week studies, were not likely related to the use of nasal corticosteroids, and were higher in the patients treated with placebo. In the year long study, as would be expected with chronic usage, local adverse reactions known to be associated with nasal corticosteroids were increased compared to the short-term studies. Study discontinuations due to adverse reactions were slightly greater in QNASL Nasal Aerosol treated patients (4%) compared to placebo (3%) and more likely related to corticosteroid effects [epistaxis (5 pts), nasal discomfort (2 pts), nasal ulceration (1 pt)*, and increased intraocular pressure (1 pt)]. Epistaxis was also reported more commonly in the long-term study (11%) compared to placebo (2%) and tended to be more

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severe. Nasal discomfort occurred in 3% of QNASL Nasal Aerosol treated patients and in 2% of patients treated with placebo.

* Note that on page 112 of Dr. Wang's primary clinical review, it is reported that there were 2 nasal ulcerations reported. This value is an error. The correct number (1) is reported in section 5.3 of his review under the individual study 303 review.

Common adverse events for the short-term studies (≥1% and greater than in the placebo group) in QNASL Nasal Aerosol treated patients in decreasing frequency were nasal discomfort, epistaxis, and headache and are shown in Table 5.

Table 5: Adverse Events with ≥ 1% Incidence and Greater than Placebo in QNASL Nasal Aerosol-Treated Patients with Seasonal or Perennial Allergic Rhinitis in Controlled Clinical Trials of 2 to 6 Weeks Duration

	QNASL Nasal Aerosol (320 mcg) (N = 575) n (%)	Placebo (N = 578) n (%)
Nasal Discomfort	30 (5.2)	28 (4.8)
Epistaxis	11 (1.9)	7 (1.2)
Headache	13 (2.3)	9 (1.6)

As agreed upon with the company, detailed ophthalmologic data were collected on a subset of patients in the year-long safety study (303) to assess for corticosteroid-related ocular effects, including visual acuity, lens opacification, and intra-ocular pressure (IOP). The subset consisted of 245 subjects (197 in the QNASL Nasal Aerosol 320 mcg group and 48 in placebo group). Eye examinations conducted by an ophthalmologist were performed at screening, week 30 and week 52 for best corrected visual acuity (BCVA), intraocular pressure (IOP), and cataracts. BCVA was evaluated by use of a Logarithmic Visual Acuity Chart and IOP was measured using a calibrated tonometer affixed to a slit lamp biomicroscope. A value ≥21 mmHg was considered as abnormal eye pressure. The evaluation of lens opacification/cataracts used the Lens Opacities Classification System Version III (LOCS III), a standard method of grading lens opacities.

The ophthalmologic data derived from the QNASL Nasal Aerosol long-term safety study were generally negative and did not identify any new or otherwise concerning ocular safety issues. No cataracts were observed in the study and LOCS grading of lens opacities was similar between QNASL Nasal Aerosol and placebo-treated patients. There was one AE of visual impairment of mild intensity reported in a subject treated with BDP Nasal Aerosol 320 mcg/day. The subject was referred to an ophthalmologist and it was determined the patient required new corrective lenses.

Intraocular pressure measurements revealed no consistent elevations in IOP in patients treated with QNASL Nasal Aerosol with the exception of 2 adverse reactions of increased IOP in patients treated with QNASL Nasal Aerosol 320 mcg once daily. One patient was a 45-year-old female who had baseline IOP values of 20 and 20 mmHg in left and right eye who was subsequently found to have elevated IOP of 32 and 33 mmHg at the week 30 visit. A recheck of IOP confirmed the elevated values (30 mmHg in each eye) and she was withdrawn from the study. The patient's IOP continued to be monitored and despite discontinuation of QNASL,

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the IOP remained elevated for several months necessitating peripheral iridotomy of both eyes with subsequent resolution. The second patient was a 17-year- male who had baseline IOP values of 20 mmHg in the right eye and 19 mmHg in the left eye who was also found to have elevated intraocular pressures at week 30 (IOP values of 22 and 26 mmHg in right and left eyes). He was not discontinued from treatment and follow-up measurements made 3 weeks later revealed that IOP had returned to the normal range and continued to be normal for the remainder of the study. While increased IOP and glaucoma are well-described phenomena associated with the use of nasal and ocular corticosteroids, the link between treatment with QNASL Nasal Aerosol and the 2 episodes of increased IOP adverse reactions is not clear. For the first patient described above, while IOP increased while receiving QNASL, it seems unusual that IOP remained elevated for several months after the corticosteroid was discontinued. Regarding the second patient, he was noted to have a transient elevation of increased IOP which spontaneously returned to the normal range while he continued receiving QNASL Nasal Aerosol.

HPA axis effect was assessed in patients 12-45 years of age with PAR (results described in Section 5 above). While this study demonstrated little effect of QNASL Nasal Aerosol administered as 320 mcg once daily, Teva will likely need to conduct another HPA axis study in pediatric patients below 12 years of age if systemic exposure is higher in the younger pediatric population.

A linear growth study is generally required for nasal corticosteroid programs as even low doses of corticosteroids can affect growth in pediatric patients. A new growth study with QNASL Nasal Aerosol is not necessary because a growth study has been conducted with the closely related product, QVAR inhalation Aerosol and systemic from QNASL is lower compared to QVAR (see Section 5 above). The Division does not require a separate growth study for the same active moiety when linear growth data are available with a different formulation for the same active moiety with higher exposure.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. BDP is a well characterized corticosteroid and has been used for many years in nasally and orally administered products to treat allergic rhinitis and asthma. The efficacy and safety findings seen in the clinical program were consistent with other BDP nasal products. AS such, there were no issues that warrant discussion at an advisory committee meeting.

10. Pediatrics

Adolescents aged 12 years and older were included in all of the pivotal trials for this application and in the HPA axis study. The Applicant asked for a partial waiver for pediatric studies in children less than two years and a deferral for children 2-11 years of age.
The lower age bound of 2 years is typical for a nasal corticosteroid, and the Division has not asked that drugs of this class be studied in children younger than 2 years. The Division has historically taken the position that SAR occurs in children 2 years of age and older and PAR occurs in children 6 months of age and older. Although this lower age cut-off is somewhat arbitrary, there is literature support on the lower age bound (J Allergy Clin Immunol 2000, 106:832). For children younger than 2 years nasal corticosteroids is not an optimum choice

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because of possible local nasal and systemic corticosteroid-related adverse effects and the availability of other non-steroid medications effective in allergic rhinitis. Therefore, a waiver for patients under age 2 is acceptable. The application was reviewed by the FDA Pediatric Review Committee (PeRC) on January 25, 2012. The PeRC agreed with the Division to grant a partial waiver for children less than two years and, since the product was ready for approval in patients 12 years of age and older, a deferral in patients 2-11 years.

Teva plans to investigate the safety and efficacy of QNASL Nasal Aerosol in 6-11 year olds and 2-5 year olds sequentially, which is appropriate to assure local nasal and systemic safety in the younger age group. Studies will include PK assessments of several BDP doses in order to establish an appropriate dose for younger children.

Growth studies are also required for pediatric development programs. For the QNASL Nasal Aerosol program, Teva is relying on the growth study used to support the QVAR Inhalation Aerosol asthma program. This is reasonable since the products are identical except for the different actuators (nasal vs oral) and the overall systemic exposure of BDP and its active metabolite is substantially lower when delivered intranasally than by oral inhalation.

11. Other Relevant Regulatory Issues

- Financial Disclosure: There were two investigators with significant equity interest in Teva Pharmaceuticals, (b) (6) . The number of subjects that these investigators enrolled (b) (6) was not large enough to alter the outcome of the study. In addition, since the study encompassed 35 sites, it would be highly unlikely that the interests of one or two investigators could have influenced the results of the study.
- DSI audits: Clinical site inspections were not conducted for Teva QNASL program. Budesonide dipropionate is a well-characterized corticosteroid with a known efficacy and safety profile that has been used in several other nasal products for SAR and PAR. In addition, during review of the submission, there were no irregularities found that would raise issues related to data integrity. All studies were performed in accordance with acceptable ethical standards.
- Other: Consults by other groups within the Agency (DDMAC, OMPP, DMEPA) have been reviewed and incorporated into the reviews and label accordingly.

12. Labeling

- Proprietary name: Teva initially submitted under the IND (#101639) the name QNAZE as a potential proprietary name that was rejected by DMEPA based on potential confusion with the name of a currently marketed product, Avage. They subsequently submitted the name QNASL, which was found to be acceptable by DMEPA.
- Physician Labeling: Labeling in the Physician Labeling Rule format that generally was submitted by Teva with the application. It generally contained information consistent with other product label of this class (b) (4)

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The label was reviewed by each individual discipline in DPARP and by DDMAC and DMEPA. Appropriate changes to different sections of the label were made to reflect the data accurately and truthfully, including limiting the indication to treatment of nasal symptoms of allergic rhinitis rather than the proposed more broad indication of [redacted] (b) (4) Labeling discussions are ongoing at the time of this review. Carton and container labeling and patient instruction labeling discussions have been reviewed by DPARP, DDMAC, and DMPP and discussions with Teva are also ongoing.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended action for this application is Approval. Teva has submitted adequate data to support approval of QNASL Nasal Aerosol (BDP nasal aerosol) for the treatment of nasal symptoms associated with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older at the proposed dose of 2 actuations per nostril once daily (80 mcg ex actuator per actuation). [redacted] (b) (4)

- Risk Benefit Assessment

The overall risk and benefit assessment of QNASL Nasal Aerosol supports its approval for relief of the nasal symptoms of allergic rhinitis in patients 12 years of age and older. Efficacy was evidenced by patients with SAR and PAR who were treated with QNASL demonstrating significant improvements in reflective and instantaneous TNSS, the standard efficacy endpoints used in allergic rhinitis efficacy trials. Safety findings were consistent with those observed for other nasally administered corticosteroid products and included local side effects such as epistaxis, nasal discomfort and rare nasal ulcerations. There were no nasal septal perforations noted in the clinical development program nor cataracts observed in the year-long safety trial.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

- Recommended Comments to Applicant

None

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/s/

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03/09/2012