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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	March 23, 2012
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-2813
Applicant Name:	Teva Pharmaceuticals
Date of Submission:	May 24, 2011
PDUFA Goal Date:	March 24, 2012
Proprietary Name:	Qnasl Nasal Aerosol
Established Name:	Beclomethasone Dipropionate Nasal Aerosol
Dosage form:	Nasal Aerosol
Strength:	80 mcg beclomethasone dipropionate ex actuator (100 mcg ex valve) per actuation of 59 mg of formulation in solution
Proposed Indications:	Treatment of nasal symptoms of seasonal allergic rhinitis and perennial allergic rhinitis in adult and adolescent patients 12 years of age and older
Action:	Approval

1. Introduction

Teva Pharmaceuticals submitted this 505(b)(2) application for use of Qnasl Nasal Aerosol (beclomethasone dipropionate, HFA propelled) for the treatment of (b) (4) seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older. The proposed dose, 320 mcg per day, is administered as 2 nasal aerosol sprays in each nostril once daily (80 mcg ex actuator per aerosol spray). The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are many drugs approved for use in patients with allergic rhinitis (AR) that include oral and intranasal H1 antihistamines, intranasal corticosteroids, and the oral leukotriene receptor antagonist montelukast. There are various intranasal corticosteroids marketed for the treatment of AR in the United States. Beclomethasone is a corticosteroid and is marketed in the United States in several formulations, including an inhalation aerosol formulated as a solution containing the propellant HFA-134a and ethanol delivered via a metered-dose inhaler (MDI) for the treatment of asthma (marketed as Qvar Inhalation Aerosol), and a nasal spray in an aqueous suspension delivered via a pump spray for the relief of symptoms of SAR and PAR (marketed as Beconase AQ Nasal Spray). The current application proposes to expand the available intranasal corticosteroid treatment options for AR. The proposed Qnasl Nasal Aerosol product utilizes the MDI canister

from Qvar Inhalation Aerosol, which is coupled with a new nasal actuator to allow for nasal administration of the existing MDI formulation.

Prior to the approval of Zetonna (ciclesonide) Nasal Aerosol in January 2012, all intranasal corticosteroids available in the US for the treatment of AR were aqueous-based, which are often associated with back-of-the-throat run off or post-nasal drip. Earlier there were CFC-based intranasal corticosteroid aerosol products, but these are not currently available because of the phase-out of CFCs. Qnasl Nasal Aerosol is proposed to provide a second non-CFC based intranasal corticosteroid aerosol treatment option for patients with AR.

3. Chemistry, Manufacturing, and Controls

The drug substance beclomethasone dipropionate is a known compound that is already approved in commercial inhalation and nasal spray products as mentioned above. Qnasl Nasal Aerosol is a pressurized metered dose aerosol canister containing a solution formulation of beclomethasone dipropionate with ethanol (b) (4) and HFA-134a as propellant (same as that used in Qvar as described above), and fitted with a nasal actuator (b) (4) The product has an integrated dose counter that has acceptable robustness and reliability. Qnasl Nasal Aerosol delivers 80 mcg beclomethasone dipropionate from the actuator (100 mcg from the valve) in 59 mg of formulation per actuation. The commercial presentation provides 120 actuations after priming and has a net fill weight of 8.7 gm.

The drug substance is manufactured by Teva Parenteral Medicines, Inc. (previously Sicor) in a facility in Rho, Italy. The drug filled canister is manufactured at 3M Drug Delivery Systems, Northridge, CA, and the assembly of the finished dosage form is done by Teva Pharmaceuticals, Waterford, Ireland. All manufacturing and testing facilities associated with this application have acceptable EER status. The submitted stability data support storage at room temperature and an expiry of 24 months.

4. Nonclinical Pharmacology and Toxicology

A full toxicology assessment for beclomethasone dipropionate was submitted previously and reviewed under the NDAs for Qvar Inhalation Aerosol and was found to be acceptable. Toxicology data to support the nasal route of administration was submitted previously to support a nasal formulation containing beclomethasone dipropionate and was also found to be acceptable. No new preclinical data were submitted with this application.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for beclomethasone dipropionate were addressed in the previous NDAs for Qvar Inhalation Aerosol and Beconase AQ Nasal Spray.

Beclomethasone dipropionate (BDP) is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. It is a prodrug that is extensively converted to the active metabolite, beclomethasone 17 monopropionate (17-BMP) that binds to the human glucocorticoid receptor.

Teva Pharmaceuticals submitted data from two clinical pharmacology studies with this application. The goal of one study (AR-101) was to compare the relative bioavailability of the Qnasl Nasal Aerosol product following intranasal administration to that for QVAR Inhalation Aerosol following oral inhalation. The goal of the other study (AR-304) was to characterize the effects of intranasal administration of the Qnasl on hypothalamic-pituitary-adrenal (HPA)-axis function.

Study AR-101 was single-dose, randomized, open-label, 3-period, crossover in design conducted in healthy volunteers. The results of this study demonstrated that the systemic bioavailability of Qnasl Nasal Aerosol 320 mcg was approximately 27.5% of that of orally inhaled Qvar Inhalation Aerosol 320 mcg based on the plasma concentrations of 17-BMP (AUC_{last}: 1139.7 vs 4140.3 hr*pg/mL; GMR: 0.275; 90% CI for the GMR: 0.214, 0.354). The peak exposure of Qnasl Nasal Aerosol 320 mcg was approximately 19.5% of that of orally inhaled Qvar Inhalation Aerosol 320 mcg as measured by 17-BMP (C_{max}: 262.7 vs 1343.7 pg/mL; GMR: 0.195; 90% CI for the GMR: 0.158, 0.241).

Study AR-304 was 6-week, randomized, double-blind, parallel-group in design conducted in adult and adolescent patients 12 to 45 years of age with PAR. Qnasl Nasal Aerosol 320 mcg, once daily, was compared with both a placebo nasal aerosol and a positive control (prednisone 10 mg orally once daily for the final 7 days of the treatment period). HPA-axis function was assessed by 24-hour serial serum cortisol levels prior to the first dose and after a 6-week treatment. The change from baseline in the 24-hour serum cortisol weighted mean for Qnasl Nasal Aerosol and placebo after a 6-week of treatment was compared. Baseline geometric mean serum cortisol weighted mean values were similar in the Qnasl Nasal Aerosol 320 mcg/day and placebo treatment groups (9.04 and 8.45 mcg/dL, respectively). After the 6-week treatment, the geometric mean values were (8.18 and 8.01 mcg/dL, respectively) with a change from baseline in 24-hour serum cortisol weighted mean for the Qnasl Nasal Aerosol and placebo groups of 0.86 and 0.44, resulting in a difference of 0.42. The geometric mean ratio for Qnasl Nasal Aerosol 320 mcg/day to placebo was 0.96 (95% CI: 0.87, 1.06). For comparison, in the positive-control (prednisone) treatment group, the geometric mean ratio for placebo to placebo/prednisone 10 mg/day was 3.17 (95% CI: 2.68, 3.74). The results indicate that Qnasl Nasal Aerosol 320 mcg once daily dose had a small effect on change in mean cortisol levels in patients 12 years of age and older.

6. Clinical Microbiology

The final product is not sterile, which is acceptable for a nasal spray product. The manufacturing process is adequate from a microbiological perspective.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical program submitted with this application was relatively small but typical of an AR program covering both the SAR and PAR indications. Some characteristics of the studies that form the basis of the review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant clinical studies

ID Year *	**Study type**	**Study duration**	**Patient Age, yr**	**Treatment groups#**	**N (ITT)**	**Primary efficacy variable**	**Countries**
201 2009	Dose ranging, in SAR	2 weeks	12 - 78	BDP HFA 80 mcg QD BDP HFA 160 mcg QD BDP HFA 320 mcg QD Placebo	118 123 122 123	Reflective total nasal symptom score over 2 wks	US [Various States]
301 2009	Efficacy and Safety in SAR	2 week	12 - 73	BDP HFA 320 mcg QD Placebo	167 171	Reflective total nasal symptom score over 2 wks	US [Texas]
302 2010	Efficacy and Safety in PAR	6 weeks	12 - 82	BDP HFA 320 mcg QD Placebo	232 234	Reflective total nasal symptom score over 2 wks	US [Various States]
303 2009	Safety in PAR	30/52 weeks	12 - 74	BDP HFA 320 mcg QD Placebo	414 110	Reflective total nasal symptom score over 6 wks	US [Various States]
304 2010	HPA axis safety	6 weeks	12 - 45	BDP HFA 320 mcg QD Placebo Prednisone 10 mg for 7 day	49 41 09	Reflective total nasal symptom score over 6 wks	US [Texas, MA]

*Year study subject enrollment begun
BDP HFA = Qnasl (beclomethasone dipropionate) HFA Nasal aerosol administered as 2 nasal aerosol sprays in each nostril once daily (80 mcg ex actuator per aerosol spray);
Note: All doses are ex-actuator (end of the actuator from where the drug is delivered to patients)

b. 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 301 the allergen was specified as Texas Mountain Cedar. The studies had a 1-3 week single-blind placebo run-in period followed by double-blind treatment period of 2 weeks for SAR studies 201 and 301, and 6 weeks for PAR study 302 (Table 1). 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 and averaged over 2 weeks of treatment for SAR studies or 6 weeks of treatment for the PAR study (Table 1). Some key secondary efficacy variables included: (1) the instantaneous recording of the same four symptoms (iTNSS) for all studies, (2) Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) for SAR studies 201 and 301 and PAR study 302 of patients with impaired quality of life defined as RQLQ score 3 or higher during the run-in period, and (3) 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 of symptomatic patients defined as TOSS of 4 or higher 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 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 typical of an AR program with two caveats. First, there was a single efficacy study for SAR where the allergen was specified as Texas Mountain Cedar. This is acceptable because demonstration of efficacy in one allergen sensitive SAR patient group is expected to support efficacy in other allergen sensitive patient groups in SAR because the underlying pathophysiology of SAR is similar across allergens. Texas Mountain Cedar produces intense symptoms and clinical studies conducted in SAR patients allergic to this allergen may show a larger treatment effect size compared to clinical studies conducted in SAR patients allergic to heterogeneous seasonal allergens. Nevertheless, Texas Mountain Cedar is an acceptable model to study 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.

c. Efficacy findings and conclusions

The submitted studies support efficacy of Qnasl Nasal Aerosol at a dose of 320 mcg (two, 80 mcg sprays in each nostril) administered once daily for the treatment of nasal 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, the treatment effect for the 320 mcg dose (-0.63) was relatively small compared to other products of the class. Teva Pharmaceuticals 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 2. 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	118	8.36	-1.77	-0.27	-0.77, 0.22	0.278
	BDP HFA 160 mcg QD	123	8.28	-1.71	-0.22	-0.70, 0.27	0.385
	BDP HFA 320 mcg QD	122	8.32	-2.10	-0.60	-1.09, -0.11	0.016
	Placebo	123	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 first 6-week treatment period in PAR studies.
† BDP HFA = Qnasl (beclomethasone dipropionate) HFA Nasal aerosol administered as 2 nasal aerosol sprays in each nostril once daily (80 mcg ex actuator per aerosol spray);

Table 3. Change from baseline in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and Reflective Ocular Symptoms Scores (rTOSS) in confirmatory SAR and PAR studies (ITT population)

	Treatments †	n	Baseline LS mean	End of treatment	Difference from placebo LS mean	95% CI	P value
SAR study 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 study 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 HFA = Qnasl (beclomethasone dipropionate) HFA Nasal aerosol administered as 2 nasal aerosol sprays in each nostril once daily (80 mcg ex actuator per aerosol spray);

(b) (4)

As shown in Table 3, 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. (b) (4) [redacted] The indication of Qnasl will (b) (4) be (b) (4) the treatment of nasal symptoms associated with SAR and PAR.

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).

To support the onset of action claim, Teva Pharmaceuticals did not conduct dedicated studies such as an "allergen chamber" study or a "day-in-the-park" study that provides pharmacodynamics onset of action. Instead, onset of action for Qnasl Nasal Aerosol was assessment by frequent recording of rTNSS (not iTNSS) for each individual day in the confirmatory SAR and PAR studies. 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 could provide more clinically meaningful onset of action information than the pharmacodynamic "allergen chamber" and "day-in-the-park" type studies, if onset of action information was available with iTNSS score (not rTNSS). The data submitted are an estimate of an onset of action, which is approximately 48-72 hours for Qnasl Nasal Aerosol, noting the limitation that the time is calculated on rTNSS and not iTNSS.

8. Safety

a. Safety database

The safety assessment of Qnasl Nasal Aerosol is primarily based on studies listed in Table 1. The overall safety database was adequate.

b. Safety findings and conclusion

The submitted data support the safety of Qnasl Nasal Aerosol in patients 12 years of age and older. There were no deaths in the clinical program. Serious adverse events were few, did not appear to be related to beclomethasone dipropionate, and did not suggest a new safety signal. The safety findings with Qnasl Nasal Aerosol were generally consistent with nasally administered corticosteroids for the treatment of SAR and PAR.

Serious adverse events (SAEs) were uncommon and most that did occur were not likely to be related to a nasally administered corticosteroid. There was one SAE of angioedema reported in a 27-year-old female patient enrolled in the dose-ranging study who received the Qnasl Nasal Aerosol160 mcg once daily dose that deserves further comment. The angioedema did not occur acutely, but occurred over the course of days. She was treated with antihistamines 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 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 patients), nasal discomfort (2 patients), nasal ulceration (1 patient), and increased intraocular pressure (1 patient)]. Epistaxis was also reported more commonly in the long-term study (11%) compared to placebo (2%) and tended to be more severe. Nasal discomfort occurred in 3% of Qnasl Nasal Aerosol treated patients and in 2% of patients treated with placebo.

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.

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 Qnasl 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, 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 known to be 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, although 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 that 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). The results indicate that Qnasl Nasal Aerosol at 320 mcg once-daily dose had a small effect on change in mean cortisol levels in patients 12 years of age and older. Teva Pharmaceuticals 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.

c. REMS/RiskMAP

There are no substantial safety concerns that would require a REMS or RiskMAP. Other nasal corticosteroids also do not have REMS and RiskMAP.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Beclomethasone dipropionate is not a new molecular entity. Nasal corticosteroids are a well-studied drug class, and efficacy and safety of this class of drugs, and other nasal formulations of beclomethasone dipropionate, are well understood. The efficacy and safety findings seen in the clinical program were obvious. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

Teva Pharmaceuticals has submitted a request for deferral of pediatric studies below 12 years of age and waiver of pediatric studies below 2 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 the 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 are not an optimum choice because of possible nasal and systemic adverse effects. Such young patients are better treated with drugs of other classes such as antihistamines. Teva Pharmaceutical's lower age cut off for the clinical program is appropriate. The application was reviewed by the FDA Pediatric Review Committee (PeRC) on January 25, 2012. The PeRC agreed to grant a partial waiver for children less than two years and a deferral in patients 2-11 years.

Teva Pharmaceuticals plans to investigate the safety and efficacy of Qnasl Nasal Aerosol in 6 to 11 year olds and in 2 to 5 year olds sequentially, which is appropriate to assure safety in the younger age group.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audits were not requested for the clinical program because beclomethasone dipropionate is a well-characterized corticosteroid with a known efficacy and safety profile that has been used in other nasal products for SAR and PAR. During review of the submission, no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There were two investigators with significant equity interest in Teva Pharmaceutical. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consult reviews received from DDMAC and other groups within the Agency.

12. Labeling

a. Proprietary Name

Teva Pharmaceuticals initially submitted Qnaze as the proposed proprietary name. The DMEPA rejected this proposed name due to potential confusion with a currently marketed product, Avage. Teva Pharmaceuticals subsequently submitted Qnasl as the proposed proprietary name, which was found to be acceptable by the DMEPA.

b. Physician Labeling

Teva Pharmaceuticals submitted a label in the Physician Labeling Rule format that generally contains information consistent with other product label of this class. The label was reviewed by various disciplines of this Division, and by OPDP. Various changes to different sections of the label were recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and the applicant have agreed to the final version of the label.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, OPDP, and DMEPA, and the last version was found to be acceptable.

d. Patient Labeling and Medication Guide

The patient instructions for use was reviewed by various disciplines of this Division, DMPP and DRISK, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Teva Pharmaceuticals has submitted adequate data to support approval of Qnasl (beclomethasone dipropionate) Nasal Aerosol for the treatment of (b) (4) seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and adolescents 12 years of age and older at the proposed dose of 320 mcg (two, 80 mcg sprays in each nostril). The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk and benefit assessment of Qnasl Nasal Aerosol supports its approval for relief of (b) (4) SAR and PAR in patients 12 years of age and older without any specific restrictions. Safety findings with Qnasl Nasal Aerosol were consistent with those observed with 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. Also cataracts were not observed in the program. Efficacy was demonstrated in patients with SAR and PAR treated with Qnasl demonstrated by statistically significant improvements in reflective and instantaneous TNSS compared to placebo, the standard efficacy endpoints used in allergic rhinitis efficacy trials.

Qnasl Nasal Aerosol will provide a second non-CFC based intranasal corticosteroid aerosol treatment option for patients with AR. Prior to until the approval of Zetonna (ciclesonide) Nasal Aerosol in January 2012, all intranasal corticosteroids available in the US for the treatment of AR were aqueous-based, which are often associated with back-of-the-throat run off or post-nasal drip. In the past there were CFC-based intranasal corticosteroid aerosol products, but these are not currently available because of the phase-out of CFCs.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

There will be 5 Pediatric Post-marketing Study Requirements. Teva has committed to conduct the following studies:

A 2-week double-blind, placebo-controlled dose-ranging trial in children 6-11 years of age with seasonal allergic rhinitis. At least 2 doses of BDP-HFA will be evaluated.

A 12-week double-blind, placebo-controlled safety and efficacy trial in children 6-11 years of age with perennial allergic rhinitis.

A 6-week double-blind, placebo-controlled trial to assess the effects of BDP-HFA on the HPA axis in children 6-11 years of age with perennial allergic rhinitis.

A 12-week double-blind, placebo-controlled safety trial in children 2-5 years of age with perennial allergic rhinitis.

A 6-week double-blind, placebo-controlled trial to assess the effects of BDP-HFA on the HPA axis in children 2-5 years of age with perennial allergic rhinitis.

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/s/

BADRUL A CHOWDHURY
03/23/2012
Div Dir Summary Review