QNASL® (beclomethasone dipropionate) Nasal Aerosol

Warnings and Precautions

- Nasal discomfort, epistaxis, nasal ulceration, Candida albicans infection, nasal septal perforation, impaired wound healing. Monitor patients periodically for signs of adverse effects on the nasal mucosa. Avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma. (5.1)
- Eye Disorders. Monitor patients closely with a change in vision or with a history of intraocular pressure, blurred vision, glaucoma, and/or cataracts. (5.2)
- Hypersensitivity, rash, and urticaria may occur after administration of QNASL Nasal Aerosol. (5.3)
- Potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections. (5.4)
- Hypercorticism and adrenal suppression with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue QNASL Nasal Aerosol slowly. (5.5)
- Potential reduction in growth velocity in pediatric patients. Monitor growth routinely in pediatric patients receiving QNASL Nasal Aerosol. (5.6, 8.4)

Adverse Reactions

The most common adverse reactions (≥1% and greater than placebo) in patients 12 years of age and older include nasal discomfort, epistaxis, and headache. (6.1)

The most common adverse reactions (≥2% and greater than placebo) in children 4 to 11 years of age include headache, pyrexia, upper respiratory tract infection, and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Respiratory, LLC at 1-888-482-9522 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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QNASL Nasal Aerosol over several months or longer should be examined periodically for possible changes in the nasal mucosa. If an adverse reaction (e.g., erosion, ulceration) is noted, discontinue QNASL Nasal Aerosol [see Adverse Reactions (6.1)].

Candida Infection: In previous clinical trials with an aqueous formulation of beclomethasone dipropionate administered intranasally, localized infections of the nose and pharynx with Candida albicans had been reported. There were no instances of similar infections in clinical trials with QNASL Nasal Aerosol. If such an infection develops, it may require treatment with appropriate local therapy and discontinuation of QNASL Nasal Aerosol treatment. Thus, patients using QNASL Nasal Aerosol over several months or longer should be examined periodically for evidence of Candida infection.

Nasal Septal Perforation: Instances of nasal septal perforation have been reported in patients following the intranasal application of beclomethasone dipropionate. There were no nasal septal perforations reported during clinical trials in the indicated dose of QNASL 80 mcg Nasal Aerosol administered as 320 mcg once daily in adults and adolescents. There was one report of nasal septal perforation observed in the dose-ranging pediatric clinical trial.

Impaired Wound Healing: Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use QNASL Nasal Aerosol until healing has occurred.

Use of intranasal and inhaled corticosteroids may result in the development of increased intraocular pressure, blurred vision, glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts. Gonioscopic examinations were performed on 10 patients who received QNASL Nasal Aerosol and 1 patient who received placebo that had intraocular pressure measurements and slit lamp examinations in 245 adolescent and adult patients (12 years of age and older) with perennial allergic rhinitis who were treated with QNASL Nasal Aerosol 320 mcg daily (N=197) or placebo (N=48) for up to 52 weeks. In 94% of patients, intraocular pressure (IOP) remained within normal range (+/-1 mmHg) throughout the treatment portion of the trial. There were 15 patients (6%) treated with QNASL Nasal Aerosol and 2 patients (1%) treated with placebo who had IOP greater than normal range (+2 mmHg) and greater than baseline during the treatment portion of the trial. Two of these occurrences in patients treated with QNASL Nasal Aerosol were reported as adverse events; one was severe and the other was mild. No instances of cataract formation or other clinically significant ocular incidents were reported in this 52-week safety trial [see Adverse Reactions (6.1)].

5.2 Immunosuppression

People who are using drugs that suppress the immune system (e.g., corticosteroids) are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been previously vaccinated to avoid exposure, was taken to avoid exposure. However, because the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. Similarly, if a chickenpox-associated rash develops in a patient treated with QNASL Nasal Aerosol, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated (see the respective package inserts for complete immunization). If chickenpox or measles develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract, untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections, or ocular herpetic simplex because of the potential for worsening of these infections.

5.5 Hypothalamic-Pituitary-Adrenal Axis Effect

When intranasal steroids are used at higher-than-recommended dosages or in susceptible patients with untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections, or ocular herpetic simplex because of the potential for worsening of these infections.

When intranasal steroids are used at higher-than-recommended dosages or in susceptible patients with untreated local or systemic fungal or bacterial infections, systemic viral or parasitic infections, or ocular herpetic simplex because of the potential for worsening of these infections.

5.6 Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to children. Therefore, regularly monitor the growth of pediatric patients receiving QNASL Nasal Aerosol [see Use in Specific Populations (8.4)].

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Epistaxis, nasal discomfort, nasal ulcerations,
- Candida albicans infection, and
- Imbalance wound healing [see Warnings and Precautions (5.1)]
- Eye Disorders [see Warnings and Precautions (5.2)]
- Hypercorticism, adrenal suppression, and growth reduction [see Warnings and Precautions (5.3)]
- Immunosuppression [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1.1 Adults and Adolescents 12 Years of Age and Older:

The safety data described below for adults and adolescents 12 years of age and older were derived from controlled clinical trials of QNASL Nasal Aerosol. Four placebo-controlled trials were conducted in 2 to 6 weeks duration evaluating doses of beclomethasone nasal aerosol from 80 to 320 mcg once daily. These short-term trials included a total of 1394 patients with either seasonal or perennial allergic rhinitis. Of these, 575 (378 female and 197 male) received at least one dose of QNASL Nasal Aerosol, 320 mcg once daily and 578 (360 female and 128 male) received placebo. Patients ages ranged from 12 to 62 years and the racial distribution of patients was 81% white, 16% black, and 4% other. Short-Term (2-6 Weeks) Trials: Less than 2% of patients in the clinical trials discontinued treatment because of adverse reactions with the rate of withdrawal among patients who received QNASL Nasal Aerosol similar to or lower than the rate among patients who received placebo. QNASL Nasal Aerosol displays the common adverse reactions (>1% and greater than placebo-treated patients).

Table 1. Adverse Events With > 1% Incidence and Greater than Placebo in QNASL Nasal Aerosol-Treated Adult and Adolescent Patients with Seasonal or Perennial Allergic Rhinitis in Controlled Clinical Trials of 2 to 6 Weeks Duration (Safety Population)

<table>
<thead>
<tr>
<th>Condition</th>
<th>QNASL Nasal Aerosol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Discomfort</td>
<td>30 (5.2)</td>
<td>28 (4.8)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>11 (1.9)</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (2.3)</td>
<td>9 (1.6)</td>
</tr>
</tbody>
</table>

Nasal ulcerations occurred in 2 patients treated with placebo and 1 patient treated with QNASL Nasal Aerosol. There were no differences in the incidence of adverse reactions based on gender or race. Clinical trials did not have sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients.

Long-Term 52-Week Safety Trial: In a 52-week placebo-controlled long-term safety trial with PAR, 415 patients (128 males and 287 females, aged 12 to 74 years) were treated with QNASL Nasal Aerosol at a dose of 320 mcg once daily and 444 patient (203 males and 241 females, aged 12 to 67 years) were treated with placebo. Of the 415 patients treated with QNASL Nasal Aerosol, 219 patients were treated for 52 weeks and 196 patients were treated for 30 weeks. While most adverse events were similar in type and rate between the treatment groups, epistaxis occurred more frequently in patients who received QNASL Nasal Aerosol (45 out of 219, 21%) than in patients who received placebo (21 out of 111, 19%). Epistaxis also tended to be more severe in patients treated with QNASL Nasal Aerosol. In 45 reports of epistaxis in patients who received QNASL Nasal Aerosol, 27, 13, and 5 cases were of mild, moderate, and severe intensity, respectively, while the reports of epistaxis in patients who received placebo were of mild (1) and moderate (1) intensity. Seventeen patients treated with QNASL Nasal Aerosol experienced adverse reactions that led to withdrawal from the trial compared to 3 patients treated with placebo. There were 4 nasal erosions and 1 nasal septal ulceration which occurred in patients who received QNASL Nasal Aerosol, and no erosions or ulcerations noted in patients who received placebo. No patient experienced a nasal septal perforation during the trial.

6.1.2 Pediatric Patients Aged 4 to 11 Years

The safety data described below for pediatric patients 4 to 11 years of age with seasonal or perennial allergic rhinitis are based on 4 placebo-controlled clinical trials of QNASL Nasal Aerosol. These trials were 2 to 12 weeks in duration, evaluated doses of beclomethasone nasal aerosol 80 mcg to 160 mcg once daily and included a total of 1360 patients with seasonal or perennial allergic rhinitis. Of these, 688 (312 female and 356 male) received at least one dose of QNASL Nasal Aerosol, 80 mcg once daily, 241 (116 female and 125 male) received QNASL Nasal Aerosol 160 mcg once daily, and 451 (203 female and 248 male) received placebo. The racial distribution of patients was 73% white, 20% black, and 7% other. Based on the results from the dose-ranging trial, 80 mcg once daily was chosen as the dose in pediatric patients. Less than 1.5% of patients in the clinical trials discontinued treatment because of adverse reactions with the rate of withdrawal among patients who received QNASL Nasal Aerosol 80 mcg once daily similar to or lower than the rate among patients who received placebo. Table 2 displays the common adverse reactions (>1% and greater than placebo-treated patients). Additionally, epistaxis was reported at a rate of 4% for both QNASL Nasal Aerosol 80 mcg once daily and placebo treated patients.

Table 2. Adverse Events With > 1% Incidence and Greater than Placebo in QNASL Nasal Aerosol-Treated Pediatric Patients Aged 4 to 11 Years with Seasonal or Perennial Allergic Rhinitis in Controlled Clinical Trials of 2 to 6 Weeks Duration (Safety Population)

<table>
<thead>
<tr>
<th>Condition</th>
<th>QNASL Nasal Aerosol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Discomfort</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Headache</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Headache</td>
<td>1.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>
8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with QNASL Nasal Aerosol or beclomethasone dipropionate in pregnant women. No published studies, including studies of large birth registries, have to date related the use of inhaled corticosteroids to limb and neural tube malformations or other adverse perinatal outcomes. Thus, available human data do not establish the presence or absence of drug-associated risk to the fetus. In animal reproduction studies, beclomethasone dipropionate resulted in adverse developmental effects in mice and rabbits at subcutaneous doses equal to or greater than approximately 1.5 times the maximum recommended human dose (MRHD) in adults (0.32 mg/day) (see Data). In rats exposed to beclomethasone dipropionate by inhalation, dose-related gross injury to the fetal adrenal glands was observed at doses greater than 350 times the MRHD, but there was no evidence of external or skeletal malformations or embryolethality at inhalation doses of up to 860 times the MRHD.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Labor or Delivery

There are no specific human data regarding any adverse effects of intranasal beclomethasone dipropionate on labor and delivery.

Data

Animal Data

In an embryofetal development study in pregnant rats, beclomethasone dipropionate administration during organogenesis from gestation days 6 to 15 at inhalation doses 350 times the MRHD in adults and higher (on a mg/m² basis at maternal doses of 11.5 and 28.3 mg/kg/day) produced dose-dependent gross injury (characterized by red foci) of the adrenal glands in fetuses. There were no findings in the adrenal glands of rat fetuses at an inhaled dose that was 75 times the MRHD in adults (on a mg/m² basis at a maternal dose of 2.4 mg/kg/day). There was no evidence of external or skeletal malformations or embryolethality in rats at inhaled doses up to 860 times the MRHD (on a mg/m² basis at maternal doses up to 28.3 mg/kg/day).

In an embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 15 at subcutaneous doses equal to and greater than 1.5 times the MRHD in adults (on a mg/m² basis at maternal doses of 0.1 mg/kg/day and higher) produced adverse developmental effects (increased incidence of cleft palate). No-effect dose in mice was not identified. In a second embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 15 at subcutaneous doses equal to and greater than 5 times the MRHD in adults (on a mg/m² basis at a maternal dose of 0.3 mg/kg/day) produced embryolethical effects (increased fetal resorptions) and decreased pup survival.

8.2 Lactation

Risk Summary

There are no data available on the presence of beclomethasone dipropionate in human milk, the effects on the breastfed child, or the effects on milk production. However, other corticosteroids have been detected in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for QNASL and any potential adverse effects on the breastfed child from beclomethasone dipropionate or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Impairment of fertility was observed in rats and dogs at oral doses of beclomethasone dipropionate corresponding to 500 and 50 times the MRHD for adults on a mg/m² basis, respectively. [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of QNASL Nasal Aerosol in children 4 years and older have been established. [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14)]. The safety and effectiveness of QNASL Nasal Aerosol in children younger than 4 years of age have not been established. Controlled pediatric clinical trials with QNASL Nasal Aerosol included 909 children 4 to 11 years of age and 188 adolescent patients 12 to 17 years of age (see Clinical Studies (14)). Controlled clinical trials have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of reduction in growth velocity associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for “catch-up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including QNASL Nasal Aerosol, should be monitored routinely (e.g., via stadiometry).

A 12-month, randomized, controlled clinical trial evaluated the effects of QVAR®, an orally inhaled HFA beclomethasone dipropionate product, without spacer versus chlorofluorocarbon-propelled (CFC) beclomethasone dipropionate with large volume spacer in children with asthma ages 5 to 17 years. A total of 429 patients were enrolled, of whom 394 received HFA-beclomethasone dipropionate (100 to 400 mcg/day ex-valve) and 126 received CFC-beclomethasone dipropionate (200 to 800 mcg/day ex-valve). When comparing results at month 12 to baseline, the mean growth velocity in children treated with HFA-beclomethasone dipropionate was approximately 0.5 cm/year less than that noted with children treated with CFC-beclomethasone dipropionate via large volume spacer. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives.

The potential for QNASL Nasal Aerosol to cause reduction in growth velocity in pediatric patients or when given at higher than recommended dosages cannot be ruled out.

8.5 Geriatric Use

Clinical trials of QNASL Nasal Aerosol did not include sufficient subjects of ages 65 years and older to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, administration to elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism [see Warnings and Precautions (5.5)]. There are no data available on the effects of acute or chronic overdosage with QNASL Nasal Aerosol.

11 DESCRIPTION

Beclomethasone dipropionate USP, the active component of QNASL Nasal Aerosol, is an anti-inflammatory steroid having the chemical name 9-chloro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17, 21-dipropionate and the following chemical structure:

Beclomethasone dipropionate, a di-ester of beclomethasone (a synthetic cortico-steroid chemically related to dexamethasone), is a white almost white, odorless powder with a molecular formula of C₂₈H₃₇ClO₇ and a molecular weight of 521.1. It is practically insoluble in water, very soluble in chloroform, and soluble in acetone and in dehydrated alcohol.
QNASL® (beclomethasone dipropionate) Nasal Aerosol

QNASL Nasal Aerosol is a pressurized, nonaqueous solution in a metered-dose aerosol device intended ONLY for intranasal use. It contains a solution of beclomethasone dipropionate in propellant HFA-134a (1,1,1,2-tetrafluoroethane) and dehydrated ethanol. QNASL 40 mcg Nasal Aerosol delivers 40 mcg of beclomethasone dipropionate from the nasal actuator and 50 mcg from the valve. QNASL 80 mcg Nasal Aerosol delivers 80 mcg of beclomethasone dipropionate from the nasal actuator and 100 mcg from the valve. QNASL 320 mcg Nasal Aerosol delivers 320 mcg of beclomethasone dipropionate from the nasal actuator and 50 mcg from the valve with each actuation. Each QNASL 80 mcg Nasal Aerosol canister contains 10.6 g of drug and excipients and provides 120 actuations. Each QNASL 40 mcg Nasal Aerosol canister contains 6.8 g of drug and excipients and provides 60 actuations.

12.2 Pharmacodynamics

Adrenal Function: The effects of QNASL Nasal Aerosol in the HPA axis were evaluated in two 6-week, double-blind, randomized, placebo-controlled trials – one in adult and adolescent patients 12 to 45 years of age and another in children 6 to 11 years of age. In the first study with adolescent and adult patients aged 12 to 45, QNASL Nasal Aerosol 320 mcg, once daily, was compared with both placebo nasal aerosol and a positive control (a placebo/prednisone group that received prednisone 10 mg once daily on the first 7 days of the treatment period). In the second study with pediatric patients aged 6 to 11, QNASL Nasal Aerosol 80 mcg once daily was compared to placebo nasal aerosol. HPA-axis function was assessed by 24-hour serum cortisol levels at the first dose and after 6 weeks of treatment. Patients were domiciled for the 24-hour serum cortisol assessments. The change from baseline in the 24-hour serum cortisol weighted mean for QNASL Nasal Aerosol and placebo after 6 weeks of treatment was compared.

In the HPA-axis study in patients 12 to 45 years of age, 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 6 weeks of treatment, geometric mean serum cortisol weighted 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 prednisone 10 mcg/day was 3.17 (95% CI: 2.68, 3.74).

In the HPA-axis study in patients 6 to 11 years of age, baseline geometric mean serum cortisol weighted mean values were similar in the QNASL Nasal Aerosol 80 mcg/day and placebo treatment groups (5.57 and 6.47 mcg/dL, respectively). After 6 weeks of treatment, the geometric mean values were 6.19 and 7.13 mcg/dL, respectively, with no decrease from baseline values in both treatment groups. The geometric mean ratio for QNASL Nasal Aerosol 80 mcg/day to placebo was 0.91 (95% CI: 0.81, 1.03).

12.3 Pharmacokinetics

Absorption

Following intranasal administration, most of the beclomethasone dipropionate undergoes extensive conversion to its active metabolite, beclomethasone-17-monopropionate, during absorption. Plasma concentrations of beclomethasone dipropionate and beclomethasone-17-monopropionate have been measured with QNASL Nasal Aerosol in 2 adult and/or adolescent clinical trials and 1 pediatric clinical trial.

The single-dose pharmacokinetics of QNASL Nasal Aerosol were evaluated in 8 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials of 2 to 6 weeks duration in adult and adolescent patients aged 12 years and older with symptoms of seasonal or perennial allergic rhinitis. The 3 clinical trials included one 2-week dose-ranging trial in patients with seasonal allergic rhinitis, one 2-week efficacy trial in patients with seasonal allergic rhinitis, and one 6-week efficacy trial in patients with perennial allergic rhinitis. The trials included a total of 1049 patients (366 males and 683 females). About 81% of patients were Caucasian and 17% African American, the mean age was approximately 38 years. Of these patients 521 received QNASL Nasal Aerosol 320 mcg once daily administered as 2 actuations in each nostril.

Assessment of efficacy was based on the total nasal symptom score (TNSS). TNSS is calculated as the sum of the patients’ scoring of the 4 individual nasal symptoms (rhinorrhea, sneezing, nasal congestion, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) as reflective (rTNSS) or instantaneous (iTNSS). rTNSS required the patients to record symptom severity over the previous 12 hours; iTNSS required the patients to record symptom severity over the previous 10 minutes. Morning and evening TNSS scores were averaged over the treatment period and the difference from placebo in the change from baseline rTNSS was the primary efficacy endpoint. The morning rTNSS reflects the TNSS at the end of the 24-hour dosing interval and is an indication of whether the effect was maintained over the 24-hour dosing interval.

Dose-Ranging Trial: The dose-ranging trial was a 2-week trial that evaluated the efficacy of 3 doses of beclomethasone dipropionate nasal aerosol (80, 160, and 320 mcg, once daily) in patients with seasonal allergic rhinitis. In this trial, only treatment with beclomethasone dipropionate nasal aerosol at the dose of 320 mcg/day resulted in statistically significant improvements compared with placebo in the primary efficacy endpoint, iTNSS (Table 3).

<table>
<thead>
<tr>
<th>Dose (mcg/day)</th>
<th>rTNSS</th>
<th>iTNSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>320</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14 CLINICAL STUDIES

14.1 Seasonal and Perennial Allergic Rhinitis

Clinical studies: The clinical studies were performed in non-special populations.

14.1.1 Seasonal Allergic Rhinitis

The clinical studies were performed in non-special populations.

14.1.2 Perennial Allergic Rhinitis

The clinical studies were performed in non-special populations.
QNASL® (beclomethasone dipropionate) Nasal Aerosol

Table 3. Mean Changes from Baseline in Reflective Total Nasal Symptom Score Over 2 Weeks in Adult and Adolescent Patients with Seasonal Allergic Rhinitis (ITT Population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline (SD)</th>
<th>LS Mean (SE)</th>
<th>Difference From Placebo</th>
<th>LS Mean 95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate 320 mcg/day</td>
<td>122</td>
<td>9.17 (1.66)</td>
<td>-2.22 (0.18)</td>
<td>-0.63</td>
<td>-1.13, 0.13</td>
<td></td>
</tr>
<tr>
<td>Beclomethasone dipropionate 160 mcg/day</td>
<td>123</td>
<td>9.24 (1.57)</td>
<td>-1.87 (0.18)</td>
<td>-0.29</td>
<td>-0.78, 0.21</td>
<td></td>
</tr>
<tr>
<td>Beclomethasone dipropionate 80 mcg/day</td>
<td>118</td>
<td>9.33 (1.72)</td>
<td>-1.88 (0.18)</td>
<td>-0.29</td>
<td>-0.80, 0.21</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>123</td>
<td>8.98 (1.47)</td>
<td>-1.59 (0.18)</td>
<td>-0.63</td>
<td>-1.13, 0.13</td>
<td></td>
</tr>
</tbody>
</table>

The 320 mcg dose also demonstrated a statistically significant decrease in morning iTNSS than placebo, indicating that the effect was maintained over the 24-hour dosing interval.

Table 4. Mean Changes from Baseline in Reflective and Instantaneous Total Nasal Symptom Scores Over 2 Weeks in Pediatric Patients with Seasonal or Perennial Allergic Rhinitis (ITT Population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline (SD)</th>
<th>LS Mean (SE)</th>
<th>Difference From Placebo</th>
<th>LS Mean 95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflective Total Nasal Symptom Scores</td>
<td>234</td>
<td>8.1 (1.99)</td>
<td>-1.6 (0.13)</td>
<td>-0.63</td>
<td>-1.0, -0.3</td>
<td></td>
</tr>
<tr>
<td>Instantaneous Total Nasal Symptom Scores</td>
<td>234</td>
<td>8.2 (2.10)</td>
<td>-1.0 (0.13)</td>
<td>-0.63</td>
<td>-1.0, -0.3</td>
<td></td>
</tr>
</tbody>
</table>

The 320 mcg daily dose also demonstrated a statistically significant decrease in morning iTNSS than placebo, indicating that the effect was maintained over the 24-hour dosing interval. Based on the results from the dose ranging trial, the 320 mcg dose was chosen as the dose for pediatric patients 4-11 years of age.

Table 5. Mean Changes from Baseline in Reflective and Instantaneous Total Nasal Symptom Scores Over 2 Weeks in Pediatric Patients with Perennial Allergic Rhinitis (ITT Population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Baseline (SD)</th>
<th>LS Mean (SE)</th>
<th>Difference From Placebo</th>
<th>LS Mean 95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflective Total Nasal Symptom Scores</td>
<td>167</td>
<td>9.6 (1.51)</td>
<td>-2.0 (0.16)</td>
<td>-0.91</td>
<td>-1.3, -0.5</td>
<td></td>
</tr>
<tr>
<td>Instantaneous Total Nasal Symptom Scores</td>
<td>167</td>
<td>9.0 (1.74)</td>
<td>-1.7 (0.15)</td>
<td>-0.92</td>
<td>-1.3, -0.5</td>
<td></td>
</tr>
</tbody>
</table>

For pediatric patients 4-11 years of age, improvements in average patient-reported rTNSS and iTNSS were also significantly greater in QNASL Nasal Aerosol 80 mcg per day treated patients compared with placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

QNASL Nasal Aerosol is supplied in 2 strengths and supplied as a pressurized aluminum canister inserted into a blue and white plastic nasal actuator with a built-in dose counter and white dust cap, as follows: QNASL 80 mcg Nasal Aerosol contains 10.6 g of drug and excipients and provides 120 actuations (NDC 59310-410-12). Each actuation delivers 80 mcg of beclomethasone dipropionate from the nasal actuator and 100 mcg from the valve. QNASL 80 mcg Nasal Aerosol contains 6.8 g of drug and excipients and provides 60 actuations (NDC 59310-406-06). Each actuation delivers 40 mcg of beclomethasone dipropionate from the nasal actuator and 50 mcg from the valve. Each canister of QNASL Nasal Aerosol has a dose counter, which initially reads 60 sprays or 120 sprays for the respective products, and counts down each time a spray is released. The correct amount of medication in each intranasal dose cannot be ensured after the counter reads 0; therefore, the device should be discarded when the counter reads 0.

Do not remove the QNASL Nasal Aerosol canister from the actuator. The QNASL Nasal Aerosol canister should only be used with the QNASL Nasal Aerosol actuator and the actuator should not be used with any other drug product.

CONTENTS UNDER PRESSURE

Do not puncture. Do not store near heat or open flame. Do not expose to temperatures higher than 49°C (120°F) as this may cause bursting of the canister. Never throw the device into a fire or an incinerator.

Store at temperature between 20° and 25°C (68° and 77°F); excursions are permitted between 15° and 30°C (59° and 86°F). Keep out of reach of children.
PATIENT INFORMATION

PATIENT INFORMATION

QNALS® (beclomethasone dipropionate) Nasal Aerosol

QNALS Nasal Aerosol is available in 2 different strengths:
• QNALS Nasal Aerosol 40 mcg is only for use in children 4 years to 11 years of age and should be given under the supervision of a parent, guardian or caregiver.
• QNALS Nasal Aerosol 80 mcg is only for use in adolescents and adults 12 years of age and older.

What is QNALS Nasal Aerosol?
QNALS Nasal Aerosol is a prescription medicine that treats seasonal nasal and year-round nasal allergy symptoms in children 4 years of age and older.
It is not known if QNALS Nasal Aerosol is safe and effective in children under 4 years of age.

Who should not use QNALS Nasal Aerosol?
Do not use QNALS Nasal Aerosol if you or your child is allergic to beclomethasone dipropionate or any of the ingredients in QNALS Nasal Aerosol. See the end of this leaflet for a complete list of ingredients in QNALS Nasal Aerosol.

What should you tell your or your child’s healthcare provider before using QNALS Nasal Aerosol?
Before using QNALS Nasal Aerosol, tell the healthcare provider about all of your medical conditions, including if you or your child:
• has had recent nose problems such as nasal sores, nasal surgery, or a nasal injury.
• has or have had eye problems, such as blurred vision, increased pressure in their eye (glaucoma) or cataracts.
• has tuberculosis or any untreated fungal, bacterial, or viral infections, or eye infections caused by herpes.
• has not had or been vaccinated for chickenpox or measles.
• is pregnant or plans to become pregnant. It is not known if QNALS Nasal Aerosol will harm an unborn baby. Talk to the healthcare provider if you or your child is pregnant or plans to become pregnant.
• is breastfeeding or plans to breastfeed. It is not known if QNALS Nasal Aerosol passes into breast milk. Talk to the healthcare provider about the best way to feed the baby if you or your child is using QNALS Nasal Aerosol.

Tell the healthcare provider about all of the medicines you or your child takes, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
QNALS Nasal Aerosol and other medicines may affect each other and cause side effects. QNALS Nasal Aerosol may affect the way other medicines work, and other medicines may affect the way QNALS Nasal Aerosol works.

Especially tell the healthcare provider if you or your child takes other corticosteroid medicines.
Ask the healthcare provider for a list of these medicines if you are not sure.

How should you or your child use QNALS Nasal Aerosol?
• QNALS Nasal Aerosol 40 mcg is only for use in children 4 years to 11 years of age and should be given under the supervision of a parent, guardian or caregiver.
• QNALS Nasal Aerosol 80 mcg is only for use in adolescents 12 years of age and older.
• Read the step-by-step Instructions for Use at the end of this leaflet for specific information about the right way to use QNALS Nasal Aerosol.
• QNALS Nasal Aerosol is for use in the nose only. Do not spray it in your eyes or mouth and do not let your child spray it in their eyes or mouth.

continued
- Use QNASL Nasal Aerosol exactly as the healthcare provider tells you or your child to use it. Do not use more of your medicine or use it more often or let your child use more of the medicine or use it more often than the healthcare provider tells you.
- QNASL Nasal Aerosol does not need to be primed.
- QNASL Nasal Aerosol 40 mcg:
  - contains 60 sprays, and
  - has a spray counter which initially should read 60 sprays, and counts down each time a spray is released.
- QNASL Nasal Aerosol 80 mcg:
  - contains 120 sprays, and
  - has a spray counter which initially should read 120 sprays, and counts down each time a spray is released.
- Do not use the QNASL Nasal Aerosol after the spray counter reads 0. You or your child may not get the right amount of medicine.
- The usual dose of QNASL Nasal Aerosol:
  - 40 mcg is 1 spray in each nostril, 1 time a day for children who are 4 years to 11 years of age. Your child should not use more than a total of 2 sprays per day.
  - 80 mcg is 2 sprays in each nostril, 1 time a day for adolescents and adults 12 years of age and older. You should not use more than a total of 4 sprays per day.
- You and your child will get the best results if they keep using QNASL Nasal Aerosol regularly each day. If you or your child’s symptoms do not improve or get worse, call the healthcare provider.

What are the possible side effects of QNASL Nasal Aerosol? QNASL Nasal Aerosol may cause serious side effects, including:
- nose bleeds or nasal ulcers. The healthcare provider should check the inside of you or your child’s nose (nasal mucosa) for problems during treatment with QNASL Nasal Aerosol. Talk to the healthcare provider if the nose bleeds or has nasal ulcers.
- fungal infections (thrush) in the nose, mouth, or throat. Tell the healthcare provider if you or your child has any redness or white colored patches in the mouth or throat.
- slow wound healing. You or your child should not use QNASL Nasal Aerosol until the nose has healed if there was a sore in the nose, if you or your child had surgery on the nose, or the nose has been injured.
- eye problems. If you or your child has had glaucoma, cataracts or blurred vision in the past, you or your child should have regular eye exams while using QNASL Nasal Aerosol. Tell the healthcare provider if you or your child has any change in vision during treatment with QNASL Nasal Aerosol.
- serious allergic reactions. Stop using QNASL Nasal Aerosol and call the healthcare provider right away or get emergency medical help right away if you or your child get any of the following signs and symptoms of a serious allergic reaction:
  - hives
  - swelling of your lips, tongue or face
  - rash
  - breathing problems
- immune system effects and a higher chance for infections. Tell your or your child’s healthcare provider about any signs or symptoms of infection such as:
  - fever
  - feeling tired
  - pain
  - body aches
  - vomiting
  - chills
- reduced adrenal function (adrenal insufficiency). Adrenal insufficiency can happen in people who take higher doses of QNASL than recommended over a long period of time. Symptoms of adrenal insufficiency may include:
  - feeling tired
  - weakness
  - dizziness
  - vomiting
  - nausea

How should I store QNASL Nasal Aerosol? Store QNASL Nasal Aerosol at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not puncture the QNASL Nasal Aerosol canister.
- Do not store the QNASL Nasal Aerosol canister near heat or a flame. Temperatures above 120°F (49°C) may cause the canister to burst.
- Do not throw the QNASL Nasal Aerosol canister into a fire or an incinerator.
- Safely throw away medicine that is out of date or no longer needed.

Keep QNASL Nasal Aerosol and all medicines out of the reach of children.

General information about the safe and effective use of QNASL Nasal Aerosol
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use QNASL Nasal Aerosol for a condition for which it was not prescribed. Do not give QNASL Nasal Aerosol to other people, even if they have the same symptoms that you or your child has. It may harm them. You can ask your pharmacist or healthcare provider for information about QNASL Nasal Aerosol that is written for health professionals.

What are the ingredients in QNASL Nasal Aerosol? Active ingredient: beclomethasone dipropionate
Inactive ingredient: propellant HFA-134a and dehydrated ethanol

For more information, go to www.QNASL.com or call 1-855-55-QNASL (1-855-557-6275).

QNSPL-001
Rev. 03/2018
PLEASE SEE REVERSE SIDE FOR INSTRUCTIONS FOR USE.
INSTRUCTIONS FOR USE

QNASL® (kyoo nay’ zel) 80 mcg
(beclomethasone dipropionate)
Nasal Aerosol

Read these Instructions for Use for QNASL Nasal Aerosol before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

Note: For Use in the Nose Only.

• Do not spray QNASL Nasal Aerosol in your eyes, mouth or directly onto your nasal septum (the wall between your 2 nostrils).

The parts of your QNASL Nasal Aerosol

The QNASL Nasal Aerosol device comes as a canister that fits into a nasal actuator with a built-in spray counter and protective dust cap. (See Figure A).

• Do not use the QNASL Nasal Aerosol actuator with a canister of medicine from any other inhaler.

• Do not use the QNASL Nasal Aerosol device with an actuator from any other inhaler.

• Do not remove the QNASL Nasal Aerosol canister from the actuator.

• When you first remove the QNASL Nasal Aerosol device from the carton, the spray counter should read “120” (See Figure B).

• You do not need to prime your QNASL Nasal Aerosol device.

Using Your QNASL Nasal Aerosol Device

Step 1: Blow your nose to clear your nostrils.
Step 2: Remove the protective dust cap from your QNASL Nasal Aerosol device by pulling it straight off.
Step 3: Look at the nasal actuator tip to make sure it is clear of foreign objects.
Step 4: Hold your QNASL Nasal Aerosol device upright and insert the nasal actuator tip into one nostril (See Figure C).

Step 5: Point the QNASL Nasal Aerosol device slightly away from the wall between your nostrils (nasal septum) while holding your other nostril closed (See Figure D).

Step 6: Hold your breath and press down firmly and completely on the canister to release 1 spray (See Figure E). Continue to hold your breath for 5 seconds after releasing the spray and then breathe out slowly through your mouth. Take the QNASL Nasal Aerosol device out of your nostril.

Step 7: Repeat steps 3-6 for the second spray in the same nostril.
Step 8: Repeat steps 3-7 for your other nostril.
Step 9: You should not blow your nose for the next 15 minutes
Note: The spray counter will count down each time there is a spray released from your QNASL Nasal Aerosol device.
Step 10: Clean and store your device. See “Cleaning Your QNASL Nasal Aerosol device.”

Cleaning Your QNASL Nasal Aerosol device

• Wipe the nasal actuator tip with a clean, dry tissue or cloth (See Figure F).

• Do NOT wash or put any part of the QNASL Nasal Aerosol canister or actuator in water (See Figure G).

• Replace the protective dust cap.

• Keep your device clean and dry at all times.

How to know when to stop using your QNASL Aerosol device

• The QNASL Nasal Aerosol device has a spray counter, which is there to let you know how many sprays of medicine you have left.

• Do not use your QNASL Nasal Aerosol device when 0 is shown in the spray counter window (See Figure H).

• Throw away your QNASL Nasal Aerosol device when the spray counter reaches 0.

• Do not throw your QNASL Nasal Aerosol canister into a fire or an incinerator.
INSTRUCTIONS FOR USE

QNALS® (kyoo nay'zel) 40 mcg (beclomethasone dipropionate) Nasal Aerosol

Read these Instructions for Use for QNASL Nasal Aerosol before your child starts using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to the healthcare provider about your child’s medical condition or treatment.

Note: For Use in the Nose Only.

• Do not spray QNASL Nasal Aerosol in the eyes, mouth or directly onto the nasal septum (the wall between the 2 nostrils).

The parts of your QNASL Nasal Aerosol

The QNASL Nasal Aerosol device comes as a canister that fits into a nasal actuator with a built-in spray counter and protective dust cap. (See Figure A)

• Do not use the QNASL Nasal Aerosol actuator with a canister of medicine from any other inhaler.
• Do not use the QNASL Nasal Aerosol canister with an actuator from any other inhaler.
• Do not remove the QNASL Nasal Aerosol canister from the actuator.
• When you first remove the QNASL Nasal Aerosol device from the carton, the spray counter should read “60” (See Figure B).

• You do not need to prime the QNASL Nasal Aerosol device.

Using the QNASL Nasal Aerosol 40 mcg device in Children 4 years to 11 Years of Age

Children may need help from parents, guardians or caregivers.

Step 1: Have your child blow their nose to clear their nostrils.
Step 2: Remove the protective dust cap from the QNASL Nasal Aerosol device by pulling it straight off.

Step 3: Look at the nasal actuator tip to make sure it is clear of foreign objects.
Step 4: Hold the QNASL Nasal Aerosol device upright and insert the nasal actuator tip into 1 nostril (See Figure C).

Step 5: Point the QNASL Nasal Aerosol device slightly away from the wall between the nostrils (nasal septum) while holding the other nostril closed (See Figure D).

Step 6: Have your child hold their breath and press down firmly and completely on the canister to release 1 spray (See Figure E). Continue to have your child hold their breath for 5 seconds after releasing the spray and then have them breathe out slowly through their mouth. Take the QNASL Nasal Aerosol device out of the nostril.

Step 7: Repeat steps 3-6 for the other nostril.
Step 8: Your child should not blow their nose for the next 15 minutes.
Note: The spray counter will count down each time there is a spray released from the QNASL Nasal Aerosol device.
Step 9: Clean and store the device. See “Cleaning the QNASL Nasal Aerosol device.”

Cleaning the QNASL Nasal Aerosol device

• Wipe the nasal actuator tip with a clean, dry tissue or cloth (See Figure F).
• Do NOT wash or put any part of the QNASL Nasal Aerosol canister or actuator in water (See Figure G).
• Replace the protective dust cap.
• Keep QNASL Nasal Aerosol device clean and dry at all times.

How to know when to stop using the QNASL Nasal Aerosol device

• The QNASL Nasal Aerosol device has a spray counter, which is there to let you know how many sprays of medicine are left.
• Do not use the QNASL Nasal Aerosol device when 0 is shown in the spray counter window (See Figure H).
• Throw away the QNASL Nasal Aerosol device when the spray counter reaches 0.
• Do not throw the QNASL Nasal Aerosol canister into a fire or an incinerator.
• Talk with the healthcare provider before the QNASL Nasal Aerosol medicine runs out to see if you should get a refill.

Manufactured for:
Teva Respiratory, LLC
Frazer, PA 19355

By:
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Waterford, Ireland
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