QVAR REDIHALER® (beclomethasone dipropionate HFA) inhalation aerosol, for oral inhalation use

1 INDICATIONS AND USAGE

QVAR REDIHALER® is a corticosteroid indicated for maintenance treatment of asthma as prophylactic therapy in adults and pediatric patients 4 years of age and older. (1)

2 DOSAGE AND ADMINISTRATION

2.1 General Overview

QVAR REDIHALER is not indicated for the relief of acute bronchospasm. (2.1)

For oral inhalation only. (2.3)

• Starting dosage is based on prior asthma therapy and disease severity. (2.2)
• Treatment of asthma in patients 4 to 11 years of age: 40 mcg or 80 mcg twice daily. (2.2)
• Treatment of asthma in patients 12 years of age and older: 40 mcg, 80 mcg, 160 mcg, or 320 mcg twice daily. (2.2)
• Discard QVAR REDIHALER inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first. (2.1)
• Do not use a spacer or volume holding chamber. (2.1)

Inhalation: 40 mcg or 80 mcg per breath actuation. (3)

2.2 Recommended Dosage

• Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. (4)
• Hypersensitivity to any of the ingredients of QVAR REDIHALER. (4)

2.3 Administration

• Priming: QVAR REDIHALER does not require priming. (2.3)

• Routine maintenance is not required. If the mouthpiece needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed.

• Keep the inhaler clean and dry at all times. Never wash or put any part of the inhaler in water.

• Routine maintenance is not required. If the mouthpiece needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed.

3 DOSAGE FORMS AND STRENGTHS

Inhalation: 40 mcg or 80 mcg per breath actuation. (3)

4 CONTRAINDICATIONS

• Oropharyngeal candidiasis: Candida albicans infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk. (5.1)
• Deterioration of asthma and acute episodes: Do not use QVAR REDIHALER for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma.(5.2)

5 WARNINGS AND PRECAUTIONS

5.1 Oropharyngeal Candidiasis

• Transfer patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to QVAR REDIHALER. (5.3)
• Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. Use with caution in patients with these infections because of the potential for worsening of these infections. (5.4)
• Paradoxical bronchospasm: Bronchospasm, with an immediate increase in wheezing, may occur after dosing. Treat bronchospasm immediately with inhaled, short-acting bronchodilator and discontinue QVAR REDIHALER. (5.5)
• Hypersensitivity reactions: Hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm may occur. Discontinue QVAR REDIHALER if such reactions occur. (5.6)
• Hypertension and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue QVAR REDIHALER slowly. (5.7)
• Effects on growth: Monitor growth of pediatric patients. (5.8)
• Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.9)
• Glaucome and cataracts: Monitor patients with change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts closely. (5.10)

6 ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3% and > placebo) include oral candidiasis, upper respiratory tract infection, nasopharyngitis, allergic rhinitis, oropharyngeal pain and sinusitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 01/2021

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1 INDICATIONS AND USAGE

QVAR REDIHALER® is indicated for maintenance treatment of asthma as prophylactic therapy in adults and pediatric patients 4 years of age and older. (1)

Limitations of Use: QVAR REDIHALER is not indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 General Overview

Administer QVAR REDIHALER by oral inhalation. After inhalation, rinse mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis. Consistent dose delivery is achieved, whether using the 40- or 80-mcg strengths, due to proportionality of the 2 products (i.e., 2 actuations of 40-mcg strength should provide a dose comparable to 1 actuation of the 80-mcg strength).

Inhaler Instructions

• Patients should be instructed on the proper use of their inhaler.
• Do not use QVAR REDIHALER without a spacer or volume holding chamber.
• Shaking the inhaler prior to use is not necessary. Do not shake the inhaler with the cap open to avoid possible actuation of the device.

Priming

• QVAR REDIHALER does not require priming.

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*Sections or subsections omitted from the full prescribing information are not listed.
Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids
Transfer of patients from systemic corticosteroid therapy to QVAR REDIHALER may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

Corticosteroid Withdrawal Symptoms
During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

5.4 Immunosuppression and Risk of Infections
Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune patients on corticosteroids. In such patients who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is not known how the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection, and nor is the contribution of the underlying disease to the susceptibility. If exposed to chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

5.5 Paradoxical Bronchospasm
Inhaled corticosteroids may produce inflammation-induced bronchospasm with an immediate increase in airway resistance. If paradoxical bronchospasm occurs following dosing with QVAR REDIHALER, it should be treated immediately with an inhaled, short-acting bronchodilator. Treatment with QVAR REDIHALER should be discontinued and alternate therapy instituted.

5.6 Immediate Hypersensitivity Reactions
Hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm, may occur after administration of QVAR REDIHALER. Discontinue QVAR REDIHALER if such reactions occur (See Contraindications (4)).

5.7 Hypercorticism and Adrenal Suppression
QVAR REDIHALER will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since beclometasone dipropionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of QVAR REDIHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective HPA dose.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with QVAR REDIHALER should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when beclometasone dipropionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of QVAR REDIHALER should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for the management of asthma symptoms.

5.8 Effects on Growth
Orally inhaled corticosteroids, including QVAR REDIHALER, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving QVAR REDIHALER routinely (e.g., via stadiometry). To minimize the systemic effects of inhaled corticosteroids, QVAR REDIHALER should not be titrated to exceed the patient's dose to the lowest dosage that effectively controls his/her symptoms (See Use in Specific Populations (8.4)).

5.9 Reduction in Bone Mineral Density
Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term outcomes, such as fracture, is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids) should be monitored and treated with established standards of care.

Glaucoma and Cataracts
Glaucoma, increased intraocular pressure, blurred vision and cataracts have been reported following the use of long-term administration of inhaled corticosteroids. 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 while using QVAR REDIHALER.

6. ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Oropharyngeal candidiasis (See Warnings and Precautions (5.1))
- Immunosuppression and risk of infections (See Warnings and Precautions (5.4))
- Hypercorticism and adrenal suppression (See Warnings and Precautions (5.7))
- Reduction in bone mineral density (See Warnings and Precautions (5.9))
- Growth effects (See Warnings and Precautions (5.8) and Use in Specific Populations (8.4))
- Ocular effects (See Warnings and Precautions (5.10))

6.1 Clinical Trials Experience
A total of 1858 subjects participated in the QVAR REDIHALER clinical development program. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
QVAR® REDIHALER® (beclomethasone dipropionate HFA) inhalation aerosol

Adults and Adolescent Patients 12 years of Age and Older: The adverse reaction information presented in Table 1 is derived from 3 double-blind, placebo-controlled clinical trials in which 1230 patients (751 female and 479 male adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with QVAR REDIHALER (doses of 40, 80, 160, or 320 mcg twice daily) or QVAR (beclomethasone dipropionate HFA) Inhalation Aerosol (QVAR MDI; doses of 160 or 320 mcg twice daily) or placebo. In considering these data, differences in average duration of exposure and clinical trial design should be taken into account.

Table 1: Adverse Reactions Experienced by at Least 3% of Adult and Adolescent Patients in the QVAR REDIHALER or QVAR MDI Groups and Greater Than Placebo by Treatment and Daily Dose

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QVAR REDIHALER</td>
</tr>
<tr>
<td>Oral Candidiasis</td>
<td>0 (2)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Viral Upper Respiratory Tract Infection</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Rhinitis Allergic</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*QVAR MDI=QVAR Inhalation Aerosol

Other adverse reactions that occurred in clinical trials using QVAR REDIHALER with an incidence of 1% to 3% and which occurred at a greater incidence than placebo were back pain, headache, pain, nausea and cough.

Table 2: Adverse Reactions Experienced by at Least 3% of Patients 4 to 11 Years of Age in the QVAR REDIHALER or QVAR MDI Groups and Greater Than Placebo by Treatment and Daily Dose

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QVAR REDIHALER</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Viral Upper Respiratory Tract Infection</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*QVAR MDI=QVAR Inhalation Aerosol

Other adverse reactions that occurred in clinical trials using QVAR REDIHALER with an incidence of 1% to 3% and which occurred at a greater incidence than placebo were influenza, gastroenteritis viral, ear infection, oral candidiasis, diarrhea, and myalgia.

6.2 Postmarketing Experience

In addition to the adverse reactions reported from clinical trials with QVAR REDIHALER, the following adverse reactions have been identified during post-approval use of QVAR MDI and other inhaled corticosteroids. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

6.3 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with QVAR REDIHALER or beclomethasone dipropionate in pregnant women. There are clinical considerations with the use of inhaled corticosteroids (ICS), including beclomethasone dipropionate, in pregnant women (see Clinical Considerations). Also, no published studies, including studies of large birth registries, have to date related the use of ICS to any increases in congenital 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 0.75 times the maximum recommended human daily dose (MRHDID) in adults (0.64 mg/day [see Data]; in rats exposed to beclomethasone dipropionate inhalation, doses to behalve in the fetal adrenal glands were observed in doses greater than 180 times the MRHDID, but there was no evidence of external or skeletal malformations or embryolethality at inhalation doses of up to 440 times the MRHDID. The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. In the US general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

The risk of complications to the mother and developing fetus from inadequate control of asthma must be balanced against the risks from exposure to beclomethasone dipropionate. In women who are moderately controlled asthma, evidence demonstrated an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age for the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted to maintain optimal control.

Labor or Delivery

There is no specific human data regarding any adverse effects of inhaled 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 inhaled doses 180 times the MRHDID 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 40 times the MRHDID 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 at inhaled doses up to 440 times the MRHDID (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 18 at subcutaneous doses equal to and greater than 0.75 times the MRHDID 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). A 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 18 at subcutaneous doses equal to and greater than 2.3 times the MRHDID in adults (on a mg/m² basis at a maternal dose of 0.3 mg/kg/day) produced embryolethal effects (increased fetal resorptions) and decreased pup survival.

In an embryofetal development study in pregnant rabbits, beclomethasone dipropionate administration during organogenesis from gestation days 7 to 16 at subcutaneous doses equal to and greater than 0.75 times the MRHDID in adults (on a mg/m² basis at maternal doses of 0.025 mg/kg/day and higher) produced adverse developmental effects (increased incidence of cleft palate) at inhaled doses up to 440 times the MRHDID (on a mg/m² basis at maternal doses up to 28.3 mg/kg/day).

6.4 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 inhaled 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 QVAR REDIHALER and potential adverse effects on the breastfed child from beclomethasone dipropionate or from the underlying maternal condition.

6.5 Females and Males of Reproductive Potential

Impairment of fertility was observed in rats and dogs at oral doses of beclomethasone dipropionate corresponding to 250 and 25 times the MRHDID for adults in a mg/m² basis, respectively (see Nonclinical Toxicology (14.3)).

6.6 Pediatric Use

The safety and effectiveness of QVAR REDIHALER for the maintenance treatment of asthma as prophylactic therapy have been established in pediatric patients aged 4 years and older. Use of QVAR REDIHALER for this indication is supported by evidence from adequate and well-controlled clinical trials in children aged 6 and 11 years who were treated with at least one dose of QVAR REDIHALER or QVAR MDI in one 12-week clinical trial. The safety and effectiveness of QVAR REDIHALER in children below 4 years of age have not been established. Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. A 12-month, randomized, controlled clinical trial evaluated the effects of QVAR MDI versus beclomethasone dipropionate in a CFC propellant-based formulation (CFC-BDP) on growth in children age 5 to 11. A total of 520 patients were enrolled, of whom 394 received QVAR MDI (100 to 400 mcg/day-exvalve) and 126 received CFC-BDP (280 to 800 mcg/day-exvalve). Similar control of asthma was noted in each treatment arm. When comparing results at month 12 to baseline, the mean growth velocity in children treated with QVAR MDI was approximately 0.5 cm/year less than that noted with children treated with CFC-BDP via large-volume spacer. The long-term effects of the reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including QVAR REDIHALER, should be monitored routinely (e.g., by stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly
QVAR® REDIHALER® (beclomethasone dipropionate HFA) inhalation aerosol

sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including QVAR REDIHALER, each patient should be titrated to his/her lowest effective dose [see Dosage and Administration (2.2)].

8.5 Geometric Use

Clinical studies of QVAR REDIHALER did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

11 DESCRIPTION

The active component of QVAR REDIHALER 40 mcg Inhalation Aerosol and QVAR REDIHALER 80 mcg Inhalation Aerosol is beclomethasone dipropionate, USP, a corticosteroid having the chemical name 9-chloro-11,12[(trifluoro)-1B,1B-dimethyl]proparg-14-diene-3,20-dione (1212, dipropionate). Beclomethasone dipropionate is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. Beclomethasone differs from dexamethasone in having a chlorine at the 9-alpha carbon in place of a fluorine, and in having a 16-beta-methyl group instead of a 16-alpha-methyl group. Beclomethasone dipropionate is a white to creamy white, odorless powder with a molecular formula of C22H28Cl2O6 and a molecular weight of 521.1. Its chemical structure is:

![Chemical Structure of Beclomethasone Dipropionate](image)

**QVAR REDIHALER** is a pressurized, breath-actuated, metered-dose aerosol with a dose counter intended for oral inhalation only. Each unit consists of a sealed breath-actuated inhaler device enclosing a canister containing a solution of beclomethasone dipropionate in propellant HFA-134a (1,1,1,2-tetrafluoroethane) and ethanol (0.85 g). QVAR REDIHALER 40 mcg delivers 40 mcg of beclomethasone dipropionate from the actuator mouthpiece and 50 mcg from the canister valve. QVAR REDIHALER 80 mcg delivers 80 mcg of beclomethasone dipropionate from the actuator mouthpiece and 100 mcg from the canister valve. Both products deliver 50 microliters (59 milligrams) of solution formulation as an aerosol from the canister valve with each actuation. The 40-mcg canisters and the 80-mcg canisters provide 120 inhalations each. Since the QVAR REDIHALER canister is fitted with a primeless valve, no priming actuations are required before use. For both products, an actuation was always triggered by a 20 L/min inspiratory flow rate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Beclomethasone dipropionate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism of corticosteroid action on asthma is not known. Corticosteroids have been shown to have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and release of inflammatory mediators (e.g., histamine, leukotrienes, and cytokines). These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Beclomethasone dipropionate is a prodrug that is rapidly activated by hydrolysis to the active monoester, 17-monopropionate (17-BMP). Beclomethasone-17-monopropionate has been shown to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of beclomethasone (BOH). The clinical significance of these binding affinities is unknown.

Studies in patients with asthma have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects with recommended doses of QVAR REDIHALER.

12.2 Pharmacodynamics

**HPA Axis Effects**

The effects of QVAR MDI on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 40 corticosteroid-naive patients. QVAR MDI, at doses of 80, 160, or 320 mcg twice daily, was compared to placebo. Active treatment showed an expected dose-related reduction in 24-hour urinary-free cortisol (a sensitive marker of adrenal production of cortisol). Patients treated with the highest dose recommended of QVAR MDI (320 mcg twice daily) had a 37% reduction in 24-hour urinary-free cortisol compared to a reduction of 41.3% produced by treatment with 336 mcg twice daily of CFC-BDP. There was a 12.2% reduction in 24-hour urinary-free cortisol seen in the group of patients that received 80 mcg twice daily of QVAR MDI and a 24.6% reduction in the group of patients that received 160 mcg twice daily. An open label study of 354 asthma patients given QVAR MDI at recommended doses for one year assessed the effect of treatment with this product on the HPA axis (as measured by both morning and stimulated plasma cortisol). Less than 1% of patients treated for one year with this product had an abnormal response (peak less than 18 mcg/dL) to the test. The major route of elimination of inhaled beclomethasone dipropionate appears to be via hydrolysis. More than 90% of inhaled beclomethasone dipropionate is found as 17-BMP in the systemic circulation. The mean terminal half-life of 17-BMP is approximately 4 hours for QVAR REDIHALER.

**Excretion**

Irrespective of the route of administration (injection, oral or inhalation), beclomethasone dipropionate and its metabolites are mainly excreted in the feces. Less than 10% of the drug and its metabolites are excreted in the urine.

Specific Populations

No pharmacokinetic studies for QVAR REDIHALER have been conducted in neonates or elderly subjects.

**Pediatric Patients:** No pharmacokinetic studies for QVAR REDIHALER have been conducted in pediatric subjects aged 4 to 17 years. However, the pharmacokinetics of 17-BMP, including dose and strength proportionality, is similar in children and adults using QVAR MDI. Although the systemic exposure is highly variable. In children (mean age 10 years), the Cmax of 17-BMP was 787 pg/mL at 0.6 hour after inhalation of 160 mcg (4 actuations of the 40 mcg/actuation strength of QVAR MDI). The systemic exposure to 17-BMP from 160 mcg of QVAR MDI administered without a spacer was comparable to the systemic exposure to 17-BMP from 336 mcg CFC-BDP administered with a spacer (mean intravenous dose in 14 children was 0.1 mg/kg). This implies that approximately twice the systemic exposure to 17-BMP would be expected for comparable mg doses of QVAR MDI without a spacer and CFC-BDP with a large volume spacer.

**Male and Female Patients:** The influence of sex on the pharmacokinetics of QVAR REDIHALER has not been studied.

**Racial or Ethnic Groups:** The influence of race on the pharmacokinetics of QVAR REDIHALER has not been studied.

**Patients with Renal Impairment:** The effect of renal impairment on the pharmacokinetics of QVAR REDIHALER has not been evaluated.

**Patients with Hepatic Impairment:** The effect of hepatic impairment on the pharmacokinetics of QVAR REDIHALER has not been evaluated.

**Drug Interaction Studies:** In vitro and in vivo drug interaction studies have not been conducted with QVAR REDIHALER.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 55 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of treatment-related increases in the incidence of tumors in this study at the highest dose, which is approximately 37 and 72 times the MRHID in adults and children, respectively, on a mg/m² basis.

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

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 1 mg/kg/day (approximately 250 times the MRHID in adults on a mg/m² basis). Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 25 times the MRHID in adults on a mg/m² basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mcg (approximately 17 times the MRHID in adults on a mg/m² basis).

14 CLINICAL STUDIES

The safety and efficacy of QVAR REDIHALER were evaluated in 1,858 patients with asthma. The development program included 2 confirmatory trials of 12 weeks duration and 1 confirmatory trial of 6 weeks duration in patients 12 years of age and older, and 1 confirmatory trial of 12 weeks duration in patients 4 to 11 years of age. The efficacy of QVAR REDIHALER is based primarily on the confirmatory trials described below.

14.1 Trials in the Maintenance Treatment of Asthma

**Adult and Adolescent Patients 12 Years of Age and Older**

Two confirmatory clinical trials were conducted comparing QVAR REDIHALER with placebo in adult and adolescent patients with persistent asthma (Trial 1 and Trial 2).

**Trial 1 (NCT02040779):** This randomized, double-blind, parallel-group, placebo-controlled, 12-week, efficacy and safety trial compared QVAR REDIHALER 40 and 80 mcg given as 1 inhalation twice daily with placebo in adult and adolescent patients with persistent symptomatic asthma despite low-dose inhaled corticosteroid or non-corticosteroid asthma therapy. Patients aged 12 years and older who met the entry criteria including FEV1 40-85 percent of predicted normal, reversible bronchoconstriction of 15% with short-acting inhaled beta-agonist entered a 14-21 day run-in period. 270 patients (104 previously treated with inhaled corticosteroids) who met all the randomization criteria including asthma symptoms and rescue medication use were discontinued from asthma maintenance medication and randomized equally to treatment with QVAR REDIHALER 80 mcg/day, QVAR REDIHALER 160 mcg/day or placebo. Baseline FEV1 values were similar across treatments. The primary endpoint for this trial was the standardized...
Baseline-adjusted trough morning forced expiratory volume in 1 second (FEV₁) area under the effect curve from time zero to 12 weeks. Patients in both treatment groups had significantly greater improvements in trough FEV₁, compared to placebo (QVAR REDIHALER 80 mcg/day, LS mean change of 0.214 L and QVAR REDIHALER 160 mcg/day, LS mean change of 0.196 L over 12 weeks) (Table 3).

In addition, the mean change from baseline is displayed in Figure 1. Both doses of QVAR REDIHALER were effective in improving asthma control with significantly greater improvements in FEV₁, and morning PEF when compared to placebo. Reduction in asthma symptoms was also supportive of the efficacy of QVAR REDIHALER.

Figure 1: A 12-Week Clinical Trial in Patients with Asthma: Mean Change in FEV₁

### Table 3: Primary Analysis of Standardized Baseline-Adjusted Trough Morning FEV₁, (L) AUEC from Time Zero to the End of the Treatment Period 12-week Study and 6-week Dose Response Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>QVAR REDIHALER 80 mcg/day (N=80)</th>
<th>QVAR REDIHALER 160 mcg/day (N=82)</th>
<th>Placebo</th>
<th>QVAR REDIHALER 320 mcg/day (N=108)</th>
<th>QVAR REDIHALER 640 mcg/day (N=105)</th>
<th>QVAR MDI* 320 mcg/day (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference from placebo</td>
<td>0.24</td>
<td>0.196</td>
<td>0.144</td>
<td>0.050</td>
<td>0.148</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.054 to 0.193</td>
<td>-0.048 to 0.185</td>
<td>-0.0807 to 0.2066</td>
<td>-0.0868 to 0.2122</td>
<td>-0.0842 to 0.2194</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*QVAR MDI= QVAR Inhalation Aerosol

Pediatric Patients 4 to 11 Years of Age

This randomized, double-blind, parallel-group, placebo-controlled, 12-week, global efficacy and safety trial (NCT01002476) compared QVAR REDIHALER 40 or 80 mcg, QVAR MDI 40 or 80 mcg or placebo given as 1 inhalation twice daily in pediatric patients aged 4 through 11 years old with persistent symptomatic asthma despite treatment with non-corticosteroid, low dose inhaled corticosteroid (with or without a long acting beta agonist [LABA]). Patients aged 4 to 5 years who were technically unable to complete spirometry participated in the safety population. Patients who met the entry criteria including FEV₁ 40-90% predicted normal and reversible baseline asthma symptoms were randomized equally across treatment groups. Five hundred sixty-eight (568) pediatric patients with symptomatic asthma of which 410 had previously been treated with low dose inhaled corticosteroids with or without a LABA were randomized to receive either 40 mcg or 80 mcg twice daily of QVAR REDIHALER, QVAR MDI or placebo. The primary endpoint was the change from baseline in trough percent predicted FEV₁, AUEC (0-12 weeks). While the primary endpoint, was not statistically significant, change in weekly average of daily morning peak expiratory flow (PEF, L/min) over the 12 week treatment period was 11.3% (95% CI: 5.5, 17.06) and 8.5% (95% CI: 2.7, 14.24) for the 80 mcg/day and 160 mcg/day doses of QVAR REDIHALER, respectively, at nominal significance. Similar results were seen with evening PEF.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### How Supplied

QVAR REDIHALER (beclomethasone dipropionate HFA) inhalation aerosol:
- 40 mcg is supplied in a box of ten 0.6-g canister containing 120 actuations which is enclosed within a sealed maroon plastic actuator with a dose counter and hinged white cap, and Patient Information and Instructions for Use; box of one; 120 Actuations – NDC 59310-302-40
- 80 mcg is supplied in a box of one 0.6-g canister containing 120 actuations which is enclosed within a sealed maroon plastic actuator with a dose counter and hinged white dust cap, and Patient Information and Instructions for Use; box of one; 120 Actuations – NDC 59310-304-80

The correct amount of medication in each inhalation cannot be assured after 120 actuations from the 10.6-g canister even though the canister is not completely empty. Patients should be informed to discard the QVAR REDIHALER when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

#### Storage and Handling

Store at 25ºC (77ºF). Excursions between 15ºC and 30ºC (59ºF and 86ºF) are permitted (see USP Controlled Room Temperature). For optimal results, QVAR REDIHALER should be at room temperature when used. Contents under pressure. Do not use or store near heat or open flame. Exposure to temperatures above 45ºC (120ºF) may cause bursting. Never throw QVAR REDIHALER into fire or incinerator. Keep out of reach of children.

### 17 PATIENT COUNSELING INFORMATION

Advisers must be given the following information:

#### Oropharyngeal Candidiasis

Inform patients that localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while continuing therapy with QVAR REDIHALER, but at times therapy with QVAR REDIHALER may need to be temporarily interrupted under close medical supervision. Rinsing the mouth with water without swallowing after inhalation is advised to help reduce the risk of thrush.

#### Status Asthmaticus and Acute Asthma Symptoms

Inform patients that QVAR REDIHALER is not a bronchodilator and is not intended for use as rescue medicine for acute asthma exacerbations. Advise patients to treat acute asthma symptoms with an inhaled, short-acting beta-agonist such as albuterol. Instruct the patient to contact their physicians immediately if there is deterioration of their asthma.

#### Immunosuppression and Risk of Infections

Warn patients who are immunosuppressed on doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

#### Hypercorticism and Adrenal Suppression

Advise patients that QVAR REDIHALER may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, instruct patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to QVAR REDIHALER.
QVAR® REDIHALER® (beclomethasone dipropionate HFA) inhalation aerosol

Immediate Hypersensitivity Reactions
Advise patients that immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, and hypotension), including anaphylaxis, may occur after administration of QVAR REDIHALER. Patients should discontinue QVAR REDIHALER if such reactions occur and contact their healthcare provider or get emergency medical help.

Reduction in Bone Mineral Density
Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk.

Reduced Growth Velocity
Inform patients that orally inhaled corticosteroids, including QVAR REDIHALER, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of adolescents taking corticosteroids by any route.

Ocular Effects
Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts, glaucoma or blurred vision); consider regular eye examinations.

Pregnancy
Inform patients that QVAR REDIHALER has a dose counter attached to the actuator at the rear of the mouthpiece. When the patient receives the inhaler, the number 120 will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the number of sprays left in the inhaler in units of two (e.g., 120, 118, 116, etc.). When the counter displays 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their healthcare provider for a prescription refill. When the dose counter reaches 0, the background will change to solid red. Inform patients to discard QVAR REDIHALER when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

Caring for and Storing the Inhaler
For normal hygiene, the mouthpiece of QVAR REDIHALER should be cleaned weekly with a clean, dry tissue or cloth. Never wash or put any part of QVAR REDIHALER in water. Patient should replace QVAR REDIHALER in a clean or disinfected place, and then reassemble the inhaler. Inform patients to store the inhaler at room temperature and to avoid exposure to extreme heat and cold. Inform patients that shaking the inhaler prior to use is not necessary. Instruct patients not to shake the inhaler with the cap open to avoid possible actuation of the device. Instruct patients to never take QVAR REDIHALER apart.

Inform patients that QVAR REDIHALER has a dose counter attached to the actuator at the rear of the mouth piece. When the patient receives the inhaler, the number 120 will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the number of sprays left in the inhaler in units of two (e.g., 120, 118, 116, etc.). When the counter displays 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their healthcare provider for a prescription refill. When the dose counter reaches 0, the background will change to solid red. Inform patients to discard QVAR REDIHALER when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

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QVARH-003

PATIENT INFORMATION
QVAR® REDIHALER® (kue’ var red-ee-hay’ ehr) (beclomethasone dipropionate HFA) inhalation aerosol

What is QVAR REDIHALER?
• QVAR REDIHALER is a breath-actuated inhaled prescription medicine used as a maintenance treatment for the prevention and control of asthma in people 4 years of age and older.
• QVAR REDIHALER is not used to relieve sudden breathing problems. It is not known if QVAR REDIHALER is safe and effective in children less than 4 years of age.

Who should not use QVAR REDIHALER?
Do not use QVAR REDIHALER:
• to treat sudden severe symptoms of asthma.
• as a rescue inhaler.
• if you are allergic to beclomethasone dipropionate or any of the ingredients in QVAR REDIHALER. See the end of this Patient Information leaflet for a complete list of ingredients in QVAR REDIHALER.

What should I tell my healthcare provider before using QVAR REDIHALER?
Before using QVAR REDIHALER, tell your healthcare provider about all of your medical conditions, including if you:
• are exposed to chickenpox or measles.
• have or have had tuberculosis (TB) or any untreated fungal, bacterial or viral infections, or eye infections caused by herpes.
• have weak bones (osteoporosis).
• have an immune system problem.
• have or have had eye problems, such as blurred vision, increased pressure in your eye (glaucoma) or cataracts.
• are pregnant or plan to become pregnant. It is not known if QVAR REDIHALER will harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if QVAR REDIHALER passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use QVAR REDIHALER.

Tell your healthcare provider about all of the medications you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use QVAR REDIHALER?
Read the step-by-step Instructions for Use for QVAR REDIHALER at the end of this Patient Information leaflet.
• Use QVAR REDIHALER exactly as your healthcare provider tells you to. Do not use QVAR REDIHALER more often than it is prescribed.
• Do not shake the inhaler before using it. Especially, do not shake the inhaler with the cap open. This could cause the device to accidentally release medicine before you are ready to take it.
• Do not prime QVAR REDIHALER. The inhaler does not need to be primed.
• If your child needs to use QVAR REDIHALER, watch your child closely to make sure your child uses the inhaler correctly.
• Do not change or stop using QVAR REDIHALER or other asthma medicines used to treat your breathing problems unless your healthcare provider tells you to. Your healthcare provider will change your medicines as needed.
• You must use QVAR REDIHALER regularly. It may take 2 to 4 weeks, or longer, after you start using QVAR REDIHALER for your asthma symptoms to get better. Do not stop using QVAR REDIHALER, even if you are feeling better, unless your healthcare provider tells you to.
• QVAR REDIHALER comes in 2 strengths (40 mcg and 80 mcg). Your healthcare provider has prescribed the strength that is best for you. Pay attention to the differences between QVAR REDIHALER and your other inhaled medicines, including their prescribed use and the way they look.
• QVAR REDIHALER does not relieve sudden asthma symptoms. Always have a rescue inhaler with you to treat sudden symptoms. Use your rescue inhaler if you have breathing problems between doses of QVAR REDIHALER. If you do not have a rescue inhaler, call your healthcare provider to have a rescue inhaler prescribed for you.

continued
The most common side effects of QVAR REDIHALER include:

• breathing problems
• swelling of your lips, tongue or face
• rash
• breathing problems

slow growth in children. Children should have their growth checked regularly while using QVAR REDIHALER.

• lower bone density. This may be a problem for people who already have a higher chance for low bone density (osteoporosis).

• eye problems. If you have had glaucoma, cataracts or blurred vision in the past, you should have regular eye exams while using QVAR REDIHALER.

The most common side effects of QVAR REDIHALER include:

• yeast infection in the mouth (oral candidiasis)
• cold symptoms (upper respiratory tract infection)
• pain in the throat (oropharyngeal pain)
• pain or swelling in your nose and throat (nasopharyngitis)
• sinus irritation (sinusitis)
• hay fever (allergic rhinitis)
QVAR® REDIHALER® (beclomethasone dipropionate HFA) inhalation aerosol

- Always use the inhaler in the upright position (with the mouthpiece down).
- After the inhaler is prepared, it will deliver 1 inhalation of medicine when you breathe in (inhale) through the mouthpiece. Your dose might require more than 1 inhalation.
- **Do not** open the white cap or leave it open unless you are ready for your next inhalation. If the cap has been opened for more than 2 minutes or left in the open position, you will need to close the white cap before use.
- **Do not breathe out or blow into any part of the inhaler.** Breathing out or blowing into the inhaler can damage it.
- **Do not** suddenly stop using your QVAR REDIHALER. Contact your healthcare provider immediately if you stop using your QVAR REDIHALER.

There are 2 main parts of your QVAR REDIHALER including:
- the inhaler body with the mouthpiece. See Figure A.
- the white cap that covers the mouthpiece of the inhaler. See Figure A.

**Figure A**

About the Dose Counter
There is a dose counter in the back of the inhaler with a viewing window that shows you how many inhalations of medicine you have left. See Figure B.
- Your QVAR REDIHALER contains 120 inhalations. See Figure B.
- The counter on the back of your inhaler shows how many inhalations you have left. When there are 20 inhalations left, the numbers in the dose counter will change to red and you should refill your prescription or ask your healthcare provider for another prescription.
- When the dose counter shows '0', the background will turn solid red and your inhaler is empty. You should stop using the inhaler and throw it away. **Do not** put your inhaler into a fire or incinerator. See Figure B.

**Figure B**

**Important:**
- The white cap must be closed to prepare the inhaler before each inhalation or you will not receive your medicine. See Figure C.
- If the white cap is open, close the white cap to prepare your inhaler and look at the dose counter window to make sure that your inhaler is not empty. See Figure B.
- **Do not** open the cap until you are ready to take your inhalation.

**Figure C**

Using your QVAR REDIHALER:

**Step 1. Open the white cap**
- Open the white cap. See Figure D.
- Breathe out fully, away from the inhaler. **Do not** blow into the inhaler.

**Figure D**

**Remember:**
- **Do not** open the cap until you are ready to take your inhalation.
- **Never breathe out or blow into the inhaler.** Breathing out or blowing into the inhaler can damage it.

**Step 2. Inhale 1 Time**
- Place the mouthpiece in your mouth and close your lips around it so you form a good seal.
- Inhale deeply to release the medicine.
- Remove the inhaler and hold your breath for 5 to 10 seconds, then breathe out slowly, away from the inhaler.

**Figure E**

**Remember:**
- Hold the inhaler upright as you take your inhalation. See Figure E.

**Step 3. Close the white cap**
- Close the white cap after inhaling to prepare your next inhalation. See Figure F.

**Figure F**

If your healthcare provider has told you to take more than 1 inhalation per dose, make sure the white cap is closed and repeat Step 1 to Step 3.

After taking your prescribed number of inhalations, rinse your mouth with water **without swallowing** to help reduce the risk of a fungal infection (thrush) in your mouth.

**How to store your QVAR REDIHALER**
- Store QVAR REDIHALER at room temperature between 68°F to 77°F (20°C to 25°C). Avoid exposure to extreme heat or cold.
- Keep the white cap on the inhaler closed during storage.
- Keep your QVAR REDIHALER inhaler dry and clean at all times.
- If you drop your QVAR REDIHALER, inspect it for damage before use. If the QVAR REDIHALER is damaged, **do not** use the damaged QVAR REDIHALER. Call your doctor or pharmacist to replace the QVAR REDIHALER.
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- **Do not** use or store your QVAR REDIHALER near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause the canister to burst.
- **Do not** throw QVAR REDIHALER into fire or an incinerator.
- Throw away QVAR REDIHALER when the dose counter displays '0,' or after the expiration date on the package, whichever comes first.
- **Keep your QVAR REDIHALER and all medicines out of the reach of children.**

**Cleaning your QVAR REDIHALER**

- **Do not wash or put any part of your QVAR REDIHALER in water.**
- Clean the mouthpiece of your QVAR REDIHALER weekly with a clean, dry tissue or cloth.

**Support**

- If you have any questions about QVAR REDIHALER or how to use your inhaler, go to www.QVAR.com or call 1-888-483-8279.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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