No pressing. No shaking. No spacer.*

QVAR RediHaler® (beclomethasone dipropionate HFA)
Breath-Actuated Inhalation Aerosol  40 mcg • 80 mcg

Approved Use
QVAR RediHaler Inhalation Aerosol 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 Inhalation Aerosol is not used to relieve sudden breathing problems and won’t replace a rescue inhaler.

Important Safety Information
• Do not use QVAR RediHaler to treat sudden severe symptoms of asthma. Always have a rescue inhaler with you to treat sudden symptoms.
• Do not use QVAR RediHaler if you are allergic to beclomethasone dipropionate or any of the ingredients in QVAR RediHaler.
• Do not use QVAR RediHaler more often than prescribed.
• Tell your healthcare provider about all the medicines you take and about all of your health conditions.
• QVAR RediHaler may cause serious side effects, including:
  • Fungal infections (thrush) in your mouth and throat. Rinse your mouth with water without swallowing after using QVAR RediHaler to help prevent an infection in your mouth or throat.

Please see Important Safety Information throughout and accompanying full Prescribing Information including Patient Information.

*I CAN DO IT!*

*Do not use a spacer.*
With the innovative QVAR RediHaler inhalation aerosol the medicine automatically comes out when you breathe in!

There are three basic steps

1. Open the white cap and breathe out fully. Do not open the cap until you are ready to take a dose.

2. Place the mouthpiece in your mouth and close your lips around it so a good seal is formed. Inhale deeply to release the medicine. Remove inhaler, holding your breath for 5 to 10 seconds, then breathe out slowly away from the inhaler. Remember, hold the inhaler upright.

3. Close the white cap and you are ready for the next inhalation.

See our demo video at QVARstepbystep.com

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

It’s important not to shake QVAR RediHaler and the white cap must be closed to prepare the inhaler for each inhalation or you will not receive your medicine.

Never breathe out into the inhaler mouthpiece.

Important Safety Information (continued)

- QVAR RediHaler may cause serious side effects, including:
  - **Worsening asthma or sudden asthma attacks.**
    After using your rescue inhaler, contact your healthcare provider right away if you do not get relief from your sudden asthma attacks.
  - **Reduced adrenal function (adrenal insufficiency).**
    This potentially life-threatening condition can happen when you stop taking oral corticosteroid medicines and start using inhaled corticosteroid medicines (such as QVAR RediHaler). Tell your healthcare provider right away about any signs and symptoms of adrenal insufficiency such as: feeling tired or exhausted (fatigue); lack of energy; low blood pressure (hypotension); dizziness or feeling faint; nausea and vomiting; or weakness.

Please see Important Safety Information throughout and accompanying full Prescribing Information including Patient Information.
Important Safety Information (continued)

- QVAR RediHaler® (beclomethasone dipropionate HFA) Inhalation Aerosol may cause serious side effects, including:
  - **Immune system effects and a higher chance for infections.** Tell your healthcare provider about any signs or symptoms of infection such as: fever, chills, pain, feeling tired, body aches, nausea, or vomiting
  - **Increased wheezing (bronchospasm) right after using QVAR RediHaler.** Always have a rescue inhaler with you to treat sudden wheezing.
  - **Serious allergic reactions.** Stop using QVAR RediHaler and call your healthcare provider or get emergency medical help right away if you get any of the following: hives; swelling of your lips, tongue, or face; rash; or breathing problems
  - **Slowed 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.

- **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); and hay fever (allergic rhinitis)

- These are not all the possible side effects of QVAR RediHaler. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see Important Safety Information throughout and accompanying full Prescribing Information including Patient Information.

To learn more go to QVAR.com
QVAR® REDIHALER™ (beclomethasone dipropionate HFA) inhalation aerosol

- Transferring 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.
- 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, such as urticaria, angioedema, rash, and bronchospasm may occur. Discontinue QVAR REDIHALER if such reactions occur. (5.6)
- Hypercorticism 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)
- Eye Disorders: Monitor patients with change in vision or with a history of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts closely. (5.10)

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: 3/2018
QVAR® REDIHALER™ (beclomethasone dipropionate HFA) inhalation aerosol

corticosteroid product and disease severity: 40, 80, 160 or 320 mcg twice daily. For patients who do not respond adequately to the initial dosage after 2 weeks of therapy, increasing the dosage may provide additional asthma control. The maximum recommended dosage for patients 4 to 11 years of age is 80 mcg twice daily. Pediatric Patients 4 to 11 years

The starting dosage is based on previous asthma therapy and disease severity, including consideration of the patients’ current control of asthma symptoms and risk of future exacerbation. The recommended starting dosage for patients aged 4 to 11 years of age is 40 mcg twice daily, approximately 12 hours apart. For patients who do not respond adequately to QVAR REDIHALER 40 mcg after 2 weeks of therapy, increasing the dosage to QVAR REDIHALER 80 mcg twice daily may provide additional asthma control. The maximum recommended dosage for patients 4 to 11 years of age is 80 mcg twice daily.

General Dosing Recommendations

The onset and degree of symptom relief will vary in individual patients. Improvement in asthma symptoms can occur within 24 hours of the beginning of treatment and should be expected within the first or second week, but maximum benefit should not be expected until 3 to 4 weeks of therapy. Improvement in pulmonary function is usually apparent within 1 to 4 weeks after the start of therapy. If a dosage regimen of QVAR REDIHALER fails to provide adequate control of asthma, the therapeutic regimen should be re-evaluated and additional therapeutic options (e.g., replacing the current strength of QVAR REDIHALER with a higher strength, or adding additional controller therapies) should be considered. As with any inhaled corticosteroid, physicians are advised to titrate the dose of QVAR REDIHALER downward over time to the lowest level that maintains proper asthma control. Titration of the dose is particularly prudent in asthma patients since a controlled study has shown that beclomethasone dipropionate has the potential to affect growth in children. The maximum number of inhalations should not exceed 8 per day.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Aerosol. QVAR REDIHALER is a pressurized, breath-actuated, metered-dose aerosol with a dose counter intended for oral inhalation containing beclomethasone dipropionate strengths:

- QVAR REDIHALER 40 mcg is supplied in an aluminum canister contained within a beige plastic actuator with a dose counter and a hinged white cap. Each breath-induced actuation delivers 50 mcg from the valve and 40 mcg from the actuator. QVAR REDIHALER 40 mcg is available as a 120-inhalation/10.6-g canister.
- QVAR REDIHALER 80 mcg is supplied in an aluminum canister contained within a maroon plastic actuator with a dose counter and a hinged white cap. Each breath-induced actuation delivers 100 mcg of beclomethasone dipropionate from the valve and 80 mcg from the actuator. QVAR REDIHALER 80 mcg is available as a 120-inhalation/10.6-g canister.

4 CONTRAINDICATIONS

4.1 Status Asthmaticus

QVAR REDIHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required [see Warnings and Precautions (5.2)].

4.2 Hypersensitivity

QVAR REDIHALER is contraindicated in patients with known hypersensitivity to beclomethasone dipropionate or any of the ingredients in QVAR REDIHALER [see Warnings and Precautions (5.6)].

5 WARNINGS AND PRECAUTIONS

5.1 Local Effects

Localized infections with Candida albicans have occurred in the mouth and pharynx in some patients receiving QVAR REDIHALER. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with QVAR REDIHALER therapy, but at times therapy with QVAR REDIHALER may need to be temporarily interrupted under close medical supervision. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

5.2 Deterioration of Asthma and Acute Episodes

QVAR REDIHALER is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta-agonist held in the mouthpiece of QVAR REDIHALER, should be used to relieve insufficiency symptoms such as shortness of breath. Instruct patients to contact their physician immediately if episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with QVAR REDIHALER. During such episodes, patients may require therapy with oral corticosteroids.

5.3 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed in patients who are transferred from systemically active corticosteroids to QVAR REDIHALER because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections (particularly gastroenteritis) or other conditions with severe electrolyte loss. Although QVAR REDIHALER may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid that is necessary for coping with these emergencies. During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

5.4 Glaucoma, Increased Intraocular Pressure, and Cataracts

History of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts have been associated with the use of 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 age, low body weight, 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.

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 (4.2)].

5.7 Hypercorticism and Adrenal Suppression

QVAR REDIHALER will often help control asthma symptoms with less suppression of HPA function as a result of less suppression of the adrenal cortex than systemic corticosteroids. Other systemic corticosteroid effects include bone loss, cataracts, increased intraocular pressure, and decreased bone mineral density. 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 of administration, and duration of systemic corticosteroid therapy influence the safety and effects of QVAR REDIHALER in patients with a history of increased intraocular pressure, blurred vision, glaucoma, and/or cataracts. QVAR REDIHALER is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

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 orally inhaled corticosteroids, including QVAR REDIHALER, titrate 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 age, low body weight, 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.

5.10 Eye Disorders

Growth of 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.
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>
<th>QVAR REDIHALER</th>
<th>QVAR MDI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Candidiasis</td>
<td>0</td>
<td>N=126</td>
<td>N=211</td>
<td>N=304</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>9 (4)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (4)</td>
<td>2 (2)</td>
<td>3 (1)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>1 (&lt;1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Viral Upper Respiratory Tract Infection</td>
<td>3 (3)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3 (3)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Rhinitis Allergic</td>
<td>0</td>
<td>3 (3)</td>
<td>2 (&lt;1)</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 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>
<th>QVAR REDIHALER</th>
<th>QVAR MDI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>3 (2.4)</td>
<td>1 (0.8)</td>
<td>6 (4.8)</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (4.0)</td>
<td>11 (8.8)</td>
<td>6 (4.8)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Viral Upper Respiratory Tract Infection</td>
<td>5 (4.0)</td>
<td>5 (4.0)</td>
<td>3 (2.4)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3 (3.2)</td>
<td>4 (3.2)</td>
<td>4 (3.2)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (0.8)</td>
<td>3 (2.4)</td>
<td>9 (7.2)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1.6)</td>
<td>2 (1.6)</td>
<td>3 (4.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (1.6)</td>
<td>5 (4.0)</td>
<td>4 (3.2)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (0.8)</td>
<td>4 (3.2)</td>
<td>3 (2.4)</td>
<td>3 (2.4)</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.
**QVAR® REDIHALER™** (beclomethasone dipropionate HFA) inhalation aerosol

and health benefits of breastfeeding should be considered along with the mother's clinical need for QVAR REDIHALER 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 250 and 25 times the MRHDID for adults on a mg/m² basis, respectively. 

**Nonclinical Toxicology (13.1)**

**8.4 Pediatric Use**

Five hundred and one children between the ages of 4 and 11 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.

Do not use QVAR REDIHALER with a spacer or volume holding chamber.

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 children were enrolled, of whom 394 received QVAR MDI (100 to 400 mcg/day ex-valve) and 126 received CFC-BDP (200 to 800 mcg/day ex-valve).

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 in children treated with QVAR MDI has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including QVAR REDIHALER, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the 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 Geriatric 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, and in 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-11ß,17,21-trihydroxy-16ß-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate. Beclomethasone dipropionate is a diester prodrug that is rapidly activated by hydrolysis in the lungs to its active metabolite, 17-BMP, which is then inactivated by metabolism. Beclomethasone-21-monopropionate (21-BMP) is another metabolite formed in the lungs.

#### Metabolism

Irrespective of the route of administration (injection, oral or inhalation), beclomethasone dipropionate is extensively metabolized. The major metabolites are beclomethasone-17-monopropionate (17-BMP) and beclomethasone-21-monopropionate (21-BMP). Beclomethasone dipropionate undergoes rapid and extensive conversion to beclomethasone-17-monopropionate (17-BMP) after inhalation. The metabolism is believed to be by non-specific lung esterases, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

#### 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.

### 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 monopropionate, 17-monopropionate (17-BMP). Beclomethasone-17-monopropionate has been shown in vitro to inhibit a binding affinity for the human glucocorticoid receptor. Beclomethasone dipropionate, 17-BMP, and beclomethasone dipropionate in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol (0.85 g).

Beclomethasone dipropionate is a white to creamy white, odorless crystaline solid. Beclomethasone dipropionate is insoluble in water and slightly soluble in ethanol. Beclomethasone dipropionate is a prodrug that is rapidly activated by hydrolysis to its active metabolite, 17-BMP, which is then inactivated by metabolism. 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 peak plasma concentration (Cmax) of BDP was 6635 pg/mL at 2 minutes after inhalation of 320 mcg using QVAR REDIHALER (4 inhalations of the 80 mcg/inhalation dose).

The mean peak plasma concentration of the major and most active metabolite, 17-BMP, was 1464 pg/mL at 10 minutes after inhalation of 320 mcg of QVAR REDIHALER.

QVAR REDIHALER has not been evaluated.
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 95 weeks. 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of treatment-related increases in the incidence of tumors in this study at the highest dose, which is approximately 37 and 72 times the MRHDID 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 16 mg/kg/day (approximately 250 times the MRHDID 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 MRHDID 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 mg/kg (approximately 17 times the MRHDID 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

Two confirmatory Phase 3 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 40-90% predicted normal, reversible bronchoconstriction of at least 10% with short-acting inhaled beta-agonist, and asthma symptoms were randomized equally to QVAR REDIHALER 320 mcg/day, QVAR REDIHALER 640 mcg/day, QVAR MDI 320 mcg/day, or placebo. Baseline FEV₁, values were similar across treatments.

The primary endpoint for this trial was the change from baseline in morning trough forced expiratory volume in 1 second (FEV₁) area under the effect curve from time zero to 6 weeks (FEV₁ AUEC(0-6wk)). Treatment with QVAR REDIHALER was effective in improving asthma control with significantly greater improvements in FEV₁, morning PEF, weekly average of daily trough morning PEF, reduced rescue medication use and improved asthma symptom scores than with placebo. Similar results were demonstrated with QVAR MDI.

Figure 2: A 6-Week Dose Response Clinical Trial in Patients with Inhaled Corticosteroid-Dependent Asthma: Mean Change in FEV₁, as Percent of Predicted

Side-by-side comparison of the primary analysis of standardized baseline-adjusted trough morning FEV₁, from time zero to the end of the treatment period for both studies is shown below in Table 3.

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>Statistic</th>
<th>Placebo (N=90)</th>
<th>QVAR REDIHALER 320 mcg/day (N=80)</th>
<th>QVAR REDIHALER 640 mcg/day (N=82)</th>
<th>Placebo (N=107)</th>
<th>QVAR REDIHALER 320 mcg/day (N=108)</th>
<th>QVAR REDIHALER 640 mcg/day (N=105)</th>
<th>MDI* 320 mcg/day (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference from placebo</td>
<td>0.124</td>
<td>0.116</td>
<td>0.144</td>
<td>0.150</td>
<td>0.148</td>
<td>0.054</td>
<td>0.193</td>
<td>0.087</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.193</td>
<td>0.185</td>
<td>0.087</td>
<td>0.206</td>
<td>0.0888</td>
<td>0.2132</td>
<td>0.0847</td>
<td>0.2114</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 (NCT02040766) 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 or 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 bronchoconstriction of at least 12% with short acting inhaled beta agonist entered a 14-21 day run in period. Patients who met the randomization criteria including asthma symptoms and rescue medication use and stricken asthma therapy were randomized equally across treatment groups. Five hundred sixty-eight (568) 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

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

Inhalation Aerosol (QVAR MDI) 40 mcg, 4 inhalations twice daily. Patients aged 12 years and older who met the entry criteria including FEV₁, 50-90% predicted normal, reversible bronchoconstriction of at least 10% with short-acting inhaled beta-agonist discontinued baseline asthma treatment and entered a 2-4 week run-in period. 425 patients (257 previously treated with ICS with or without LABA) who met all the randomization criteria including FEV₁, 40-85% predicted and 15% reversibility with short acting inhaled beta-agonist, and asthma symptoms were randomized equally to QVAR REDIHALER 320 mcg/day, QVAR REDIHALER 640 mcg/day, QVAR MDI 320 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 6 weeks (FEV₁ AUEC(0-6wk)). Patients in both treatment groups had significantly greater improvements in trough FEV₁, compared to placebo (QVAR REDIHALER 320 mcg/day, LS mean change of 0.144 L and QVAR REDIHALER 640 mcg/day, LS mean change of 0.150 L over 6 weeks) (Table 3). Treatment with QVAR MDI was similar. The change from baseline in morning FEV₁ during the trial is displayed in Figure 2. Both doses of QVAR REDIHALER were effective in improving asthma control with significantly greater improvements in FEV₁, morning PEF, weekly average of daily trough morning PEF, reduced rescue medication use and improved asthma symptom scores than with placebo. Similar results were demonstrated with QVAR MDI.

Figure 2: A 6-Week Dose Response Clinical Trial in Patients with Inhaled Corticosteroid-Dependent Asthma: Mean Change in FEV₁, as Percent of Predicted

Side-by-side comparison of the primary analysis of standardized baseline-adjusted trough morning FEV₁, from time zero to the end of the treatment period for both studies is shown below in Table 3.

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>Statistic</th>
<th>Placebo (N=90)</th>
<th>QVAR REDIHALER 320 mcg/day (N=80)</th>
<th>QVAR REDIHALER 640 mcg/day (N=82)</th>
<th>Placebo (N=107)</th>
<th>QVAR REDIHALER 320 mcg/day (N=108)</th>
<th>QVAR REDIHALER 640 mcg/day (N=105)</th>
<th>MDI* 320 mcg/day (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference from placebo</td>
<td>0.124</td>
<td>0.116</td>
<td>0.144</td>
<td>0.150</td>
<td>0.148</td>
<td>0.054</td>
<td>0.193</td>
<td>0.087</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.193</td>
<td>0.185</td>
<td>0.087</td>
<td>0.206</td>
<td>0.0888</td>
<td>0.2132</td>
<td>0.0847</td>
<td>0.2114</td>
</tr>
</tbody>
</table>

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Pediatric Patients 4 to 11 Years of Age

This randomized, double-blind, parallel-group, placebo-controlled, 12-week, global efficacy and safety trial (NCT02040766) 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 or 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 bronchoconstriction of at least 12% with short acting inhaled beta agonist entered a 14-21 day run in period. Patients who met the randomization criteria including asthma symptoms and rescue medication use and stricken asthma therapy were randomized equally across treatment groups. Five hundred sixty-eight (568) 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: 5.58, 17.06) and 8.5 (95% CI: 2.71, 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

16.1 How Supplied

QVAR REDIHALER is supplied in 2 strengths:

- **QVAR REDIHALER 40 mcg** is supplied in a box of one 10.6-g canister containing 120 actuations – NDC 59310-302-40
- **QVAR REDIHALER 80 mcg** is supplied in a box of one 10.6-g canister containing 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.

16.2 Storage and Handling

Store at 25°C (77°F). Excursions between 15°C and 30°C (59° and 86°F) 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 49°C (120°F) may cause bursting. Never throw QVAR REDIHALER into fire or incinerator.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advisors to the patient to read the FDA-Approved Patient Labeling (Patient Information and Instructions for Use).

Patients should be given the following information:

**Local Effects**

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 still 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**

Warn patients who are on immunosuppressant 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.

**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 who are pregnant or nursing that they should contact their physician about the use of QVAR REDIHALER.
QVAR® REDIHALER™ (beclomethasone dipropionate HFA) inhalation aerosol

PATIENT INFORMATION
QVAR REDIHALER (kue’ var red-ee-haye’ ler) (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 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 using 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.
• You do not need to prime QVAR REDIHALER.
• 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 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.

continued
**QVAR® REDIHALER™** (beclomethasone dipropionate HFA) inhalation aerosol

**How should I store QVAR REDIHALER?**
- Store QVAR REDIHALER at room temperature between 68°F to 77°F (20°C to 25°C).
- Your QVAR REDIHALER canister should only be used with the QVAR REDIHALER actuator. Do not use any other medicines in your QVAR REDIHALER actuator.
- The contents of your QVAR REDIHALER canister are under pressure. Do not puncture the QVAR REDIHALER canister.
- Do not store your QVAR REDIHALER canister near heat or a flame. Temperatures above 120°F may cause the canister to burst.
- Do not throw your QVAR REDIHALER canister into a fire or incinerator.
- Keep QVAR REDIHALER and all medicines out of the reach of children.

**General information about the safe and effective use of QVAR REDIHALER.**

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

**What are the ingredients in QVAR REDIHALER?**
- **Active ingredient:** beclomethasone dipropionate
- **Inactive ingredients:** propellant HFA-134a and ethanol

For more information, go to www.QVAR.com or call 1-888-483-8279.

QVARHIPIL-003
Rev. 3/2018
QVAR® REDIHALER™ (beclomethasone dipropionate HFA) inhalation aerosol

Inhaler Full
120 Doses

Inhaler Empty
0 Doses

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.

Using your QVAR REDIHALER:

Step 1. Open the white cap
• Open the white cap. See Figure D.
• Breathe out fully.

Figure D

Remember:
• Do not open the cap until you are ready to take your inhalation.
• Never breathe out into the inhaler mouthpiece.

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 inhaler, hold breath for 5 to 10 seconds, then, breathe out slowly, away from the inhaler.

Figure E

Remember:
• Hold 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 steps 1-3.

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 - 25°C). Excursions between 59°F and 86°F (15°C and 30°C) are permitted. Do not use or store 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. Keep the white cap on the inhaler closed during storage.
• Keep your QVAR REDIHALER inhaler dry and clean at all times.
• Keep your QVAR REDIHALER and all medicines out of the reach of children.
• Throw away QVAR REDIHALER when the dose counter displays ‘0,’ or after the expiration date on the package, whichever comes first.

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.QvarRedihaler.com or call 1-888-483-8279.
This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Marketed by: Teva Respiratory, LLC, Frazer, PA 19355; Manufactured by: Norton (Waterford) Limited, Ireland; Copyright ©2018, Teva Respiratory, LLC; All rights reserved.

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Rev. 3/2018
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