QVAR* (beclomethasone dipropionate HFA), Inhalation Aerosol

WARNINGS AND PRECAUTIONS

• Localized infections: 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 after inhalation. (5.1)
• Deterioration of asthma and acute episodes: Do not use QVAR for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)
• 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. (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. (5.5)
• Hypersensitivity Reactions: Hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm may occur. Discontinue QVAR 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 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. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (incidence >3% and > placebo) include headache, pharyngitis, oral symptoms (inhaled route), and sinusitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Respiratory, LLC at 1-888-482-9522 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 05/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Treatment of Asthma

2 DOSAGE AND ADMINISTRATION
2.1 Administration Information

Administer QVAR by the orally inhaled route only. Patients should prime QVAR by actuating into the air twice before using for the first time or if QVAR has not been used for over 10 days. Avoid spraying in the eyes or face when priming QVAR. QVAR is a solution aerosol, which does not require shaking. 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). Rinsing the mouth after inhalation is advised. QVAR has a dose counter attached to the actuator. When the patient receives the inhaler, a black dot will appear in the viewing window until it has been primed 2 times, at which point the total number of actuations will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the total number of actuations; when it reaches 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 physician for a prescription refill. When the dose counter reaches 0, the background will change to red. Discard QVAR inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

2.2 Maintenance Treatment of Asthma

QVAR should be administered by the oral inhaled route in patients 5 years of age and older. Use of QVAR with a spacer device in children less than 5 years of age is not recommended.ife using for the first time or if QVAR has not been used for over 10 days. Avoid spraying in the eyes or face when priming QVAR. QVAR is a solution aerosol, which does not require shaking. 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). Rinsing the mouth after inhalation is advised. QVAR has a dose counter attached to the actuator. When the patient receives the

3 DOSAGE FORMS AND STRENGTHS

QVAR® is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. (1.1)

Treatment of asthma in patients who require oral corticosteroid therapy. QVAR may reduce or eliminate the need for the systemic corticosteroids. (1.1)

Important Limitations:
• Not indicated for the relief of acute bronchospasm. (1.1)

DOSE AND ADMINISTRATION

For oral inhalation only. (2.1)

• Discard QVAR inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first. (2.1)

Patient's Previous Therapy Recommended Starting Dose Highest Dose Recommended

| Patients aged 12 years or older | | |
|----------------------------------|------------------|
| Bronchodilators Alone | 40 to 80 mcg twice daily | 320 mcg twice daily |
| Inhaled Corticosteroids | 40 to 160 mcg twice daily | 320 mcg twice daily |

| Children aged 5-11 years | | |
|------------------------|------------------|
| Bronchodilators Alone | 40 mcg twice daily | 80 mcg twice daily |
| Inhaled Corticosteroids | 40 mcg twice daily | 80 mcg twice daily |

DOSAGE FORMS AND STRENGTHS

• Inhalation aerosol with 40 or 80 mcg per actuation (3)

CONTRAINDICATIONS

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
1.1 Treatment of Asthma

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Local Effects

5.2 Deterioration of Asthma and Acute Episodes

5.3 Transferring Patients from Systemic Corticosteroid Therapy

5.4 Immunosuppression

5.5 Paradoxical Bronchospasm

5.6 Immediate Hypersensitivity Reactions

5.7 Hypercorticism and Adrenal Suppression

5.8 Effects on Growth

5.9 Reduction in Bone Mineral Density

5.10 Eye Disorders

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Adult and Adolescent Patients Greater Than 12 Years of Age

14.2 Pediatric Patients 5 to 12 Years of Age

15 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
QVAR® (beclomethasone dipropionate HFA), Inhalation Aerosol

QVAR® (beclomethasone dipropionate HFA), Inhalation Aerosol

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.

Patients requiring oral or other systemic corticosteroids should be weaned slowly from oral or other systemic corticosteroid use after transferring to QVAR. Lung function (FEV1 or PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral or other systemic corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to QVAR may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis, and eosinophilic conditions.

As with any inhaled corticosteroid, physicians are advised to titrate the dose of QVAR downward over time to the lowest level that maintains proper asthma control. This is particularly important in children since a controlled study has shown that QVAR has the potential to affect growth in children. Patients should be instructed on the proper use of their inhaler.

Patients Not Receiving Systemic Corticosteroids

Patients who require maintenance therapy of their asthma may benefit from treatment with QVAR at the doses recommended above. In patients who respond to QVAR, improvement in pulmonary function is usually apparent within 1 to 4 weeks after the start of therapy. Once the desired effect is achieved, consideration should be given to tapering to the lowest effective dose.

Patients Maintained on Systemic Corticosteroids

Prednisone or other corticosteroids should be weaned slowly beginning at least a week of QVAR therapy. Monitor carefully for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency during steroid taper and following discontinuation of oral corticosteroid therapy [See Warnings and Precautions (5.2)].

QVAR® (beclomethasone dipropionate HFA), Inhalation Aerosol

Table 2 Recommended Dosing for Children 5 to 11 Years

<table>
<thead>
<tr>
<th>Patient's Previous Therapy</th>
<th>Recommended Starting Dose</th>
<th>Highest Dose Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilators Alone</td>
<td>40 mcg twice daily</td>
<td>80 mcg twice daily</td>
</tr>
<tr>
<td>Inhaled Corticosteroids</td>
<td>40 mcg twice daily</td>
<td>80 mcg twice daily</td>
</tr>
</tbody>
</table>

Table 1 Recommended Dosing for Patients Aged 12 Years and Older

<table>
<thead>
<tr>
<th>Patient's Previous Therapy</th>
<th>Recommended Starting Dose</th>
<th>Highest Dose Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilators Alone</td>
<td>80 mcg twice daily</td>
<td>320 mcg twice daily</td>
</tr>
<tr>
<td>Inhaled Corticosteroids</td>
<td>160 mcg twice daily</td>
<td>320 mcg twice daily</td>
</tr>
</tbody>
</table>

Table 2 Recommended Dosing for Children 5 to 11 Years

<table>
<thead>
<tr>
<th>Patient's Previous Therapy</th>
<th>Recommended Starting Dose</th>
<th>Highest Dose Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilators Alone</td>
<td>40 mcg twice daily</td>
<td>80 mcg twice daily</td>
</tr>
<tr>
<td>Inhaled Corticosteroids</td>
<td>40 mcg twice daily</td>
<td>80 mcg twice daily</td>
</tr>
</tbody>
</table>

5.4  Immunosuppression

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 children or adults on corticosteroids. In such children or adults who have not had these diseases or been previously immunized, particular care should be taken to avoid exposure. It is not known how the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection. Nor is the contribution of the underlying disease and/or prior corticosteroid treatment known. 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.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, parasitic or viral infections; or ocular herpes simplex.

5.5 Paradoxical Bronchospasm

Inhaled corticosteroids may produce inhalation induced bronchospasm with an immediate increase in wheezing after dosing that may be life-threatening. If bronchospasm occurs with QVAR, it should be treated immediately with an inhaled, short-acting bronchodilator. Treatment with QVAR 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. Discontinue QVAR if such reactions occur [see Contraindications (4.2)].

5.7 Hypercorticism and Adrenal Suppression

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

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with QVAR 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 beclomethasone dipropionate is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of QVAR should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

Effects on Growth

Orally inhaled corticosteroids, including QVAR, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving QVAR routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including QVAR, titrate each 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 inhaled corticosteroids. The clinical significance of these 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.

Eye Disorders

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...
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6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- **Candida albicans infection** [see Warnings and Precautions (5.1)]
- **Immunosuppression** [see Warnings and Precautions (5.4)]
- **Hypercorticism and adrenal suppression** [see Warnings and Precautions (5.7)]
- **Growth effects** [see Warnings and Precautions (5.8) and Use in Specific Populations (8.4)]
- **Eye Disorders** [see Warnings and Precautions (5.10)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following reporting rates of common adverse experiences are based upon four clinical trials in which 1196 patients (671 female and 525 male adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with QVAR (doses of 40, 80, 160, or 320 mcg twice daily) or CFC-BDP (doses of 42, 168, or 336 mcg twice daily) or placebo. Table 3 below includes all events reported by patients taking QVAR (whether considered drug related or not) that occurred at a rate over 5% for QVAR. In considering these data, difference in average duration of exposure and clinical trial design should be taken into account.

### Table 3 Adverse Events Reported by at Least 3% of Patients by Treatment and Daily Dose

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=289)</th>
<th>Total (N=624)</th>
<th>80-160 mcg (N=233)</th>
<th>320 mcg (N=335)</th>
<th>640 mcg (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADACHE</td>
<td>9</td>
<td>12</td>
<td>15</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>PHARYNGITIS</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>UPPER RESP TRACT INFECTION</td>
<td>11</td>
<td>9</td>
<td>7</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>RHEINITIS</td>
<td>9</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>INCREASED ASTHMA SYMPTOMS</td>
<td>18</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ORAL SYMPTOMS INHALATION ROUTE</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>SINUSITIS</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PAIN</td>
<td>&lt;1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>BACK PAIN</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>&lt;1</td>
<td>4</td>
</tr>
<tr>
<td>DYSPHONIA</td>
<td>2</td>
<td>&lt;1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Other adverse events that occurred in these clinical trials using QVAR with an incidence of 1% to 3% and which occurred at a greater incidence than placebo were nausea, dysmenorrhea, and coughing. Oropharyngeal candidiasis occurred in <1% of patients in both QVAR and placebo treatment groups.

6.2 Postmarketing Experience

In addition to adverse experiences reported in the clinical trials, the following adverse events have been reported during post-approval use of QVAR. Because they 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.

#### Local Effects: Localized infections with *Candida albicans* have occurred in patients treated with QVAR or other orally inhaled corticosteroids [see Warnings and Precautions (5.1)].

#### Psychiatric and Behavioral Changes: Aggression, depression, sleep disorders, psychomotor hyperactivity, and suicidal ideation have been reported (primarily in children).

#### Eye Disorders: Blurred vision, central serous chorioretinopathy (CSC).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with QVAR in pregnant women. Animal studies were conducted with beclomethasone dipropionate in rats, mice, and rabbits. Systemic exposure data were not determined in the animal studies. In rats exposed to beclomethasone dipropionate by inhalation at doses greater than 180 times the maximum recommended adult human daily inhalation dose (MRHDID), dose-related gross injury to the fetal adrenal glands was observed. However, there was no evidence of external or skeletal malformations or embryolethality in rats at inhalation doses up to 440 times the MRHDID. Beclomethasone dipropionate was administered to a nursing mother.

Beclomethasone dipropionate treatment was embryolethal and caused decreased pup survival in mice at subcutaneous doses equal to or greater than 2.3 times the MRHDID. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

**Disease-Associated Maternal and Fetal Risk**

In women with poorly controlled asthma, evidence demonstrates that there is 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 as necessary to maintain optimal control.

**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 (0.64 mg/kg/day) 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 in rat fetuses 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 teratogenic effects (increased incidence of cleft palate). No effect dose in mice was not identified. In a second embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 13 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 and higher) 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 teratogenic (external and skeletal malformations) and embryolethal effects (increased fetal resorptions). There were no effects in fetuses of pregnant rabbits administered a subcutaneous dose 0.2 times the MRHDID in adults (on a mg/m² basis at a maternal dose of 0.006 mg/kg/day).

8.2 Nursing Mothers

Corticosteroids are secreted in human milk. Caution should be exercised when QVAR is administered to a nursing mother.

8.3 Pediatric Use

Eight-hundred and thirty-four children between the ages of 5 and 12 were treated with beclomethasone dipropionate (HFA-BDP) in clinical trials. The safety and effectiveness of QVAR in children below 5 years of age have not been established. Use of QVAR with a spacer device in children less than 5 years of age is not recommended. In *vitro* dose characterization studies were performed with QVAR 40 mcg/actuation with the OptiChamber and AeroChamber Plus® spacer utilizing inspiratory flows representative of children under 5 years old. These studies indicated that the amount of medication delivered through the spacing device decreased rapidly with increasing wait times of 5 to 10 seconds as shown in Table 4. If QVAR is used with a spacer device, it is important to inhale immediately.

Based on the average inspiratory flow rates generated by children 6 months to 12 years of age, the projected daily dose derived from QVAR 40 mcg at one puff per day at various wait times is depicted in Table 4 below:

### Table 4 Average Daily Dose Based on Wait Time in Pediatric Patients

<table>
<thead>
<tr>
<th>Wait Time, seconds</th>
<th>Mean medication delivery per actuation</th>
<th>Body Weight</th>
<th>Medication delivered per dose, mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11.5</td>
<td>7.6</td>
<td>1.2</td>
</tr>
<tr>
<td>10</td>
<td>3.9</td>
<td>13.5</td>
<td>0.83</td>
</tr>
<tr>
<td>20</td>
<td>5.4</td>
<td>13.5</td>
<td>0.32</td>
</tr>
<tr>
<td>30</td>
<td>5.4</td>
<td>13.5</td>
<td>0.23</td>
</tr>
</tbody>
</table>

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

12.2 Pharmacodynamics

HFA Axis Effects

The effects of QVAR on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 40 corticosteroid-naive patients. QVAR, at doses of 80, 160 or 320 mcg twice daily, was compared with placebo and 336 mcg twice daily of beclomethasone dipropionate in a CFC propellant based formulation (CFC-BDP). Active treatment groups 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 of QVAR (320 mcg twice daily) had a 37.3% reduction in 24-hour urinary-free cortisol compared to a reduction of 47.3% 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 and a 24.6% reduction in the group of patients that received 160 mcg twice daily. Overall, 35% of 384 asthma patients given QVAR at recommended doses for one year assessed the effect of QVAR treatment on the HPA axis (as measured by both morning and stimulated plasma cortisol). Less than 1% of patients treated for one year with QVAR had an abnormal response (peak less than 16 mcg/dL) to short- Prominent (2000).

11 DESCRIPTION

The active component of QVAR 40 mcg Inhalation Aerosol and QVAR 80 mcg Inhalation Aerosol is beclomethasone dipropionate, USP, a corticosteroid having the chemical name 9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate. Beclomethasone dipropionate (BDP) 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 fluorene, 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 C_{25}H_{36}ClO_2 and a molecular weight of 421.1. Its chemical structure is:

```
\begin{center}
\begin{tikzpicture}
  \node[draw,shape=circle] (a) at (0,0) {COCOC\textsubscript{H}\textsubscript{2}};
  \node[draw,shape=circle] (b) at (1,0) {COCOC\textsubscript{H}\textsubscript{2}};
  \node[draw,shape=circle] (c) at (2,0) {Cl};
  \draw (a) -- (b);
  \draw (b) -- (c);
\end{tikzpicture}
\end{center}
```

QVAR is a pressurized, metered-dose aerosol with a dose counter intended for oral inhalation only. Each unit contains a solution of beclomethasone dipropionate in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. QVAR 40 mcg delivers 40 mcg of beclomethasone dipropionate from the actuator and 50 mcg from the valve. QVAR 80 mcg delivers 80 mcg of beclomethasone dipropionate from the actuator and 100 mcg from the valve. Both products deliver 50 microliters from the valve. QVAR 80 mcg delivers 80 mcg of beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg/day. Impairment of fertility, as evidenced by the in vitro protein binding for 17-BMP was reported to be 94-96% over the concentration range of 1000 to 5000 pg/mL. Protein binding was constant over the concentration range evaluated. There is no evidence of tissue storage of BDP or its metabolites.

Elimination: The major route of elimination of inhaled BDP appears to be via hydrolysis. More than 90% of inhaled BDP is found as 17-BMP in the systemic circulation. The mean elimination half-life of 17-BMP is 2.8 hours. Irrespective of the route of administration (injection, oral or inhalation), BDP and its metabolites are mainly excreted in the feces. Less than 10% of the drug and its metabolites are excreted in the urine.

Special Populations: Formal pharmacokinetic studies using QVAR were not conducted in any special population.

Pediatric: The pharmacokinetics of 17-BMP, including dose and strength proportions, is similar in children and adults, although the exposure is highly variable. In 17 children (mean age 10 years), the C\textsubscript{max} 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 the oral inhalation dose of the maximum recommended daily inhalation dose of 1 mg/m\textsuperscript{2} on a mg/m2 basis). More than 10 children (mean age 12 years). This implies that approximately twice the systemic exposure to 17-BMP would be expected for comparable mg doses of HFA-BDP without a spacer and CFC-BDP with a large volume spacer.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity of beclomethasone dipropionate was evaluated in rats in 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 maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m\textsuperscript{2} 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 maximum recommended daily inhalation dose in adults on a mg/m\textsuperscript{2} basis). Impairment of fertility, as evidenced by 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 maximum recommended daily inhalation dose in adults on a mg/m\textsuperscript{2} basis). None 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/kg (approximately 17 times the maximum recommended daily inhalation dose in adults on a mg/m\textsuperscript{2} basis).
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14 CLINICAL STUDIES

Blinded, randomized, parallel, placebo-controlled and active-controlled clinical studies were conducted in 940 adult asthma patients to assess the efficacy and safety of QVAR in the treatment of asthma. Fixed doses ranging from 40 mcg to 160 mcg twice daily were compared to placebo, and doses ranging from 40 mcg to 320 mcg twice daily were compared with doses of 42 mcg to 336 mcg twice daily of an active CFC-BDP comparator. These studies provided information about appropriate dosing through a range of asthma severity. A blinded, randomized, parallel, placebo-controlled study was conducted in 353 pediatric patients (age 5 to 12 years) to assess the efficacy and safety of HFA beclomethasone dipropionate in the treatment of asthma. Fixed doses of 40 mcg and 80 mcg twice daily were compared with placebo in this study. In these adult and pediatric efficacy trials, at the doses studied, measures of pulmonary function forced expiratory volume in 1 second (FEV1) and morning peak expiratory flow (AM PEF) and asthma symptoms were significantly improved with QVAR treatment when compared to placebo.

In controlled clinical trials with adult patients not adequately controlled with beta-agonist alone, QVAR was effective at improving asthma control at doses as low as 40 mcg twice daily (80 mcg/day). Comparable asthma control was achieved at lower daily doses of QVAR than with CFC-BDP. Treatment with increasing doses of both QVAR and CFC-BDP generally resulted in increased improvement in FEV1. In this trial the improvement in FEV1 across doses was greater for QVAR than for CFC-BDP, indicating a shift in the dose response curve for QVAR.

14.1 Adult and Adolescent Patients Greater Than 12 Years of Age

Patients not Previously Receiving Corticosteroid Therapy: In a 6-week clinical trial, 270 steroid-naive patients with symptomatic asthma being treated with as-needed beta-agonist bronchodilators, were randomized to receive either 40 mcg twice daily of QVAR, 80 mcg twice daily of QVAR, or placebo. Both doses of QVAR were effective in improving asthma control with significantly greater improvements in FEV1, AM PEF, and asthma symptoms than with placebo. Shown below is the change from baseline in AM PEF during this trial.

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

In one 12-week clinical trial, pediatric patients (age 5 to 12 years) with symptomatic asthma (N=353) being treated with as-needed beta-agonist bronchodilators were randomized to receive either 40, 160, or 320 mcg twice-daily QVAR or 42, 168 or 336 mcg twice-daily CFC-BDP. Treatment with increasing doses of both QVAR and CFC-BDP generally resulted in increased improvement in FEV1. Both doses were effective in improving asthma control with significantly greater improvements in FEV1, (9% and 10% predicted change from baseline at week 12 in FEV1, percent predicted, respectively) than with placebo (4% predicted change).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

QVAR is supplied in 2 strengths:

- QVAR 40 mcg is supplied in a box of one 8.7 g canister containing 120 actuations with a beige plastic actuator with a dose counter and gray dust cap, and Patient Information and Instructions for Use; box of one; 120 Actuations – NDC 59310-204-12.
- QVAR 80 mcg is supplied in a box of one 8.7 g canister containing 120 actuations with a dark mauve plastic actuator with a dose counter and gray dust cap, and Patient Information and Instructions for Use; box of one; 120 Actuations – NDC 59310-204-12.

The correct amount of medication in each inhalation cannot be assured after 120 actuations from the 8.7 g canister even though the canister is not completely empty. Patients should be informed to discard the QVAR inhaler 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° and 30°C (59° and 86°F) are permitted. For optimal results, the canister should be at room temperature when used. QVAR Inhalation Aerosol canister should only be used with the QVAR Inhalation Aerosol actuator and the actuator should not be used with any other inhalation drug product.

CONTENTS UNDER PRESSURE

Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw container into fire or incinerator.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

- Risks Associated with Corticosteroid Therapy

Local Effects: Advise patients that localized infections with Candida albicans have occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing with QVAR therapy, but at times therapy with QVAR may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised.[See Warnings and Precautions (5.1)].

Systemic suppression: Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Inform patients of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.[See Warnings and Precautions (5.6)].

Hypercorticism and Adrenal Suppression: Advise patients that QVAR 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.[See Warnings and Precautions (5.7)].
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Reduction in Bone Mineral Density: Advise patients who are at an increased risk for decreased BMD that the use of inhaled corticosteroids may pose an additional risk and that they should be monitored and, where appropriate, be treated for this condition (see Warnings and Precautions (5.9)).

Reduced Growth Velocity: Inform patients that orally inhaled corticosteroids, including QVAR, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of pediatric patients taking corticosteroids by any route (see Warnings and Precautions (5.2)).

Eye Disorders: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (glaucoma, cataracts, blurred vision); regular eye examinations should be considered (see Warnings and Precautions (5.10)).

• Not for Acute: Informs
Advise patients that QVAR is not intended for use in the treatment of acute asthma. Acute asthma symptoms should be treated with an inhaled, short-acting β-2 agonist such as albuterol. Instruct the patient to contact their healthcare provider immediately if there is any deterioration of their asthma (see Warnings and Precautions (5.2)).

• Susceptibility to Infections
Warn persons who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. Inform patients of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex (see Warnings and Precautions (5.4)).

• Use Daily for Best Effect
Advise patients to use QVAR at regular intervals, since its effectiveness depends on regular use. Maximum benefit may not be achieved for 1 week or longer, after starting treatment. If symptoms do not improve after 2 weeks of therapy or if the condition worsens, patients should be instructed to contact their physician.

• Proper Use and Care of the Inhaler
Priming: Priming is essential to ensure appropriate beclometasone dipropionate content in each actuation. Inform patients to prime the inhaler before using the first time and in cases where the inhaler has not been used for more than 10 days by releasing two sprays into the air, away from the face.

Cleaning: For normal hygiene, the mouthpiece of the inhaler should be cleaned weekly with a clean, dry tissue or cloth. DO NOT WASH OR PUT ANY PART OF THE INHALER IN WATER.

Dose Counter: Inform patients that QVAR has a dose counter attached to the inhaler actuator. When the patient receives the inhaler, a black dot will appear in the viewing window until it has been primed 2 times, at which point the total number of actuations 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 physician for a prescription refill. When the dose counter reaches 0, the background will change to solid red. Inform patients to discard the QVAR inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

• Discontinuing QVAR
Do not stop QVAR use abruptly. Instruct the patient to contact their healthcare provider immediately if use of QVAR is discontinued.

Rx only
Marketed By:
Teva Respiratory, LLC
Frazer, PA 19355

Developed And Manufactured By:
3M Drug Delivery Systems AND/OR
3M Health Care, Ltd.
Northridge, CA 91324

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United States Patent Nos. 6,446,627 and 9,463,289.
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QVA-002
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- QVAR 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. If you do not have a rescue inhaler, call your healthcare provider to have a rescue inhaler prescribed for you.
- Rinse your mouth with water after each dose of QVAR. This will help lessen the chance of getting a yeast infection (thrush) in your mouth and throat.
- Do not spray QVAR in your face or eyes. If you accidentally get QVAR in your eyes, rinse your eyes with water and if redness or irritation continues, call your healthcare provider.

What should I avoid while using QVAR?
If you have not had, or have not been vaccinated against, chickenpox or measles, you should stay away from people who are infected.

What are the possible side effects of QVAR?
QVAR may cause serious side effects, including:
- Fungal infections (thrush) in your mouth and throat. You may develop a yeast infection (Candida albicans) in your mouth and throat. Tell your healthcare provider if you have any redness or white colored patches in your mouth or throat. Rinse your mouth after using QVAR to help prevent an infection in your mouth or throat.
- Worsening asthma or sudden asthma attacks. You should contact your healthcare provider right away if you do not get relief from your sudden asthma attacks, after using your rescue inhaler, during your treatment with QVAR.
- Adrenal insufficiency. Adrenal insufficiency that can lead to death can happen when you stop taking oral corticosteroid medicines and start using inhaled corticosteroid medicines. Adrenal insufficiency can also happen in people who take higher doses of QVAR than recommended over a long period of time. When your body is under stress such as from fever, trauma (such as a car accident), infection, or surgery, adrenal insufficiency can get worse. Signs and symptoms of adrenal insufficiency may include:
  - Feeling tired or exhausted (fatigue)
  - Lack of energy
  - Weakness
  - Dizziness or feeling faint
  - Nausea and vomiting
  - Low blood pressure (hypotension)
- Immune system effects and a higher chance for infections. Tell your healthcare provider about any signs or symptoms of infection such as:
  - Fever
  - Pain
  - Body aches
  - Chills
  - Feeling tired
  - Nausea
  - Vomiting
- Increased wheezing (bronchospasm) right after using QVAR. Always have a rescue inhaler with you to treat sudden wheezing.
- Serious allergic reactions. Stop using QVAR and call your healthcare provider or get emergency medical help right away if you get any of the following signs or symptoms of an serious allergic reaction:
  - Hives
  - Swelling of your lips, tongue, or face
  - Rash
  - Breathing problems
- Slowed growth in children. Children should have their growth checked regularly while using QVAR.
- Lower bone density. This may be a problem for people who already have a higher chance for low bone density (osteoporosis).
- Eye problems including glaucoma, cataracts or blurred vision. If you have had glaucoma, cataracts or blurred vision in the past, you should have regular eye exams while using QVAR.

The most common side effects of QVAR include:
- Headache
- Throat irritation (pharyngitis)
- Sinus irritation (sinusitis)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of QVAR. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store QVAR?
- Store QVAR at room temperature between 68°F to 77°F (20°C to 25°C).
- Your QVAR canister should only be used with the QVAR actuator. Do not use any other medicines in your QVAR actuator.
- The contents of your QVAR canister are under pressure. Do not puncture the QVAR canister.
- Do not store your QVAR canister near heat or a flame. Temperatures above 120°F may cause the canister to burst.
- Do not throw your QVAR canister into a fire or incinerator.
- When not in use, store QVAR so that the product rests on the concave end of the canister with the plastic actuator on top.

Keep QVAR and all medicines out of the reach of children.

General information about the safe and effective use of QVAR. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use QVAR for a condition for which it was not prescribed. Do not give QVAR to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about QVAR. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about QVAR that is written for health professionals.

For more information, go to www.QVAR.com or call 1-888-482-9522.

What are the ingredients in QVAR?
Active ingredient: beclomethasone dipropionate
Inactive ingredients: propellant HFA-134a and ethanol
QVA PL-002

Instructions for Use
QVAR (Kyü-vär)
(beclomethasone dipropionate HFA)
Inhalation Aerosol

It is important that you read these instructions before using QVAR. Correct and regular use of the inhaler will prevent or lessen the severity of asthma attacks.

- Do not use the QVAR actuator with a canister of medicine from any other inhaler.
- Do not use a QVAR canister with an actuator from any other inhaler, including another QVAR inhaler.

The parts of your QVAR:
- There are 2 main parts of your QVAR inhaler including the:
  - Metal canister that holds the medicine (See Figure A)
  - Plastic actuator that sprays the medicine from the canister (See Figure A)
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• The inhaler has a protective dust cap that covers the mouthpiece of the actuator (See Figure A). The protective dust cap should be removed before use.

• The inhaler comes with a dose counter located on the back of the actuator (See Figure B). The dose counter window will show you the number of actuations (puffs) of medicine remaining in units of 2. The inhaler contains “120” actuations (puffs).

• The first time you use QVAR inhaler, the dose counter will show “120” actuations remaining (See Figure B). Each time you press the metal canister, a puff of medicine is released and the dose counter will count down.

• When the dose counter reaches 0, it will continue to show 0 and you should replace your QVAR inhaler.

• The dose counter cannot be reset and is permanently attached to the actuator. Never change the numbers for the dose counter or touch the pin inside the actuator.

Do not remove the metal canister from the plastic actuator.

Before using your QVAR inhaler:

Remove the cap from the mouthpiece of the actuator (See Figure C). Check the mouthpiece for objects before use. Make sure the metal canister is fully inserted into the actuator.

Priming your QVAR inhaler:

Before you use your QVAR inhaler for the first time or if you have not used your QVAR Inhaler for more than 10 days, you will need to prime your QVAR Inhaler.

• Before priming, the inhaler will show a black dot in the dose counter window (See Figure D).

• Hold the QVAR Inhaler in the upright position and with the mouthpiece pointing away from you.

• Press down on the metal canister 2 times and release 2 actuations (puffs) into the air and away from your face.

• After priming 2 times, the dose counter should read “120.”

○ Your QVAR Inhaler is now ready to use.

Using your QVAR inhaler:

Step 1: Remove the cap from the mouthpiece of the actuator (See Figure C). Check the mouthpiece for objects before use. Make sure the metal canister is fully inserted into the actuator.

Step 2: Breathe out as fully as you comfortably can. Hold the inhaler in the upright position (See Figure E). Close your lips around the mouthpiece, keeping your tongue below it.

Step 3: While breathing in deeply and slowly, press down on the metal canister with your finger (See Figure E). When you have finished breathing in, hold your breath as long as you comfortably can (5 to 10 seconds).

Step 4: Take your finger off the metal canister and remove the inhaler from your mouth. Breathe out gently.

If your healthcare provider has told you to take more than 1 inhalation per dose, repeat steps 1 through 4.

After using your QVAR inhaler:

• Replace the cap over the mouthpiece right away after use.

• You should rinse your mouth with water after you finish using QVAR.

• Clean the mouthpiece of your QVAR inhaler weekly with a clean, dry tissue or cloth.

• Do not wash or put any part of your inhaler in water.

When to replace your QVAR Inhaler:

• It is important that you pay attention to the number of actuations (puffs) left in your QVAR inhaler by reading the dose counter.

• When the dose counter on the actuator reads “20”, the color of the number will change to red and you should refill your prescription or ask your healthcare provider if you need another prescription for QVAR Inhaler.

• When the dose counter reaches “0”, the background color in the dose counter window will change to solid red. Throw away your QVAR inhaler as soon as the dose counter reads “0” or by the expiration date on the QVAR Inhaler package, whichever comes first.

• Do not use QVAR past the expiration date.

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

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Teva Respiratory, LLC
Frazer, PA 19355

Developed And Manufactured By:
3M Drug Delivery Systems AND/OR 3M Health Care, Ltd.
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