Asthma is a common chronic disorder of the airways that can be difficult to treat. It is characterized by recurring and variable symptoms, obstructed airflow, bronchial hyperresponsiveness to constructing stimuli, and underlying inflammation. Asthma affects an estimated 20 million Americans, of which nearly 5 million are children. Of patients with persistent asthma, 77% have mild-to-moderate disease and 23% have severe asthma. In 2007, the total annual cost of asthma was estimated to be almost $18 billion, translating to $10 billion in direct costs and $8 billion in indirect costs.

**SMALL AIRWAY DISEASE AS A COMPONENT OF ASTHMA & QVAR® AS A TREATMENT OPTION**

Historically, the management of asthma has been geared toward the central airways. Despite increasing evidence that supports the importance of the small airways (distal lung) in the pathobiology and treatment of asthma, focused discussion and critical review of this topic have been lacking. In April 2009, researchers from the United States and Canada held a symposium to discuss and debate the various aspects of the distal airways in asthma.

Whereas inhaled corticosteroids (ICS) remain the mainstay of therapy for the long-term control of asthma, it is important for clinicians to choose an ICS therapy that reaches all target sites for optimal treatment. QVAR® with its more than 8-year history of proven safety and tolerability, provides managed care professionals with a therapeutic alternative for the long-term treatment of asthma, compared with other ICS therapies. QVAR® is the first and only small particle ICS indicated for patients as young as 5 years of age.

Most traditional ICS products are aerosol formulations containing suspended solid-drug particles delivered by a propellant. This results in larger particle sizes (2.4-4.5 µm) being deposited primarily in the central airways, leading to low total lung deposition. Other challenges with traditional ICS treatments include the need for a spacer because many patients cannot or do not follow the proper inhaler technique.

QVAR®, however, is provided in a liquid solution and requires no spacer. QVAR®’s small particle size (1.1 µm) allows more drug to reach both the large and smaller airways, even if the patient has poor inhaler technique, resulting in comprehensive central and peripheral lung deposition.

Furthermore, the ability of QVAR® to reach distal lungs and treat chronic airway inflammation provides the potential for increased symptom management that can lead to fewer asthma exacerbations and a reduction in healthcare utilization, supporting the concept that the action site of an ICS is vital to the real-world effectiveness of asthma medications.

QVAR® is a prodrug—a pharmacologically inactive com-
bound that is activated in the body after its administration.1,10 QVAR® undergoes rapid and extensive conversion to beclomethasone-17-monopropionate (17-BMP) during absorption. The mean peak plasma concentration (C_{max}) of BDP was 88 pg/mL at 0.5 hour after inhalation of 320 mcg using QVAR® (4 actuations of the 80 mcg/actuation strength). The C_{max} of the major and most active metabolite, 17-BMP, was 1419 pg/mL at 0.7 hour after inhalation of 320 mcg of QVAR®. When the same nominal dose is provided by the 2 QVAR® strengths (40 and 80 mcg/actuation), equivalent systemic pharmacokinetics can be expected. The C_{max} of 17-BMP increased the dose proportionally in the dose range of 80 and 320 mcg.1

The in vitro protein binding for the active metabolite of QVAR®, 17-BMP, has a high protein binding of 94% to 96% over the concentration range of 1000 to 5000 pg/mL. 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.1

Improvement in asthma control following inhalation with QVAR® can occur within 24 hours of beginning treatment in some patients, although maximum benefit may not be achieved for 1 to 2 weeks, or longer.1

**MANAGING ASTHMA**

The National Asthma Education and Prevention Program (NAEPP) guidelines recommend a stepwise approach for managing asthma and the use of ICS monotherapy as the first line of treatment (Step 2) for persistent asthma (mild, moderate, and severe) across all age groups, including children. For patients whose asthma is not adequately controlled on low-dose ICS monotherapy, clinicians should consider a medium-dose ICS therapy or adding a long-acting beta-agonists (LABA) to the low-dose ICS regimen (Step 3).2

Although NAEPP guidelines do not advocate ICS+LABA therapy for mild persistent asthma, it was determined from a retrospective, privately insured database evaluation that clinicians generally do not follow this recommendation and, instead use either a leukotriene modifier (LM) or initiate combination therapy with a LABA before maximizing the full potential of ICS monotherapy.11

Based on the US Food and Drug Administration’s analyses of studies showing an increased risk of severe exacerbation of asthma symptoms, resulting in hospitalizations of pediatric and adult patients as well as death in some patients using LABAs, new guidelines have been developed.12 Given the seriousness of the risks associated with LABA use and the uncertainty about the role of ICS in mitigating this risk, the FDA believes the long-term use of LABAs should be limited to patients who truly need them.11
VALUE OF LOW-DOSE ICS MONOTHERAPY

ICS therapy is considered the most effective daily long-term anti-inflammatory class available to treat asthma. Using asthma patients identified from the UK General Practice Database, one long-term study suggested greater effectiveness with QVAR® (beclomethasone dipropionate HFA) Inhalation Aerosol, compared with other ICS in the treatment of asthma.\(^4\)\(^5\) The study was a retrospective 1-year pre-evaluation and post-evaluation of 4133 asthma patients who were indexed by ICS dose increase.\(^4\) The study evaluated successful asthma control, defined as no hospitalization, emergency department (ED) visit, or unscheduled office visit; no oral corticosteroid use; and no lower respiratory tract infection. Exacerbations were defined as an unscheduled visit and oral corticosteroid use. The researchers compared QVAR®, with chlorofluorocarbon(CFC)-BDP aerosol and fluticasone.\(^4\)\(^5\)

The findings showed the odds ratio (OR) for success was lower with CFC-BDP and fluticasone, compared with QVAR® (OR=0.65; 95% CI [confidence interval] 0.47-0.90 and 0.71; 95% CI 0.50-1.02, respectively). By using exacerbations as the outcome, the rates were higher with CFC-BDP and fluticasone (OR=1.44; 95% CI 0.94-2.21 and 1.61; 95% CI 1.02-2.55, respectively). The researchers concluded that patients receiving QVAR® were more likely to achieve successful asthma control and less likely to experience exacerbations.\(^4\)\(^5\)

In addition to clinical effectiveness, treatment with ICS monotherapy is associated with lower total medical costs and total asthma-related costs.\(^1\)\(^3\)\(^4\)\(^5\)\(^6\)

In a 1-year study of 1283 patients with mild persistent asthma, researchers found the asthma-related direct costs over 1 year were significantly lower with ICS monotherapy, compared with ICS+LABA or LM ($819, $1094, and $869, respectively; \(P<.001\) for all comparisons). The ICS and LM groups had significantly lower drug costs, compared with the ICS+LABA group, and the ICS group had significantly lower drug costs than the LM group ($510 for ICS, $797 for ICS+LABA, and $869 for LM; \(P<.001\) for all comparisons).\(^1\)\(^3\)\(^4\)\(^5\)

A 2-year study of 96,631 members of a prominent health plan showed that ICS monotherapy provided an estimated cost savings of $2089 per patient/year, compared with other controller drug groups. Total costs per patient/year were $1811 less with ICS monotherapy versus ICS+LABA combination therapy (\(P<.001\)), and asthma drug costs were $398 less with ICS monotherapy (\(P<.001\)).\(^1\)\(^3\)\(^4\)\(^5\)

QVAR® was also associated with significantly lower medical-related costs, compared with fluticasone in a retrospective database analysis. Lage et al examined data from MedStat’s Commercial Claims and Encounters database for 13,968 asthma patients (QVAR®, n=3233, and fluticasone, n=10,745).\(^1\)\(^3\)\(^4\)\(^5\)\(^6\) The analysis found that the total medical costs were significantly lower for the QVAR® group, compared with the fluticasone group ($5063 vs $5377, respectively; \(P=.004\)). These results are likely driven by the significantly lower drug costs (QVAR®=$2336 vs fluticasone=$2581; \(P<.0001\)) and significantly lower ED costs (QVAR®=$185 vs fluticasone=$249; \(P<.0001\)). Furthermore, QVAR® was associated with significantly lower asthma-related outpatient costs (QVAR®=$191 vs fluticasone=$224; \(P<.0001\)) and asthma-related ED costs (QVAR®=$28 vs fluticasone=$45; \(P<.0001\)).\(^1\)\(^3\)\(^4\)\(^5\)

In its appraisal of ICS therapies, the National Institute for Health and Clinical Excellence (NICE) reported that there were no differences in clinical effectiveness between the different ICSs across dose ranges. The NICE Committee found that the unweighted mean cost of QVAR® was the lowest of the ICS therapies across all dose ranges. The Committee also concluded that, in light of the assumed equivalence of the clinical effectiveness of the different ICS products, the least costly product that can be used effectively by an individual should be chosen. NICE also explained that QVAR®’s HFA delivery system of extra fine particles, results in more drug deposited in the lungs, leading to a 2:1 dose ratio, compared with CFC versions.\(^1\)\(^3\)\(^4\)\(^5\)

EFFICACY AND TOLERABILITY OF QVAR®

The proven efficacy and safety of QVAR® in the treatment of asthma has been demonstrated in blinded, randomized, parallel-group, placebo-controlled, and active-controlled clinical trials in 940 adults with asthma. Fixed doses ranging from 40 mcg to 160 mcg twice daily were compared with 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.\(^1\)

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 forced expiratory volume in 1 second (FEV₁), morning peak expiratory flow (AM PEF), and asthma symptoms, compared with placebo.\(^1\)

In a 12-week clinical trial, 347 patients with symptomatic asthma, being treated with as-needed inhaled beta-agonist bronchodilators and, in some cases, ICS, were given a 7- to 12-day course of oral corticosteroids and then randomized to receive either 320 mcg daily of QVAR®, 672 mcg of CFC-BDP, or placebo. Patients treated with either QVAR® or CFC-BDP had significantly better asthma control, as assessed by AM PEF, FEV₁, and asthma symptoms, and fewer study withdrawals due to asthma symptoms, compared with those given placebo over 12 weeks.\(^1\)

In another 6-week clinical trial, 323 patients, who exhibited a deterioration in asthma control during an ICS
washout period, were randomized to daily treatment with either 40, 160, or 320 mcg twice daily of QVAR® or 42, 168, or 336 mcg twice daily CFC-BDP. Treatment with increasing doses of both QVAR® and CFC-BDP resulted in increased improvement in FEV₁, forced expiratory flow over 25% to 75% of vital capacity, and asthma symptoms.¹

PEDIATRIC PATIENTS

QVAR®’s safety and efficacy also was assessed in a blind-ed, randomized, parallel-group, placebo-controlled, 12-week study of 353 pediatric patients (aged 5-12 years) with symptomatic asthma being treated with as-needed β-agonist bronchodilators. The patients were randomized to receive either 40 mcg or 80 mcg twice daily of QVAR® or placebo. 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), compared with placebo (4% predicted change).¹

ADVERSE EVENTS

QVAR® has a low incidence of adverse events (AEs), as shown in 4 large placebo-controlled studies of 1196 (n=671 female and n=525 male) adults previously treated with as-needed bronchodilators and/or ICS. The patients were randomized to receive QVAR® (n=624), CFC-BDP (n=283), or placebo (n=289). The QVAR® group received doses of 40, 80, 160, or 320 mcg twice daily, and the CFC-BDP group received doses of 42, 168, or 336 mcg twice daily.¹ The most common AEs reported by at least 3% of patients in the QVAR® and CFC-BDP groups were headache (12% and 15%, respectively), pharyngitis (8% and 10%, respectively), upper respiratory tract infection (9% and 12%, respectively), rhinitis (6% and 11%, respectively), and increased asthma symptoms (3% and 8%, respectively).¹

DOSING AND ADMINISTRATION

QVAR® is available in 40- or 80-mcg strengths, and dosage depends on the patient’s previous therapy. See Table. 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. QVAR® is a solution aerosol that does not require shaking. Consistent dose delivery is achieved, whether using the 40- or 80-mcg strengths, due to the proportionality of the 2 products.¹

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. As with any ICS, physicians are advised to titrate the dose of QVAR® downward over time to the lowest level that maintains proper asthma control.¹

IMPORTANT SAFETY INFORMATION

QVAR® is not a bronchodilator and is not indicated for relief of acute bronchospasm.

Common side effects associated with the use of QVAR® and placebo in clinical trials include, but are not limited to, (headache 12% and 9%, respectively) and pharyngitis (8% and 4%, respectively).

CAUTION: Adrenal insufficiency may occur when transferring patients from systemic steroids (see WARN-INGS, Prescribing Information).

A reduction in growth velocity in growing children and teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment.

REFERENCES


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7. Data on File. Teva Specialty Pharmaceuticals LLC.


Please see enclosed full Prescribing Information.
QVAR® is marketed by TEVA
For more information, please visit www.qvar.com.
QVAR® is a registered trademark of IVAX LLC, a member of the TEVA Group.
PRODUCT INFORMATION

QVAR®40 mcg
(beclomethasone dipropionate HFA, 40 mcg)
INHALATION AEROSOL
For Oral Inhalation Only

QVAR®80 mcg
(beclomethasone dipropionate HFA, 80 mcg)
INHALATION AEROSOL
For Oral Inhalation Only

DESCRIPTION

The active component of QVAR 40 mcg Inhalation Aerosol and QVAR 80 mcg Inhalation Aerosol is beclomethasone dipropionate, USP, an anti-inflammatory corticosteroid having the chemical name 9-chloro-11,17,21-triacetoxy-16β-methylpregna-1,4-diene-3,20-dione. 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 C28H37ClO7 and a molecular weight of 521.1. Its chemical structure is:

\[
\text{C}_28\text{H}_{37}\text{ClO}_7
\]

QVAR is a pressurized, metered-dose aerosol 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 30 mcg chlorofluorocarbons (59 milligrams) of solution formulation from the valve with each actuation. Each canister provides 100 inhalations. QVAR should be "primed" or actuated twice prior to the first dose from a new canister, or if the canister has not been used for more than ten days. Avoid spraying in the eyes or face while priming QVAR. This product does not contain chlorofluorocarbons (CFCs).

CLINICAL PHARMACOLOGY

Aerosol delivery is known to be an important component in the pathogenesis of asthma. Inflammation occurs in both large and small airways. Corticosteroids have multiple anti-inflammatory effects, including inhibition of inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and inhibition of inflammatory mediators (e.g., histamine, leukotrienes, leukotrienes, and cytokines). These anti-inflammatory actions of corticosteroids such as beclomethasone dipropionate contribute to their efficacy in asthma.

Beclomethasone dipropionate is a prodrug that is rapidly activated by hydrolysis to the active monostere, 17-monopropionate (17-BMP). Beclomethasone 17-monopropionate has been shown in vitro to exhibit a binding affinity for the glucocorticoid receptor which is approximately 13 times that of dexamethasone 4,6-dione and 2 times that of triamcinolone acetonide. 1.5 times that of budesonide and 25 times that of beclomethasone dipropionate. In vivo studies of its anti-inflammatory and anti-asthmatic effects are described below.

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

Pharmacokinetics

Beclomethasone dipropionate (BDP) undergoes rapid and extensive conversion to beclomethasone-17-monopropionate (17-BMP) during absorption. The pharmacokinetics of 17-BMP has been studied in asthmatics given single doses.

Absorption: The mean peak plasma concentration (Cmax) of BDP was 88 pg/ml at 0.5 hour after inhalation of 320 mcg using QVAR (four actuations of the 80 mcg/inhalation strength). The mean peak plasma concentration of the major and most active metabolite, 17-BMP, was 1449 pg/ml at 0.7 hour after inhalation of 320 mcg of QVAR. When the same nominal dose is provided by the two QVAR strengths (40 and 80 mcg/inhalation), equivalent systemic pharmacokinetics can be expected. The Cmax of 17-BMP increased dose proportionally in the dose range of 80 and 320 mcg.

Metabolism: Three major metabolites are formed via cytochrome P450 catalyzed biotransformation - beclomethasone-17-monopropionate (17-BMP), beclomethasone-21-monopropionate (21-BMP) and beclomethasone (BDP). Lang slices metabolize BDP rapidly to 17-BMP and more slowly to BOR. 17-BMP is the most active metabolite.

Distribution: The α receptor protein binding for 17-BMP was reported to be 94-95% over the concentration range of 0 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 administered dose is recovered in the expired breath as dose-related reductions in 17-BMP excretion half-life from 3.3 hours at 40 mcg to 0.5 hours at 320 mcg. 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 specific populations.

Politics: The pharmacokinetics of 17-BMP, including dose and strength proportionality, is similar in children and adults, although the exposure is highly variable. In 17 children (mean age 10 years), the Cmax of 17-BMP was 787 pg/ml at 0.6 hour after inhalation of 160 mcg of HFA-BDP administered without a spacer was comparable to the systemic exposure to 17-BMP from 160 mcg of HFA-BDP administered with a spacer without a spacer was comparable to the systemic exposure to 17-BMP from 336 mcg CFC-BDP administered without a spacer. 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 (ages 5-12 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 increases of both QVAR and CFC-BDP generally resulted in increases in 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.

Patients Not Previously Receiving Corticosteroid Therapy

In a 6-week clinical trial, 270 steroid naïve patients with symptomatic asthma being treated with as-needed beta-agonist bronchodilators, were randomized to receive either 160 mcg twice daily of QVAR (delivered as either 40 mcg/actuation or 80 mcg/actuation) or placebo. Treatment with QVAR significantly improved asthma control, as assessed by FEV1, AM PEF, and asthma symptoms when compared to treatment with placebo. Comparable improvements in FEV1 were seen for patients receiving 160 mcg twice daily QVAR from the 40 mcg and 80 mcg strength products.

Patients Responsive to a Short Course of Oral Corticosteroids

In another clinical trial, 347 patients with symptomatic asthma, being treated with as-needed inhaled beta-agonist bronchodilators and, in some cases, inhaled corticosteroids, were given a 7-12 day course of oral corticosteroids and then randomized to receive either 320 mcg daily of QVAR, 672 mcg of CFC-BDP or placebo. Patients treated with either QVAR or CFC-BDP had significantly better asthma control, as assessed by AM PEF, FEV1, and asthma symptoms, and fewer study withdrawals due to asthma symptoms, than those treated with placebo over 6 weeks of treatment. A daily dose of 320 mcg QVAR administered in divided doses provided comparable control of AM PEF and FEV1, as 672 mcg of CFC-BDP. Shown below are the mean AM PEF results from this trial.

A 12-Week Clinical Trial in Moderate Symptomatic Patients with Asthma Responding to Oral Corticosteroid Therapy: Mean Change in AM PEF

In a 6-week clinical trial, 256 patients with symptomatic asthma being treated with as-needed beta-agonist bronchodilators, were randomized to receive either 160 mcg twice daily of QVAR (delivered as either 40 mcg/actuation or 80 mcg/actuation) or placebo. Treatment with QVAR significantly improved asthma control, as assessed by FEV1, AM PEF, and asthma symptoms when compared to treatment with placebo. Comparable improvements in FEV1 were seen for patients receiving 160 mcg twice daily QVAR from the 40 mcg and 80 mcg strength products.

Patients Previously on Inhaled Corticosteroids

In a 6-week clinical trial, 325 patients, who exhibited a deterioration in asthma control during an inhaled corticosteroid washout period, were randomized to daily treatment with either 40, 80, 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 resulted in increased improvement in FEV1, AM PEF (forced expiratory flow over 25-75% of the vital capacity), and asthma symptoms. Shown below is the change from baseline in FEV1, as percent predicted after 6 weeks of treatment.

A 12-Week Dose Response Clinical Trial in Patients with Inhaled Corticosteroid Dependent Asthma: Mean Change in FEV1, as Percent of Predicted

Patients Previously on Oral Corticosteroids

In a 6-week clinical trial, 325 patients, who exhibited a deterioration in asthma control during a systemic corticosteroid washout period, were randomized to daily treatment with either 40, 80, 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 resulted in increased improvement in FEV1, AM PEF (forced expiratory flow over 25-75% of the vital capacity), and asthma symptoms. Shown below is the change from baseline in FEV1, as percent predicted after 6 weeks of treatment.

A 6-Week Dose Response Clinical Trial in Patients with Inhaled Corticosteroid Dependent Asthma: Mean Change in FEV1, as Percent of Predicted
Patients Previously Maintained on Oral Corticosteroids

Clinical experience has shown that some patients with asthma who require oral corticosteroid therapy for control of asthma at the highest dose as a daily maintenance dose have been randomized to receive placebo or QVAR beclomethasone dipropionate aerosol in 80 mcg twice daily or 400 mcg twice daily as rescue therapy for episodes of asthma with symptoms not responsive to bronchodilators, which are randomized to receive placebo or QVAR beclomethasone dipropionate or placebo. Both doses were effective in improving asthma control with significantly greater improvements in FEV1, 98% and 108% predicted change from baseline at 12 and 21 FEV1, percent predicted (4% change predicted).  

INDICATIONS AND USAGE

QVAR is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. QVAR is also indicated for asthma patients who require systemic corticosteroid administration, where adding QVAR may reduce or eliminate the need for the systemic corticosteroids.

Beclomethasone dipropionate is NOT indicated for the relief of acute bronchospasm.

CONTRAINdications

QVAR is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNings

Particular care is needed in patients who are transferred from systemically active corticosteroids to QVAR because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when the systemic corticosteroid dose is rapidly tapered or stopped. This is a life-threatening situation that may require urgent medical care. During this period of adrenal suppression, patients may have coexisting infections and will require appropriate therapy. Transfer of patients from systemic steroid therapy to QVAR may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

Prescription of a systemic corticosteroid to a patient already taking an inhaled corticosteroid may potentiate the immune system making the patient more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more severe 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 properly immunized, consider prophylaxis (or reinfection precautions) or other conditions with severe electrolyte loss. Although QVAR may provide control of asthmatic symptoms during these episodes, in recommended doses, QVAR is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older.

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QVAR should be administered by the oral inhaled route in patients 5 years of age and older. Use of QVAR with dose comparable to one actuation of the 80 mcg strength). Strengths due to proportionality of the two products (i.e., two actuations of 40 mcg strength should provide a similar effect as one actuation of the 80 mcg strength). QVAR is indicated for the management of asthma in adults and children 5 years of age and older.

Adverse Events

Adverse Events Reported by at Least 3% of the Patients for Either QVAR or CFC-BDP by Treatment and Daily Dose

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>QVAR (N=283)</th>
<th>CFC-BDP (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Increased asthma symptoms</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>4%</td>
<td>3%</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: dyspnoea, dysmenorrhoea and coughing.

No patients treated with QVAR in the clinical development program developed symptomatic ophthalmic candidiasis.

If an infection develops, treatment with appropriate antifungal therapy or discontinuation of treatment with QVAR may be required.

Pediatric Studies: In two 12-week placebo controlled studies in steroid naive pediatric patients 5 to 12 years of age, no clinically relevant differences were found in the pattern, severity, or frequency of adverse events compared with those reported in adults, with the exception of conditions which are more prevalent in a pediatric population generally.

Adverse Event Reports from Other Sources: Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation of beclomethasone dipropionate.

OVERDOSAGE

There were no deaths over 15 days following the oral administration of a single dose of 3000 mcg/kg in mice, 2000 mcg/kg in rats, and 1000 mcg/kg in rabbits. The doses in mice, rats, and rabbits were 19,000, 25,000, and 10,000 mcg/kg, respectively. In mice, rats, and rabbits, the maximum recommended daily inhalation dose was 50,000, 100,000, and 25,000 mcg/kg, respectively. There was approximately one week, gradual withdrawal of the systemic corticosteroids is started by reducing the daily or alternate daily dose. Reductions may be made after an interval of one or two weeks, depending on the response of the patient. A slow rate of withdrawal is strongly recommended. Generally these decrements should not exceed 25 mg of prednisone or its equivalent. During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with the inhaler but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly.

During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

DIRECTIONS FOR USE

Illustrated Patient’s Instructions for proper use accompany each package of QVAR.

HOW SUPPLIED

QVAR is supplied in two strengths:

- QVAR 40 mcg is supplied in a 7.3 g canister containing 100 actuations with a beige plastic actuator and grey dust cap, and Patient’s Instructions; box of one; 100 Actuations – NDC 39310-175-40
- QVAR 80 mcg is supplied in a 7.3 g canister containing 100 actuations with a dark mauve plastic actuator and grey dust cap, and Patient’s Instructions; box of one; 100 Actuations – NDC 39310-177-80

The correct amount of medication in each inhalation cannot be assured after 100 actuations from the 7.3 g canister even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used.

Store QVAR Inhalation Aerosol when not being used, so that the product rests on the concave end of the canister with the plastic actuator on top.

Store at 25ºC (77ºF).

Excursions between 15º and 30ºC (59º and 86ºF) are permitted (see USP). For optimal results, the canister should be at room temperature when used. QVAR Inhalation Aerosol canister should only be used with the AeroChamber Plus 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 49ºC (120ºF) may cause bursting. Never throw container into fire or incineration.

Keep out of reach of children.

Rx only

Mkt by:
Teva Specialty Pharmaceuticals LLC – Horsham, PA 19044
Developed and Manufactured by: 3M Drug Delivery Systems OR 3M Health Care, Ltd.
Northridge, CA 91324
Loughborough, UK

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