PRODUCT MONOGRAPH

PrQVAR®
Beclomethasone Dipropionate
Inhalation Aerosol - Metered Dose Aerosol
50 mcg and 100 mcg

Corticosteroid for Oral Inhalation
Contains no chlorofluorocarbons (CFCs)
(CFC-Free)

Bausch Health, Canada Inc.
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Laval, Quebec
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ACTION AND CLINICAL PHARMACOLOGY

Beclomethasone dipropionate is a diester of beclomethasone, a synthetic corticosteroid chemically related to dexamethasone. Beclomethasone differs from dexamethasone in having a chlorine at the 9-alpha carbon in place of a fluorine, and in having a 16 beta-methyl group instead of a 16 alpha-methyl group.

Bronchial inflammation is known to be an important component in the pathogenesis of asthma, occurring in both large and small airways. Glucocorticoids have multiple anti-inflammatory effects, inhibiting both inflammatory cells and release of inflammatory mediators. It is presumed that these anti-inflammatory actions play an important role in the efficacy of beclomethasone dipropionate (BDP) in controlling symptoms and improving lung function in asthma. Inhaled BDP probably acts as a topical anti-inflammatory agent at the site of deposition in the bronchial tree.

In two studies evaluating the deposition pattern of technetium-99m labeled QVAR (beclomethasone dipropionate), approximately 50-60% of the dose from the actuator (40% of the dose from the valve) of QVAR was deposited in the lungs. The imaging data suggest that QVAR, beclomethasone dipropionate formulated in hydrofluoroalkane-134a (HFA-BDP), deposited widely throughout the central, intermediate, and peripheral airways. In contrast, approximately 4-7% dose from the actuator (5% of the dose from the valve) of beclomethasone dipropionate formulated in chlorofluorocarbons (CFC-BDP) was deposited in the lungs, and deposition was limited to the central airways. Over 90% of the CFC-BDP dose was deposited in the oropharynx. The smaller particle size of QVAR explains the different deposition patterns compared with CFC-BDP. This accounts for the dosage adjustment recommended when switching patients from CFC-BDP to QVAR (please refer to DOSAGE AND ADMINISTRATION).

INDICATIONS AND CLINICAL USE

QVAR (beclomethasone dipropionate) is indicated for the prophylactic management of steroid-responsive bronchial asthma in patients 5 years and older.

QVAR may be effective in the management of asthmatics dependent or maintained on systemic corticosteroids and may permit replacement or significant reduction in the dosage of systemic corticosteroids.

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

CONTRAINDICATIONS

QVAR (beclomethasone dipropionate) is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma or in patients with moderate to severe bronchiectasis where intensive measures are required.

QVAR is contraindicated in patients with untreated fungal, bacterial or tuberculous infections of the respiratory tract.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

For the transfer of patients being treated with oral corticosteroids, QVAR (beclomethasone dipropionate) should first be added to the existing oral steroid therapy, which is then gradually withdrawn.

After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. Particular care is needed in patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible to problems associated with adrenal insufficiency, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections, particularly gastroenteritis or other conditions with severe electrolyte loss. Although inhaled corticosteroids may provide control of asthmatic symptoms during these episodes, they do NOT provide systemically available steroid which is necessary for coping with these emergencies.

Transfer of patients from systemic steroid therapy to inhaled corticosteroids may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

During periods of stress or severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (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 severe asthma attack.

As with other inhalation therapy, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator to relieve acute asthmatic symptoms. QVAR should be discontinued immediately, the patient assessed, and if necessary, alternative therapy instituted.

Increasing use of short-acting inhaled bronchodilators to control symptoms indicates deterioration of asthma control. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. Patients should be instructed to contact their physicians if they find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual. During such episodes, patients may require therapy with systemic corticosteroids.

QVAR is not indicated for rapid relief of bronchospasm but for regular daily treatment of the underlying inflammation. Patients will require a fast and short acting inhaled bronchodilator to relieve acute asthmatic symptoms. There is no evidence that control of bronchial asthma can be achieved by the administration of QVAR in amounts greater than the recommended dosages.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of QVAR and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection.

Persons who are on drugs that 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 children or adults who have not had these diseases, 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.

Therapeutic dosages frequently cause the appearance of Candida albicans (thrush) in the mouth and throat. The development of pharyngeal and laryngeal candidiasis is a cause for concern because the extent of its penetration into the respiratory tract is unknown. Patients may find it helpful to rinse out their mouths with water after using beclomethasone dipropionate. Symptomatic candidiasis can be treated with topical antifungal therapy while still continuing to use QVAR (see PRECAUTIONS, Drug Interaction).

PRECAUTIONS

General

It is essential that the patients be instructed that QVAR (beclomethasone dipropionate) is a preventative agent which must be taken daily at the intervals recommended by their doctors and is not to be used as acute treatment for an asthmatic attack.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Treatment with QVAR should not be stopped abruptly but tapered off gradually.

The replacement of a systemic steroid with inhaled steroid must be gradual and carefully supervised by the physician since upon withdrawal systemic symptoms (e.g. joint and/or muscular pain, lassitude, depression) may occur despite maintenance or improvement of respiratory function (see DOSAGE AND ADMINISTRATION for details.)

Doses of QVAR up to 800 mcg/day may permit control of asthmatic symptoms without clinically meaningful suppression of HPA function. Doses of QVAR exceeding 800 mcg/day may cause clinically meaningful HPA suppression.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods; these effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. It is important, therefore, that the dose of QVAR is titrated to the lowest dose at which effective control is maintained (see ADVERSE REACTIONS).

Certain individuals can show greater susceptibility to the effects of inhaled corticosteroid than do most patients.

The long-term and systemic effects of BDP in human subjects are still not fully known. In particular, the effects resulting from chronic use of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. During long-term therapy, HPA-axis function and hematological status should be assessed periodically.

Rare instances of glaucoma increased intraocular pressure, and cataracts have been reported following the administration of very high doses of inhaled corticosteroids.

Eosinophilic Conditions
In rare cases, patients on inhaled beclomethasone dipropionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of beclomethasone dipropionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between beclomethasone dipropionate and these underlying conditions has not been established.

Pediatric Use
Eight-hundred and forty-three (843) children between the ages of 5 and 12 were treated with HFA beclomethasone dipropionate (HFA-BDP) in clinical trials.

Pregnancy
There are no adequate and well controlled studies of BDP in pregnant women. The use of BDP in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother, embryo, or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for hypoadrenalism.

Labor and Delivery
Use of QVAR during labor and delivery has not been studied.

Nursing Mothers
Glucocorticoids are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from BDP, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Glucocorticoids are known teratogens in rodent species and BDP is no exception. Teratology studies were done in rats, mice, and rabbits treated with subcutaneous BDP. Beclomethasone dipropionate was found to produce fetal resorptions, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and partial agenesis of the thymus in these species. Well-controlled trials relating to fetal risk in humans are not available.

Effect on Infection
Corticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localised infection has been observed during corticosteroid therapy. This may require treatment with appropriate therapy or stopping the administration of beclomethasone dipropionate until the infection is eradicated.

Hypothyroidism and Cirrhosis
There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Use of Corticosteroids and Acetylsalicylic Acid
Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Proper Use of the Inhalation Device
To ensure the proper dosage and administration of the drug, the patient must be instructed by a physician or other health professional in the use of the inhalation aerosol (see INFORMATION FOR THE CONSUMER). Inhaler actuation should be synchronised with inspiration to ensure optimum delivery of the drug to the lungs.

Oral Hygiene
In some patients, corticosteroids may cause hoarseness or candidiasis of the mouth and throat (thrush). Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as Candida albicans. Patients may find it helpful to rinse out their mouth with

water after using the inhaler (see DOSAGE AND ADMINISTRATION). Symptomatic candidiasis can be treated with topical anti-fungal therapy while still continuing treatment with QVAR (see PRECAUTIONS, Drug Interaction).

Information to be Provided to the Patient
See the illustrated INFORMATION FOR THE CONSUMER insert that is dispensed with the product. For patients switching from a CFC-BDP inhaler, the following should be mentioned:

You may notice a different taste or spray force with QVAR compared to beclomethasone dipropionate aerosol inhalers that contain CFC propellants. Laboratory tests using instruments (not on people) show that QVAR delivers a softer spray force (less than 1/3 the maximum impact force) and warmer spray temperature (more than 30°C warmer) than beclomethasone dipropionate aerosol inhalers containing CFC propellants.

There is no tail-off phenomenon observed for QVAR since the propellant and drug exhaust simultaneously, providing consistent dosing from priming through to a few sprays beyond the planned maximum number of doses. Tail-off means that as most inhalers approach empty, the delivered dose becomes unpredictable and subject to wide variation.

ADVERSE REACTIONS

In general, inhaled corticosteroid therapy may be associated with dose dependent increases in the incidence of ocular complications, reduced bone density, suppression of HPA-axis responsiveness to stress, and inhibition of growth velocity in children.

Glaucoma may be exacerbated by inhaled corticosteroid treatment for asthma or rhinitis. In patients with established glaucoma who require long-term inhaled corticosteroid treatment, it is prudent to measure intraocular pressure before commencing the inhaled corticosteroid and to monitor it subsequently. In patients without established glaucoma, but with a potential for developing intraocular hypertension (e.g. the elderly), intraocular pressure should be monitored at appropriate intervals.

In elderly patients treated with inhaled corticosteroids, the prevalence of posterior subcapsular and nuclear cataracts is probably low but increases in relation to the daily and cumulative lifetime dose. Cofactors such as smoking, ultraviolet B exposure, or diabetes may increase the risk. Children may be less susceptible.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if any adolescent's growth appears slowed. (see "Clinical Trials")

Osteoporosis and fracture are the major complications of long-term asthma treatment with parenteral or oral steroids. Inhaled corticosteroid therapy is also associated with dose-dependent

bone loss although the degree of risk is very much less than with oral steroid. This risk may be offset by estrogen replacement in post-menopausal women, and by titrating the daily dose of inhaled steroid to the minimum required to maintain optimal asthma control. It is not yet known whether the peak bone density achieved during youth is adversely affected if substantial amounts of inhaled corticosteroid are administered prior to 30 years of age. Failure to achieve maximal bone density during youth could increase the risk of osteoporotic fracture when those individuals reach 60 years of age and older.

Eosinophilic conditions
See PRECAUTIONS, Eosinophilic Conditions.

The following reporting rates of common adverse experiences are based upon three clinical trials in which 940 patients (544 female and 396 male adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with QVAR (beclomethasone dipropionate) (doses of 50, 100, 200, or 400 mcg twice daily) or CFC-BDP (doses of 50, 200, or 400 mcg twice daily) or placebo. The table below includes all events reported by patients taking QVAR (whether considered drug related or not) that occurred at a rate over 3% and more frequently than placebo, or at a rate that significantly differed across treatment groups.

Adverse events reported in ≥ 3% of the patients in the QVAR group (%)

Adverse events	**QVAR N=453**	**CFC-BDP N=283**	**HFA-placebo N=204**	**Overall N=940**	**Overall P-value[a]**
Inhalation route effects	7	11[d]	4	7	**0.028**
Oral symptoms	3	6	2	4	0.085
General	8	11	8	9	0.290
Pain	3	3	<1	2	0.143
Central & peripheral nervous system	20	20	16	19	0.442
Headache	17	15	11	15	0.213
Gastro-intestinal	6	9	4	6	0.771
Nausea	2	3[d]	0	2	**0.032**
Vomiting	<1[b]	2	<1	<1	**0.022**
Musculo-skeletal	4	5	2	4	0.275
Reproductive disorders	4	2	2	3	0.545
Dysmenorrhea	3	<1	2	2	0.131
Respiratory system	30[bc]	37	45	36	**0.001**
Increased asthma symptoms	4[bc]	8[d]	22[e]	9	**<0.001**
Pharyngitis	10	10	5	9	0.054
Respiratory disorder	0	1	0	<1	**0.037**
Sinusitis	4	4	2	4	0.599
Skin and appendage	5	5	2	5	0.254

Adverse events	QVAR N=453	CFC-BDP N=283	HFA-placebo N=204	Overall N=940	Overall P-value[a]
Vision					
Eye abnormality	0	1	0	<1	**0.037**

a. The p-value for the overall comparison is a two-sided Fisher's Exact Test.
b. The pairwise comparison between HFA-BDP and CFC-BDP was statistically significant ($p \leq 0.05$) based on the two-sided Fisher's Exact Test.
c. The pairwise comparison between HFA-BDP and HFA-placebo was statistically significant ($p \leq 0.05$) based on the two-sided Fisher's Exact Test.
d. The pairwise comparison between CFC-BDP and HFA-placebo was statistically significant ($p \leq 0.05$) based on the two-sided Fisher's Exact Test.
e. The higher incidence of increased asthma symptoms for the placebo-treated patients is not unexpected in a population requiring inhaled corticosteroids.

No patients treated with QVAR in the clinical program developed symptomatic oropharyngeal candidiasis. If such an infection develops, treatment with appropriate antifungal therapy or discontinuance of treatment with QVAR may be required.

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation of BDP.

Pediatric Studies
In two 12-week placebo-controlled studies in 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.

During post-marketing experience, psychiatric events and behavioural changes such as aggression, depression, sleep disorders, psychomotor hyperactivity, and suicidal ideation have been reported (primarily in children). Because these events 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Chronic overdosage of inhaled steroids, as a class, may cause manifestation of Cushing's syndrome, including truncal obesity, hypertension, fatigability and weakness, menstrual irregularities, hirsutism, purplish abdominal striae, edema, glucosuria, osteoporosis, etc. Managing chronic overdosage requires gradual reduction of the dose of inhaled steroid. Gradual reduction is emphasized, because chronic overdosage with inhaled steroids must be recognized as possibly causing suppression of endogenous adrenal production of corticosteroids. Careful titration downward of inhaled steroids, with monitoring of asthma control, is required. Periodic evaluation of the function of the hypothalamic-pituitary-adrenal axis is prudent during this down titration process to ensure that endogenous production of adrenal corticosteroids has resumed. It is expected that HFA-BDP will have the same potential for causing chronic overdosage as other inhaled steroids.

DOSAGE AND ADMINISTRATION

It is important that children be adequately instructed in the correct use of the pressurised metered-dose inhaler.

General

The lowest dose of beclomethasone dipropionate required to maintain good asthma control should be used. When the patient's asthma is well controlled, a reduction in the dose of beclomethasone dipropionate should be attempted in order to identify the lowest possible dose required to maintain control. Such an attempt at dose reduction should be carried out on a regular basis.

QVAR (beclomethasone dipropionate) Inhalation Aerosol is to be administered by oral inhalation only.

Since the effect of QVAR depends on its regular use and on the proper technique of inhalation, the patient should be made aware of the prophylactic nature of therapy with inhaled beclomethasone dipropionate, and that for optimum benefit QVAR should be taken regularly, even when the patient is asymptomatic. Improvement in asthma symptoms should be expected within the first or second week of starting treatment.

If patients find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention should be sought.

Patients using inhaled bronchodilators should be advised to use the bronchodilator before the QVAR in order to enhance the penetration of QVAR into the bronchial tree. Several minutes should lapse between the use of the two inhalers to allow for some bronchodilation to occur.

In the presence of excessive mucous secretion, the drug may fail to reach the bronchioles. Therefore, if an obvious response is not obtained after ten days, attempts should be made to remove the mucous with expectorants and/or with a short course of systemic corticosteroid treatment.

As a general rule, rinsing the mouth and gargling after each inhalation with water can help in preventing the occurrence of candidiasis. Cleansing dentures has the same effect.

Treatment with QVAR should not be stopped abruptly but tapered off gradually.

Dosage

QVAR (beclomethasone dipropionate) is indicated for the prophylactic management of steroid-responsive bronchial asthma in patients 5 years and older. More clinical safety and efficacy studies are required to support an indication for use in younger children.

The recommended dosing range for QVAR is 100 to 800 mcg/day. Each actuation of QVAR 50 mcg delivers 50 mcg of BDP from the valve, equivalent to 40 mcg of BDP from the actuator. Each actuation of QVAR 100 mcg delivers 100 mcg of BDP from the valve, equivalent to 80 mcg of BDP from the actuator.

Pediatric patients (5-11 years old)

Previous therapy	Recommended starting dose	Highest recommended dose
Bronchodilators alone	50 mcg of QVAR twice daily	100 mcg of QVAR twice daily
Inhaled corticosteroids	50 mcg of QVAR twice daily	100 mcg of QVAR twice daily
Oral corticosteroids	The highest recommended dose in children is 100 mcg of QVAR twice daily	

Patients 12 years and older

Mild asthma patients: 50 to 100 mcg of QVAR twice daily (total daily dose of 100 to 200 mcg).

Moderate asthma patients: 100 to 250 mcg of QVAR twice daily (total daily dose of 200 to 500 mcg).

In more severe cases: 300 to 400 mcg twice daily of QVAR (total daily dose of 600 to 800 mcg).

The recommended total daily dose of QVAR is lower than that recommended for current CFC-BDP products because of increased lung deposition. Dosage should be adjusted to the individual patient.

Suggested Conversion of Doses for Patients Switching from CFC-BDP to QVAR:

CFC-BDP Dose (mcg/day)	200	400-500	600-750	800-1000
	⇓	⇓	⇓	⇓
QVAR Dose (mcg/day)	100	200	300	400

Note: The conversion to the QVAR dose should be based on the dose of CFC-BDP that would be appropriate for the patient at the time of the switch. Symptomatic patients may require an increased dose of CFC-BDP, and this increased dose should be considered in transferring patients to QVAR

Patients Switched From Systemic to Inhaled 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.

Particular care is needed in patients who are transferred from systemic corticosteroids to inhaled corticosteroids mainly because recovery from impaired adrenocortical function caused by prolonged systemic steroid therapy is slow.

The patient's asthma should be stable before treatment with QVAR is started. Initially, QVAR should be used concurrently with the patient's usual maintenance dose of systemic corticosteroids. After 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. Gradual withdrawal of the systemic steroid is started by reducing the daily dose by 1.0 mg of prednisone, or its equivalent of other corticosteroid, at not less than weekly intervals, if the patient is under close observation. 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, patients who have been withdrawn from systemic corticosteroid should be instructed to resume systemic steroids 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 steroid during periods of stress or a severe asthma attack.

Patients who have been treated with systemic steroids for long periods of time or at high dose may have adrenocortical suppression. In these patients, adrenocortical function should be monitored regularly, and their dose of systemic steroid reduced cautiously.

There are some patients who cannot completely discontinue the oral steroid. In these cases, a minimum maintenance dosage should be given in addition to QVAR.

Administration

QVAR should be administered by the oral inhaled route in patients 5 years of age and older. The onset and degree of symptom relief will vary in individual patients. Improvement in asthma symptoms should be expected within the first or second week of starting treatment, but maximum benefit should not be expected until 3-4 weeks of therapy. After asthma stability has been achieved at the starting dose, it is always desirable to titrate to the lowest effective dose to reduce the possibility of side effects. For patients who do not respond adequately to the starting dose after 3-4 weeks of therapy, higher doses may provide additional asthma control. The safety

and efficacy of QVAR when administered in excess of recommended doses has not been established.

As with all inhalation aerosol medications, it is recommended that patients "test spray" QVAR into the air before using for the very first time after purchase. If QVAR has not been used for over 14 days, four "test sprays" are again recommended prior to use (see INFORMATION FOR THE CONSUMER.)

QVAR is a solution aerosol that does not require shaking. Consistent dose delivery is assured, whether using 50 or 100 mcg strengths, due to good proportionality of the solution aerosol. Dose proportionality means that the 100 mcg/actuation strength provides twice as much medication as the 50 mcg/actuation strength. Consistent dosing can be assured as doses are adjusted and different product strengths are used. QVAR provides consistent medication delivery actuation to actuation regardless of storage position. This allows reliable dosing with a single actuation. Consistent medication delivery is also ensured throughout the labeled product life. When the canister is nearly empty, the spray from the mouthpiece will decrease sharply and will be obvious to the patient.

No clinical trials have been conducted using a spacer with QVAR; however, in vitro studies indicate that AEROCHAMBER® is compatible with QVAR.

Use of a spacer: QVAR has been developed to be used without a spacer device being necessary. Where a spacer is considered necessary the AEROCHAMBER® is a suitable device for use with QVAR MDI as the extra fine particle fraction is maintained.

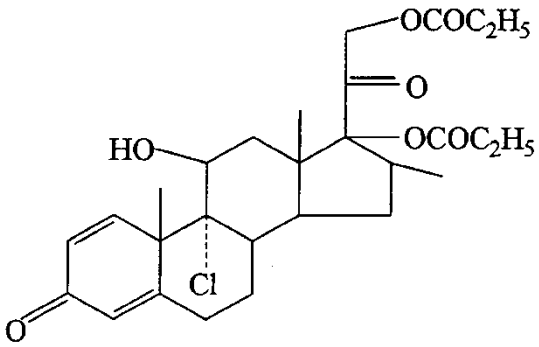
PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Beclomethasone dipropionate

Chemical name: 9-Chloro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione-17,21-dipropionate

Structural formula:



Molecular formula: $C_{28}H_{37}ClO_7$

Molecular weight: 521.1 g/mol

Physicochemical Properties

Physical form: White to creamy white, odorless powder.

Solubility: Slightly soluble in water, very soluble in chloroform and freely soluble in acetone and in alcohol.

Melting point: 205-215°C

Composition

QVAR is a pressurized, metered-dose inhaler intended for oral inhalation only. Each unit contains a solution of beclomethasone dipropionate in propellant HFA-134a (hydrofluoroalkane-134a or 1,1,1,2 tetrafluororethane) and ethanol. This product does not contain CFCs.

The mean particle size of the emitted aerosol spray for both QVAR 50 mcg and QVAR 100 mcg is finer (1 to 1.2 microns) than that of BDP formulated in chlorofluorocarbon (CFC) propellant (3.5 to 4 microns).

Stability and storage recommendations
CONTENTS UNDER PRESSURE. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 50°C may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.

Store between 15° and 30°C. If the canister is subjected to cold temperatures (as low as -10°C), it will not adversely effect delivery of medication.

AVAILABILITY OF DOSAGE FORMS

QVAR (beclomethasone dipropionate) is supplied in two strengths, each having two presentations:

QVAR 50 mcg is supplied in a 12.4 g canister containing 200 actuations with a beige plastic oral actuator and Patient's Instructions; box of one.

QVAR 100 mcg is supplied in a 12.4 g canister containing 200 actuations with a dark mauve plastic oral actuator and Patient's Instructions; box of one.

INFORMATION FOR THE CONSUMER

PrQVAR®
Beclomethasone Dipropionate
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50 mcg and 100 mcg

What you should know about QVAR Inhalation Aerosol:
Please read this leaflet carefully before you start to take your medicine. For more information or advice, ask your doctor or your pharmacist.

What QVAR contains:

Medicinal ingredient:	Beclomethasone dipropionate
Non-medicinal ingredients:	Ethanol
	1,1,1,2 tetrafluoroethane (Propellant HFA-134a)

About your medicine:
The name of this product is QVAR Inhalation Aerosol. It contains beclomethasone dipropionate, a corticosteroid medicine that can help to ease your breathing problems by relieving swelling and irritation in the small air passages in the lungs. Correct and regular use of the inhaler will prevent or lessen the severity of asthma attacks. Each puff of aerosol from the can contains 50 or 100 micrograms of beclomethasone dipropionate.

What to tell your doctor before taking your medicine:
- Have you ever had to stop taking other medicines for this illness because you were allergic to them or they caused problems?
- Have you ever had thrush in your mouth?
- Do you have any history of tuberculosis (TB) infections?
- Are you taking other "steroids" by mouth or by inhalation?
- Are you suffering any other infections, including chicken pox or measles, or taking any other drug products which may make you more prone to infection?
- Have you ever had any previous reaction to this product or any of its ingredients? (see "What QVAR contains")

If the answer is YES to any of these questions, tell your doctor or pharmacist as soon as possible if you have not already done so.

Make sure that your doctor knows what other medicines you are taking (such as those for allergies, nervousness, depression, migraine, etc.), as well as those you can buy without a prescription, including acetylsalicylic acid (ASA), and herbal and alternative medicines.

Use of this medicine during pregnancy and breast feeding:
Do not use this medication during pregnancy or breast feeding without first discussing with your doctor.

Dosing information
Your doctor has decided on the best dose of QVAR Inhalation Aerosol for you to take and on how often you should take a dose. The label that the pharmacist puts on your inhaler indicates how many puffs to take and how often. If you do not understand the instructions on the label, check with your pharmacist or your doctor.

It is very important that you follow your doctor's instructions carefully so that you receive the maximum benefit from your medication.

DO NOT take more doses or use your inhaler more often than your doctor advises.

It may take from 1 to 4 weeks before you feel the full benefits of this medicine and it is VERY IMPORTANT THAT YOU USE IT REGULARLY. If your shortness of breath or wheeze does not get better after 7 days, tell your doctor. DO NOT STOP treatment - even if you feel better - unless told to do so by your doctor.

DO NOT USE THIS MEDICINE TO TREAT A SUDDEN ATTACK OF BREATHLESSNESS. You will probably need a different kind of medicine in a different colour pack which your doctor may already have given you. If you have more than one medicine, be careful not to confuse them.

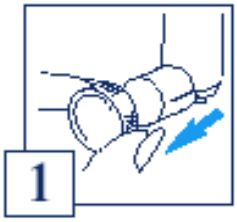
After you start taking QVAR Inhalation Aerosol, your doctor may change the dosages of your other asthma medicines. Rarely, this may make a patient feel worse rather than better. This especially applies to oral corticosteroids (sometimes referred to as steroids), including prednisone. If your doctor decreases your oral steroid dose, and you become unwell, tell your doctor immediately.

If you have to go into the hospital for an operation, take your inhaler with you and tell the doctor what medicines(s) you are taking.

How to use QVAR Inhalation Aerosol
Follow the instructions given below to use the inhaler. If you have any problems using the inhaler or if you do not understand the instructions below, ask your doctor or your pharmacist for help. Children prescribed QVAR Inhalation Aerosol should be trained in the use of the device.

QVAR should only be used with the mouthpiece supplied with the product. You should test the mouthpiece and aerosol can before using them for the first time, or if you have not used your inhaler for more than 2 weeks. After removal of the plastic cap, test by spraying 4 test sprays into the air, away from your face. This is called priming the inhaler. Avoid spraying into the eyes. QVAR will deliver a consistent dose from priming until the can is empty but must be reprimed after 2 weeks of non-use.

1. Take the cap off of the mouthpiece (see figure 1). Check the mouthpiece for dirt or other objects before you use it. Make sure the aerosol can is pushed all the way into the actuator (the small vertical cylinder in the mouthpiece). It should fit tightly, without wobbling.



2. BREATHE OUT AS BIG A BREATH AS YOU CAN THROUGH YOUR MOUTH, pushing as much air out of your lungs as possible. Place the mouthpiece in your mouth between your teeth and close your lips around it, keeping your tongue below it. Make sure the inhaler stays straight up (see figure 2).

3. AT THE BEGINNING OF A DEEP, SLOW BREATH THROUGH YOUR MOUTH, PUSH ALL THE WAY DOWN ON THE TOP OF THE AEROSOL CAN.

4. HOLD YOUR BREATH FOR AS LONG AS YOU CAN (i.e., 5-10 seconds). Before breathing out, take the inhaler out of your mouth and stop squeezing down on the aerosol can.

5. If your doctor has told you to take more than one puff per treatment repeat steps 3 through 4. Replace the cap after you are finished using the inhaler.

6. Rinse your mouth with water. Do not swallow the water after rinsing.

7. KEEPING THE PLASTIC MOUTHPIECE CLEAN IS VERY IMPORTANT TO PREVENT THE INHALER FROM BECOMING DIRTY AND CLOGGED. For normal hygiene, the mouthpiece of your inhaler should be cleaned weekly with a clean, dry tissue or cloth.

   DO NOT WASH OR PUT ANY PART OF YOUR INHALER IN WATER.

8. DISCARD THE CANISTER AFTER the date calculated by your physician or pharmacist. The correct amount of medication in each inhalation cannot be assured after the labeled number of inhalations even though the canister is not completely empty. Before the discard date you should consult your physician to determine whether a refill is needed. Just as you should not take extra doses without consulting your physician, you also should not stop QVAR without consulting your physician.

After using your QVAR Inhalation Aerosol:
If you notice that your shortness of breath or wheeze is becoming worse, or if relief from the other short-acting bronchodilator becomes less effective, or you need more inhalations than usual, tell your doctor as soon as possible.

Side Effects:
Very occasionally, some people find that their throat or tongue becomes sore after taking this medicine or that their voice becomes a little hoarse. In some people, an infection of the mouth and throat called candidiasis (thrush) may occur. Rinsing your mouth with water immediately after taking each dose may help. Some people may experience headaches. Tell your doctor but do not stop treatment unless told to do so.

If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

It is possible that some patients, especially those taking higher doses of this type of medication, may suffer from the following side effects: loss of bone density, eye problems and slowing of growth in children. These effects are much less likely to occur than with steroid tablets. Studies have shown that children whose asthma is not controlled do not grow as quickly as other children. It is very important that you use your medicine regularly to control your asthma.

Some patients may suffer from the following: depression or feeling worried, sleeping problems, restless, nervous, over-excited or irritable, suicidal thoughts. These effects are more likely to occur in children (Frequency not known).

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them.

If any side effects bother you, please contact your doctor.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking QVAR, STOP taking this medication and tell your doctor immediately:

- Sudden wheeziness and chest pain or tightness
- Swelling of eyelids, face or lips
- Lumpy skin rash or “hives” anywhere on the body

If you take too much medicine:
If you take too much medicine (more than the maximum daily dose), tell your doctor without delay or contact your nearest hospital emergency department or poison centre.

If you miss a dose: It is VERY IMPORTANT THAT YOU USE QVAR REGULARLY; however, if you miss a single dose, do not worry - just take the next dose when it is due.

What to do if you must stop taking your medicine:
If your doctor decides to stop your treatment, do not keep any left-over medicine unless your doctor tells you to.

REMEMBER: This medicine is only for YOU. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

Storing your medicine:
CONTENTS UNDER PRESSURE. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 50°C may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children. Store between 15° and 30°C.

Special features:
Due to design features in this valve, QVAR will exhibit no loss of prime for up to 14 days of non-use in any storage orientation. This means that it will deliver a consistent dose from the time it is initially primed, up to a few doses before the can is empty (See "How to use QVAR Inhalation Aerosol", second paragraph, for the explanation of how to prime your inhaler).

Please note that (CFC free symbol) shows that this inhalation aerosol does not contain chlorofluorocarbons (CFCs) which damage upper stratospheric ozone. Instead, QVAR contains a hydrofluoroalkane (HFA-134a) which does not damage the ozone layer. You may notice a slightly different taste or spray force with QVAR compared to beclomethasone dipropionate aerosol inhalers that use CFC propellants.

Laboratory tests using instruments (not on people) show that QVAR delivers a softer spray force and warmer spray temperature than beclomethasone dipropionate aerosol inhalers containing CFC propellants.

Manufactured by:
Bausch Health, Canada Inc.
Laval, Quebec
H7L 4A8

PHARMACOLOGY

Beclomethasone dipropionate inhaler

Human pharmacokinetics

Systemic absorption of BDP occurs after oral and inhaled administration. The relative bioavailability of the oral route is 20% of that of inhaled administration. The principal route of elimination of the drug and its metabolites is in the feces. Between 10% and 15% of an orally administered dose of BDP is excreted in the urine as both conjugated and free metabolites of the drug.

Because the pharmacological actions of inhaled steroids are topical, systemic levels bear no relationship to efficacy[3]. Systemic levels of inhaled corticosteroids are thought to be of value as an indicator of systemic exposure.

The pharmacokinetics of beclomethasone free base (BOH) and of total-BOH have been measured over 24 hours in mild asthmatics given single and multiple doses of QVAR (beclomethasone dipropionate). Total-BOH was obtained by hydrolyzing any beclomethasone dipropionate and monopropionates in the serum samples to BOH. Total-BOH levels were at least ten times greater than the corresponding BOH levels for the first 5 hours post dosing; total-BOH levels were at least 4 times greater than the corresponding BOH levels for the remainder of the sampling times. Peak serum concentrations of total-BOH of approximately 1 ng/mL were observed within 30 minutes following 400 mcg of QVAR. Peak levels for other doses occurred at the same time, but levels were modified in proportion to dose. Total-BOH pharmacokinetics do not change following multiple dosing.

In studies which compared CFC-BDP and QVAR, it was demonstrated that a dose of 200 mcg of QVAR achieved comparable total-BOH levels as a dose of 400 mcg of CFC-BDP. The time to peak total-BOH levels was shorter after dosing with QVAR (40 minutes) than with CFC-BDP (2 hours). These pharmacokinetic findings are consistent with the deposition results, which showed increased lung deposition and reduced oropharyngeal deposition for QVAR compared with CFC-BDP. The relative bioavailability difference between CFC-BDP and QVAR reflects the incomplete absorption of the swallowed CFC-BDP dose. The earlier time to peak serum levels reflects the rapid absorption from the lungs of the inhaled QVAR dose.

Human pharmacodynamics: In a study with steroid naive asthmatics dosed with either placebo; 160, 320 or 640 mcg/day of QVAR; or 672 mcg/day of CFC-BDP for 14 days, mean 24-hour urinary free cortisol levels (24h-UFC), a sensitive marker of adrenal function, remained within the normal range for all dosing regimens of QVAR and a daily dose of 640 mcg QVAR caused similar changes in 24h-UFC levels as a daily dose of 672 mcg of CFC-BDP. Plasma cortisol levels and responses to adrenocorticotropic hormone, monitored in large clinical trials, showed no difference in effect between placebo treatment and QVAR doses up to 640 mcg/day.

Adult Experience

Clinical trials

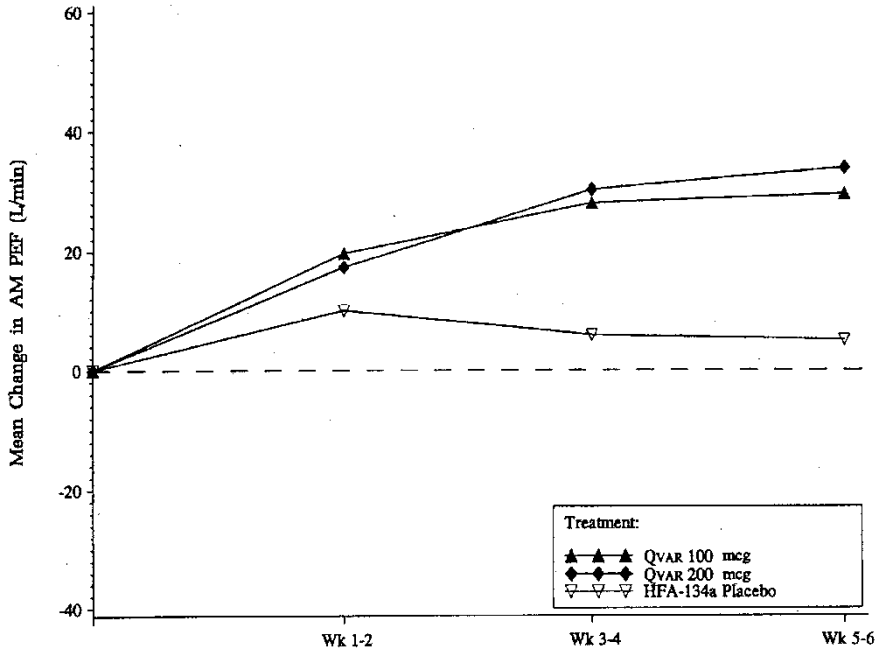
Blinded, randomized, parallel, placebo-controlled and active-controlled clinical studies were conducted in 940 adult asthma patients to assess the efficacy and safety of QVAR in the treatment of asthma. Fixed doses ranging from 50 mcg to 200 mcg twice daily were compared to placebo, and doses ranging from 50 mcg to 400 mcg twice daily were compared with doses of 50 mcg to 400 mcg twice daily of an active CFC-BDP comparator. These studies provided information about appropriate dosing through a range of asthma severity.

In all 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.

A summary of the clinical development program for QVAR shows the following key features. In a controlled clinical trial QVAR was effective at controlling asthma at doses as low as 50 mcg BID (100 mcg/day), below the recommended dose of CFC-BDP. In several controlled clinical trials, comparable asthma control was achieved at lower daily doses of QVAR than with CFC-BDP (e.g., 200 mcg of QVAR twice a day provided comparable asthma control as 400 mcg of CFC-BDP twice a day). In a dose-response dose-comparison clinical trial, treatment with increasing doses of both QVAR and CFC-BDP 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 beneficial shift in the dose response curve for QVAR. Improved efficacy of QVAR compared with CFC-BDP is due to its increased relative airways availability (as a consequence of a smaller mean particle size and improved pulmonary deposition) and a more effective topical anti-inflammatory effect in the airways. Because of this, lower doses of QVAR are required to achieve the same effect as CFC-BDP (see DOSAGE AND ADMINISTRATION).

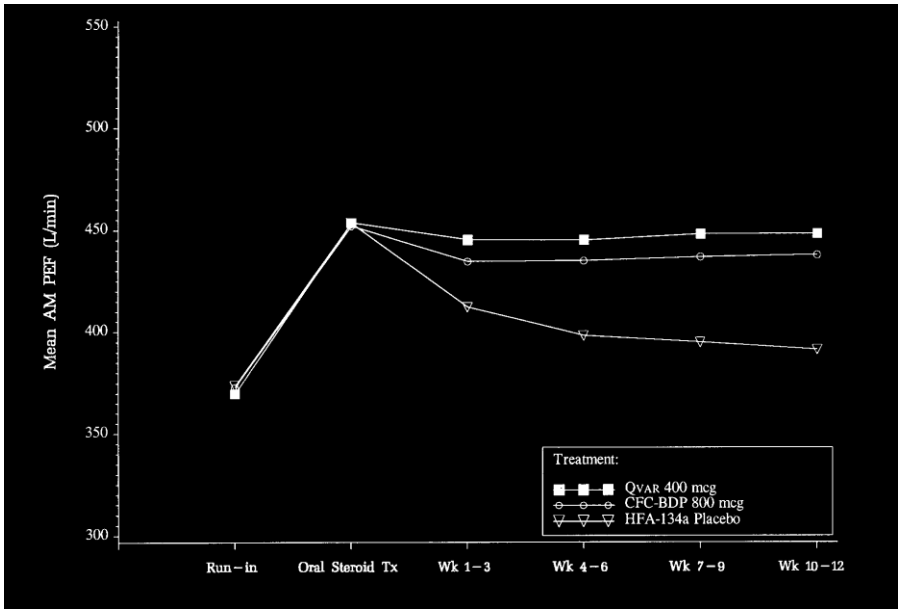
In a 6-week clinical trial, 270 steroid naive patients with symptomatic asthma being treated with as-needed beta-agonist bronchodilators, were randomized to receive either 100 mcg daily QVAR, 200 mcg daily of QVAR, or hydrofluoroalkane-134a (HFA-134a) placebo. Both doses of QVAR were effective in improving asthma control with significantly greater improvements in FEV1, AM PEF, and asthma symptoms than with HFA-134a placebo. Shown below is the change from baseline in AM PEF during this trial.

A 6-week clinical trial in mild to moderate steroid naive asthmatics -
Mean change in AM PEF



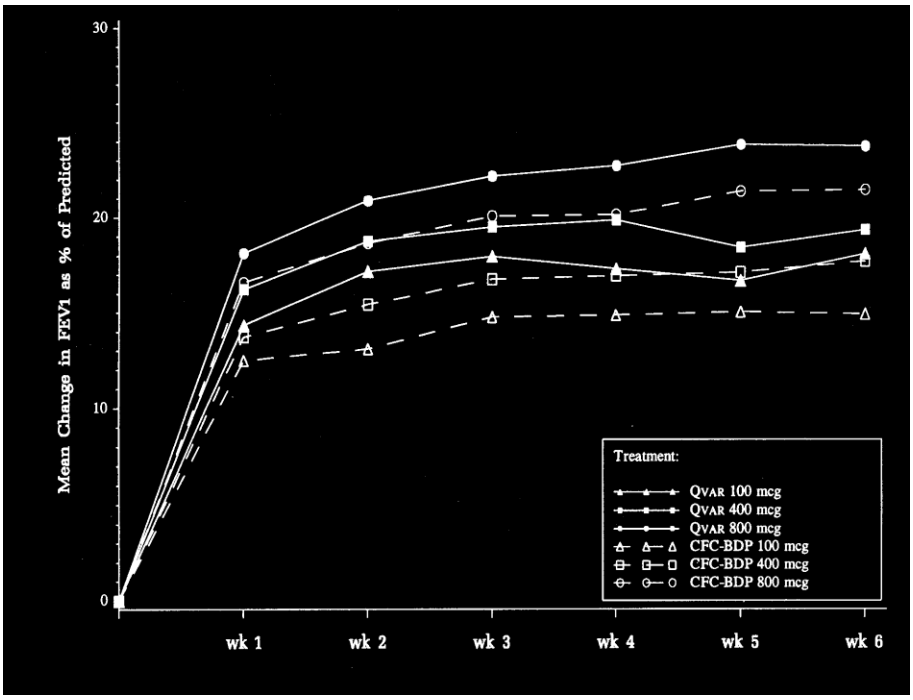
In another clinical trial, 347 patients with symptomatic asthma, being treated with as-needed inhaled beta-agonist bronchodilators and, in some cases, inhaled corticosteroids, were given a 7-12-day course of oral corticosteroids and then randomized to receive either 400 mcg daily of QVAR, 800 mcg of CFC-BDP, or HFA-134a 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 HFA-134a placebo over 12 weeks of treatment. A daily dose of 400 mcg QVAR provided equivalent control of AM PEF and FEV1 as 800 mcg of CFC-BDP. Shown below are the mean AM PEF results from this trial.

A 12-week clinical trial in moderate symptomatic asthmatics responding to oral steroid therapy - Mean AM PEF by study week.



In a 6-week dose-response dose comparison clinical trial, 323 patients, who exhibited a deterioration in asthma control during an inhaled steroid washout period, were randomized to daily treatment with either 100, 400, or 800 mcg QVAR or 100, 400, or 800 mcg CFC-BDP. Treatment with increasing doses of both QVAR and CFC-BDP resulted in increased improvement in FEV1, FEF25-75% (forced expiratory flow over 25-75% of the vital capacity), and asthma symptoms. Across the dosage range in this study there was significantly greater improvement in FEV1 percent predicted with QVAR than CFC-BDP for equivalent doses. Shown below is the change from baseline in FEV1 as percent predicted after 6 weeks of treatments.

A 6-week dose-response dose comparison clinical trial in inhaled steroid dependent asthmatics - Mean change in FEV1 as percent of predicted



Pediatric experience

Clinical Trials

In one 12-week clinical trial, pediatric patients (age 5-12 years) with symptomatic asthma (N=353) being treated with as-needed beta-agonist bronchodilators were randomized to receive either 50 mcg or 100 mcg twice daily of QVAR or placebo. Both doses of QVAR 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).

A 12-month open-label safety and efficacy study evaluated the effects of HFA beclomethasone dipropionate (HFA-BDP) without spacer versus CFC beclomethasone dipropionate (CFC-BDP) with large volume spacer on growth in children ages 5-11. A total of 520 patients were enrolled of whom 394 received HFA-BDP (100-400 mcg/day ex-valve) and 126 received CFC-BDP (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 HFA-BDP was approximately 0.5 cm/year less than that noted with children treated with CFC-BDP via large volume spacer. However, there is a growing belief that the effect of inhaled corticosteroids on growth velocity does not affect final height attainment. Although growth velocity may be reduced in the short term, in time, other, as yet poorly understood, mechanisms seem to come into play at long-term steady state, thus allowing the child to reach final "normal" height.

Beclomethasone dipropionate

Animal studies demonstrate that BDP has potent local anti-inflammatory activity but little systemic action. When administered systemically to mice, the anti-inflammatory activity was

accompanied by other typical features of glucocorticoid action related to their metabolic and immuno-suppressant actions, including thymic involution, liver g1ycogen deposition, and pituitary-adrenal suppression.

Blood specimens were collected from dogs during a one-year study. Groups of 8 dogs were dosed by inhalation at 0.05, 0.16 and 0.50 mg/kg/day. Increasing the dose resulted in increased serum levels of both BOH and total BOH. Accumulation of BOH and total BOH occurred upon multiple dosing.

HFA-134a

The general class of halocarbons including CFCs as well as HFA-134a is known to cause non-immunologic cardiac sensitization in dogs. Specifically, cardiac arrhythmias can be induced in dogs if, during exposure to halocarbons, the dogs are challenged with an intravenous injection of epinephrine. HFA 134a by itself did not cause cardiac, respiratory, or renal dysfunction in dogs exposed to 20,000 ppm of HFA 134a. Cardiac arrhythmias were noted at concentrations of 80,000 ppm and greater when dogs were challenged with epinephrine. Commonly used CFCs in MDIs such as CFC 11 produce cardiac arrhythmias at thresholds as low as 3,500 ppm. Thus, HFA 134a has less cardiac sensitization potential than CFC 11. It should be noted, however, that there is no evidence that current CFC propellants cause cardiac sensitization in the clinical use of MDIs.

Studies by Olson et al. using liver microsomes from human, rat and rabbit have shown that HFA-134a is metabolized to a limited extent primarily by cytochrome P-450 2E1. The carbon fluorine bonds in HFA 134a are apparently very stable since the relative amount of metabolism was less than 0.01% of the exposure amount. This cytochrome P 450 isozyme is known to be inducible by certain chemicals and drugs, such as pyridine, ethanol, and isoniazid. Olson reported increases in HFA 134a metabolism of up to 10-fold with induced rat microsomes.

In vivo, the extent of HFA 134a metabolism observed has been even less than in the in vitro experiments. The metabolite trifluoroacetic acid has been identified in urine from mouse, rat, and human. An additional metabolite trifluoroacetaldehyde has been identified only in mouse urine. The amounts of these two metabolites accounted for less than 0.001% of the presented dose in each species. No metabolite of HFA 134a could be identified in dog urine.

A study by Harris et al. showed that a six-hour exposure of rats to 10,000 ppm of HFA 134a did not give rise to immunoreactive trifluoroacetyl protein adducts.

HFA-134a inhaler

Blood levels of propellant HFA-134a from the HFA-BDP formulation were measured in seven patients after inhalation of 200 and 400 mcg HFA-BDP. All patients had quantitatible HFA-134a blood concentrations through 20 minutes (the last sampling time). The rapid disappearance of HFA-134a from the blood was consistent with its reported half-life of 5 minutes.

To confirm that HFA-134a is only minimally metabolized in humans, the maximum amount of daily propellant HFA-134a exposure was administered as 8 inhalations twice a day to asthmatic patients in two different studies. To further increase the chances of detecting any propellant metabolism in the body, if it occurred, a 2-week exposure period was selected to allow for any possible metabolite accumulation. A fluorine-19 NMR assay 4-times more sensitive than previously used by other researchers was developed for these studies. Despite these measures, trifluoroacetic acid (HFA-134a metabolite) could not be detected in the urine of any patient in either study.

TOXICOLOGY

Beclomethasone dipropionate HFA-134a by inhalation

Acute toxicology
No significant toxic effects were observed when one dog was administered 250 and 400 metered doses of HFA-BDP on separate days.

Repeated dose toxicity
No treatment-related clinical signs of toxicity or ophthalmologic findings were observed in groups of 48 rats (24 males/24 females) administered 0.001 to 0.026 mg/mL one hour/day BDP HFA-134a formulation by inhalation for 90 days.

Groups of 8 dogs (4 males/4 females) were treated for one year with BDP HFA-134a and CFC formulations by inhalation. Doses ranged from 0.05 to 0.50 mg/kg/day. The majority of changes seen in the study were those that would be expected following prolonged treatment with a corticosteroid (Cushingoid syndrome). Changes showed a dose-related incidence and severity. Very marked changes were noted for both HFA-134a and CFC formulations groups dosed at 0.50 mg/kg/day.

Reproduction and teratology
Beclomethasone dipropionate HFA-134a formulation was not teratogenic in groups of 26 female rats treated with 0.05 to 0.59 mg/mL one hour/day by inhalation, from day 6 to 15 of gestation.

Beclomethasone dipropionate

Acute toxicity
Many published studies have demonstrated low toxicity by the oral, intraperitoneal, subcutaneous routes in mouse and rat. An inhalation LD50 of >56 mcg/L air was observed in rats.

Repeat dose toxicity
Findings published for repeat dose studies embraced the known range of metabolic and physiological effects of glucocorticoids. These included reduction in body weight gains, Cushingoid syndrome in dogs, reduction in the number of lymphocytes and the weights of the

tissues connected with the immune system, and hepatic glycogen deposition and fatty liver changes.

Reproduction and teratology
In reproductive studies, there was an increase in the prevalence of cleft palate in mice and rabbits and in the number of dead foetuses, and ossification was retarded. The teratogenic sensitivity of mice and rabbits differed from that of rats in which certain effects, including cleft palate were absent.

HFA-134a

Acute toxicity
Rats and mice exposed, acutely, for one hour to HFA-134a at concentration of 810,000 ppm (81% v/v), with oxygen supplementation, showed no evidence of acute toxicity. No deaths or clinical reactions occurred, indicating the low acute toxicity of HFA-134a.

Dogs were essentially unaffected by exposure to HFA-134a at concentrations of up to 80,000 ppm. However, at extremely high concentrations of 160,000 and 320,000 ppm, without oxygen supplementation, intolerance and minor motor disturbances were observed.

Repeat dose toxicity
No toxic effects were observed in repeat dose inhalation toxicity studies in rats and dogs exposed to concentrations of up to 50,000 or 120,000 ppm respectively, for periods of up to one year.

No oncologic potential was seen in rats or mice exposed for one hour daily to HFA-134a, at concentrations of 50,000 or 75,000 ppm respectively, for periods of two years.

Reproduction and teratology
No effects were observed on the rat fertility or general reproductive performance of a treated parental (F0) generation, or on the development of two successive generations.

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