

New Zealand Data Sheet

QVAR™ 50 Inhaler

QVAR™ 100 Inhaler

QVAR™ 50 Autohaler™

QVAR™ 100 Autohaler™

Each actuation of QVAR Inhaler or Autohaler delivers extrafine beclomethasone dipropionate 50 µg or 100 µg ex-valve for inhalation.

Presentation

QVAR is available in a metered dose inhaler (MDI) and a breath actuated Autohaler device. QVAR contains beclomethasone dipropionate in solution in norflurane (HFA-134a) and delivers an extrafine aerosol. The aerosol droplets are on average much smaller than the beclomethasone dipropionate particles delivered by CFC-suspension formulations or dry powder formulations of beclomethasone dipropionate.

Indications

Prophylactic anti-inflammatory treatment of reversible obstructive airways disease including asthma.

Dosage and Administration

Proper instructions and good inhaler technique is necessary to get maximum benefit from QVAR Inhaler. For patients who are unable to successfully coordinate actuation of the metered dose inhaler with inhalation, QVAR Autohaler should be substituted.

QVAR Inhaler and Autohaler deliver a consistent dose:

- Whether or not the canister is shaken by the patient
- Without the need for the patient to wait between individual actuations
- Regardless of storage orientation for periods without use of up to 14 days
- At temperatures as low as -10°C

Patients should be instructed to rinse their mouth out each time after using QVAR.

QVAR is for use by inhalation only. To be effective inhaled QVAR must be used on a regular basis even when patients are asymptomatic.

Adults

Starting and maintenance dose for mild to moderate asthma is 50 to 200 mcg twice daily. In more severe cases, doses up to 400 µg twice daily may be used. The maximum recommended daily dose is 800 µg. The same total daily dose from either QVAR 50 or QVAR 100 aerosol provides the same clinical effect.

Transferring patients from other inhaled corticosteroids to QVAR:

The general approach to switching patients to QVAR involves two steps as detailed below.

Step 1

Consider the dose of the inhaled corticosteroid appropriate to the patient's current condition. Symptomatic patients may require an increased dose of their current inhaled corticosteroid and this increased dose should be considered in transferring patients to QVAR.

Step 2

Convert the appropriate inhaled corticosteroid dose to the QVAR dose according to the table below:

	Daily Dose (µg)				
Budesonide DPI*	200	400	800	1200	1600-2000
Fluticasone pMDI**	100	200-250	400-500	600-750	1000
QVAR	100	200	400	600	800

* dry powder inhaler **pressurised metered dose inhaler

Patients should be instructed on the proper use of their inhaler, including rinsing out their mouth after use.

Inhaler cleaning

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

Use of a spacer

QVAR extrafine beclomethasone has been developed to be used without a spacer device being necessary. Unlike with traditional CFC MDIs the aerosol characteristics of QVAR MDI provide for greater lung deposition. Where a spacer is considered necessary for use with QVAR MDI, small volume spacers that may be suitable in maintaining the extrafine particle fraction include the Aerochamber Plus spacer.

Children

Children aged over 5 years: the recommended starting dose for mild to moderate asthma is 50 µg twice daily. In more severe cases this may be increased up to 100 mcg twice daily, which is the maximum recommended dose. To minimise the systemic effects of orally inhaled corticosteroids, the dose should be titrated down to the lowest that provides effective asthma control.

Special patient groups

No special dosage recommendations are made for elderly or patients with hepatic or renal impairment.

Contraindications

Hypersensitivity to beclomethasone dipropionate or any other ingredient in QVAR.

Warnings and Precautions

QVAR is not indicated for immediate relief of asthma attacks or status asthmaticus. Patients should be made aware of the prophylactic nature of treatment with inhaled beclomethasone and that it should be taken regularly, even when they are asymptomatic. Patients should be instructed to seek medical advice if the prescribed dose of QVAR is no longer effective or if symptoms get worse.

Inhaled corticosteroids are designed to direct glucocorticoid activity to the lungs in order to reduce the overall systemic glucocorticoid exposure and side effects. In sufficient doses, however, all inhaled corticosteroids can have adverse effects, notably depression of the hypothalamic-pituitary-adrenal (HPA) axis, reduction of bone density and retardation of growth in children. In steroid dependent patients prior systemic corticosteroid usage may be a contributing factor, but such effects can occur amongst patients who regularly use only inhaled corticosteroids.

Individual patients may vary in their sensitivity to the systemic effects of inhaled corticosteroids. Beclomethasone, like other inhaled corticosteroids, is absorbed into the systemic circulation from the lungs. Beclomethasone and its metabolites may exert detectable suppression of adrenal function. However, within the dose range 100 to 800 µg daily clinical studies with QVAR have demonstrated that parameters of adrenal function usually remain within the normal range. The lowest dose of QVAR that causes suppression of the HPA axis (as indicated by 24 hour urinary cortisol concentrations), effects on bone mineral density or growth retardation in children has not yet been established.

Patients who have received systemic corticosteroids for long periods of time or at high doses, or both, need special care and subsequent management when being transferred to inhaled corticosteroid therapy. Recovery from impaired adrenocortical function caused by prolonged treatment with systemic corticosteroids is slow. Patients' asthma should be in a stable state before being given inhaled corticosteroids in addition to the usual maintenance dose of systemic corticosteroid.

Most patients can be successfully transferred to inhaled corticosteroids with maintenance of good respiratory function, but special care is necessary for the first months after the transfer, until the HPA system has sufficiently recovered to enable the patient to cope with emergencies such as trauma, surgery or serious infections.

Withdrawal of systemic corticosteroids should be gradual, starting after about seven days by reducing the daily oral dose by 1 to 2.5 mg prednisone, or equivalent, at intervals not less than one week. Adrenocortical function should be monitored regularly.

In patients who have been transferred from oral corticosteroids to inhalation therapy, systemic therapy may need to be reinstated during periods of stress or where airways obstruction or mucus prevents absorption by inhalation.

It may be advisable to provide such patients with a supply of oral corticosteroid to use in emergencies. The dose of inhaled corticosteroids should be increased at this time and then gradually reduced to the maintenance level after the systemic corticosteroid has been discontinued.

Discontinuation of systemic corticosteroids may cause exacerbation of allergic diseases such as atopic eczema and rhinitis. These should be treated as required with appropriate therapy.

Like other corticosteroids, caution is advised for patients with active or latent pulmonary tuberculosis.

Effects on ability to drive and use machines

QVAR is unlikely to produce an effect on the ability to drive or use machinery.

Use in Pregnancy (Category B3)

There is no experience of this product in pregnancy in humans; therefore the product should only be used if the benefits outweigh any potential risk to the patient. An inhalation reproductive study with this product in rats did not exhibit any teratogenic effects.

Norflurane propellant

Studies of norflurane administered to pregnant rats and rabbits have not revealed any special hazard.

Beclomethasone dipropionate

There is inadequate evidence of safety in human pregnancy. In animals, systemic administration of relatively high doses can cause abnormalities of foetal development including growth retardation and cleft palate. There may therefore be a small risk of such effects in the human foetus. However, inhalation of beclomethasone into the lungs avoids the high level of corticosteroid exposure that occurs with administration by systemic routes. The use of beclomethasone in pregnancy requires that the possible benefits of treatment be weighed against the possible hazards. It should be noted that beclomethasone has been in widespread use for many years without apparent hazard.

Use in Lactation

There is no experience of this product in lactation in humans; therefore the product should only be used if the benefits outweigh any potential risk to the patient. An inhalation reproductive study with this product in rats did not exhibit any teratogenic effects.

Norflurane propellant

Studies of norflurane administered to lactating rats and rabbits have not revealed any special hazard.

Beclomethasone dipropionate

It is probable that beclomethasone is secreted in milk. However, given the relatively reduced doses used by the inhalation route, the levels are likely to be low. In mothers who are breast feeding their baby, the therapeutic effects of the medicine should be weighed against the potential hazards to mother and baby.

Other

Propellant

QVAR Autohaler and MDI contain norflurane propellant. In animal studies, norflurane has been shown to have no significant pharmacological effects other than at very high exposure concentrations, where narcosis and a relatively weak cardiac sensitising effect were found. The potency of cardiac sensitisation is less than that of CFC-11 (trichlorofluoromethane). There are no reasons to consider norflurane as a potential mutagen, clastogen or carcinogen judged from *in vitro* and *in vivo* studies including long-term administration by inhalation in rodents.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Potential carcinogenicity, mutagenicity and impairment of fertility have not been adequately investigated in animal studies of beclomethasone dipropionate. Other glucocorticoids (budesonide, prednisolone and triamcinolone acetate) have been shown to increase the incidence of hepatocellular tumours in rats by a non-genotoxic mechanism.

Adverse Effects

When taking QVAR an occasional incidence of hoarseness and/or a rare occurrence of candidiasis of throat and mouth may occur; patients may find it helpful to rinse out their mouth with water after using their inhaler to reduce the risk of candidiasis and hoarseness. Topical anti-fungal therapy can be used for the treatment of candidiasis while continuing treatment with QVAR.

As with other inhaled therapy, paradoxical bronchospasm with wheezing may occur immediately after dosing. Immediate treatment with an inhaled short-acting bronchodilator is required. QVAR should be discontinued immediately and alternate prophylactic therapy introduced.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These may include adrenal suppression, growth

retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

As with other beclomethasone dipropionate products the potential for hypersensitivity reactions including rashes, urticaria, pruritus and erythema, and oedema of the eyes, face, lips and throat should be considered.

For QVAR a rare incidence of nausea has been reported.

Clinical Trial Data

Table 1 shows the adverse events reported amongst adult patients in multiple dose studies of inhaled QVAR for 6 to 12 weeks. Table 2 shows the adverse events reported amongst adult and paediatric patients in large multicentre trials of inhaled QVAR vs CFC-BDP for 12 months. Each table includes all adverse events probably or possibly related to study drug with an incidence of 1% or greater. A dash represents an incidence of less than 1%.

Table 1

	QVAR (n=812)	Placebo (n=289)	CFC-BDP (n=487)
Application Site Disorders			
Inhalation Site Sensation	4%	2%	6%
Inhalation Admin – Dysphonia	3%	1%	3%
Inhalation Taste Sensation	2%	-	2%
Inhalation Admin – Cough	-	1%	2%
Centr & Periph Nerv Syst Disorders			
Headache	-	-	1%
Respiratory System Disorders			
Pharyngitis	1%	-	-
Increased Asthma Symptoms	-	4%	-

Table 2

	QVAR (n=566)	CFC-BDP (n=194)
Application Site Disorders		
Inhalation Site Sensation	3%	3%
Inhalation Admin – Dysphonia	2%	2%
Inhalation Taste Sensation	1%	0%
Centr & Periph Nerv Syst Disorders		
Headache	2%	1%
GI System Disorders		
Stomatitis	1%	2%
Respiratory System Disorders		
Pharyngitis	4%	6%
Rhinitis	1%	1%
Bronchitid	-	1%
Increased asthma symptoms	1%	-

The following adverse reactions, probably or possibly related to the use of QVAR, were recorded during clinical trials with a frequency of less than 1%.

Application Site Disorders

Uncommon: cough; increased asthma symptoms

General Disorders

Uncommon: chest pain. Rare: asthenia; back pain; fatigue; oedema; pain

Cardiovascular Disorders, General

Rare: hypertension.

Central & Peripheral Nervous System Disorders

Uncommon: dizziness; dysphonia; migraine. Rare: neuropathy; tremor; vertigo.

Gastro-Intestinal System Disorders

Uncommon: abdominal pain; constipation. Rare: dyspepsia; GI disorders (unspecified); nausea; tongue discolouration; toothache.

Heart Rate and Rhythm Disorders

Rare: palpitations.

Metabolic and Nutritional Disorders

Uncommon: weight increase.

Musculo-Skeletal System Disorders

Uncommon: myalgia.

Myo Endo Pericardial & Valve Disorders

Rare: angina pectoris.

Platelet, Bleeding & Clotting Disorders

Uncommon: epistaxis.

Psychiatric Disorders

Uncommon: increased appetite. Rare: anxiety; depression; insomnia.

Resistance Mechanism Disorders

Uncommon: infection. Rare: infection bacterial

Respiratory System Disorders

Uncommon: bronchitis; coughing; upper respiratory tract infection. Rare: acute asthma episode; hemoptysis; respiratory disorder; sinusitis.

Skin & Appendages Disorders

Uncommon: rash. Rare: photosensitivity reaction; skin disorder; urticaria

Vascular (Extracardiac) Disorders

Uncommon: purpura.

Post-marketing experience

No new or previously unrecognised suspected adverse reactions associated with QVAR have been reported

Interactions

Pharmacokinetic interactions

No clinically significant drug interactions have been associated with therapeutic doses of beclomethasone dipropionate

Pharmacodynamic interactions

None known.

Overdosage

Acute overdose is unlikely to cause problems. The only harmful effect that follows inhalation of large amounts of beclomethasone over a short time period is suppression of HPA function. Specific emergency action need not be taken. Treatment with QVAR Inhaler or Autohaler should be continued at the recommended dose to control the asthma and HPA function can be expected to recover in a day or two.

If very large and excessive doses of beclomethasone were taken over a prolonged period a degree of atrophy of the adrenal cortex could occur in addition to HPA suppression. In this event the patient should be treated as corticosteroid dependent and transferred to a suitable maintenance dose of a systemic corticosteroid such as prednisone. Once the condition is stabilised, the patient should be transferred to QVAR at the doses recommended above according to the instructions in the PRECAUTIONS section.

Further Information

Actions

Inhaled beclomethasone dipropionate is well characterised for the management of asthma. It is a synthetic glucocorticoid and at usual doses exerts a topical, anti-inflammatory effect on the lungs, without significant systemic activity.

Pharmacokinetics

The pharmacokinetic profile of QVAR shows that the peak serum concentration for total BOH (total of any beclomethasone dipropionate or monopropionate) after single and multiple doses is achieved after 30 minutes. The value at the peak is approximately 2 ng/ml after the highest recommended dose of 800 µg and the serum levels after 100, 200 and 400 µg are proportionally lower. In both single dose and multiple dose pharmacokinetic studies, a daily dose of 200 µg of QVAR achieved comparable total-BOH levels as a dose of 400 µg of CFC beclomethasone aerosol.

Radio-labelled deposition studies have demonstrated that the majority of drug (>55% ex-actuator) is deposited in the lung and a small amount (<35%) is deposited in the oropharynx. These delivery characteristics result in equivalent therapeutic effects at lower total daily doses of QVAR compared to CFC beclomethasone inhalers.

Pharmacodynamic studies in patients with mild asthma given QVAR for 14 days have shown that there is a linear correlation between urinary free cortisol suppression, dose administered and serum total-BOH levels obtained. At a daily dose of 800 µg QVAR, suppression of urinary free cortisol was comparable to that observed with the same daily dose of CFC beclomethasone, indicating that there is a wider safety margin if QVAR is administered at lower doses than CFC inhalers.

The principal route of elimination of beclomethasone dipropionate and its several metabolites is in the faeces. Between 10% and 15% of an orally administered dose is excreted in the urine as both conjugated and free metabolites of the drug.

Pharmacokinetic studies with QVAR have not been carried out in any special populations.

Other

Clinical Trials

QVAR versus CFC-BDP

In controlled clinical trials in adults QVAR was effective at controlling asthma at doses as low as 50µg twice daily (100µg/day), below the recommended dose of CFC-BDP. Comparable asthma control was achieved at lower daily doses of QVAR than with CFC-BDP (eg 200µg of QVAR twice a day provided comparable asthma control as 400µg or 500µg of CFC-BDP twice a day). 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 to CFC-BDP is due to its increased relative airways availability (as a consequence of a smaller mean particle size and improved pulmonary deposition). Because of this, doses of QVAR required to achieve the same effect as CFC-BDP are 2 to 2.5 times lower than CFC-BDP.

A 12 month large multicentre safety study in paediatric patients with asthma showed that stable patients on CFC-BDP (200-400 µg/day with spacer) can be switched to lower daily doses of QVAR (100-200µg/day via Autohaler) with good maintenance of asthma control.

Clinical studies indicate that CFC-BDP and QVAR inhalers are clinically equivalent when given in a dose ratio of 2.5 to 1.

QVAR versus budesonide

A 6-week randomised, open label study in adult patients with symptomatic moderate asthma receiving 400µg/day budesonide dry powder inhaler (DPI) showed that 400µg/day QVAR delivered via the Autohaler provided equivalent control of asthma as 800µg budesonide DPI. Equivalent asthma control was shown by equivalent improvement in peak flow parameters, asthma symptoms, sleep disturbance and beta-agonist use.

In an 8-week randomised, open-label study in adult patients with symptomatic moderate to severe asthma receiving 500-1000µg/day CFC-BDP, 800µg/day QVAR delivered via the Autohaler provided equivalent asthma control to 1600µg/day budesonide DPI. An equivalent mean change from baseline in AM PEF was observed over the 8-week study period for the two treatment groups. Statistically significant improvements from baseline were seen in asthma symptom and sleep disturbance scores for patients in both groups.

These studies demonstrate that QVAR at half the daily dose of budesonide DPI provides equivalent asthma control in symptomatic adult asthma patients. Both treatments were well tolerated and there were no clinically significant differences in the safety profiles of the two treatments.

QVAR versus fluticasone

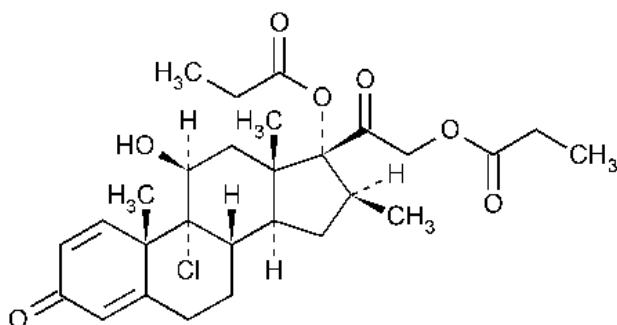
In a 6-week randomised, double-blind, double-dummy, parallel study, adult patients with symptomatic asthma taking a total daily dose of 200-500µg CFC-BDP, 100-250µg CFC-FP or 200-400µg budesonide were randomised to receive either 400µg/day QVAR or

400µg/day CFC-fluticasone (FP). Results of this study showed a clinically equivalent mean change from baseline in AM PEF over the 6-week study period. Equivalent asthma control was shown by equivalent improvements in peak flow parameters, asthma symptoms, sleep disturbance and beta-agonist use.

In an 8-week randomised open-label study adult patients with symptomatic asthma receiving up to 500µg/day FP or 500-1000µg/day BDP or 400-800µg/day budesonide were switched to 800µg/day QVAR or 1000µg/day HFA-fluticasone. There was an equivalent mean change from baseline in AM PEF observed over the 8-week study for the two treatment groups. No statistically significant differences in pulmonary parameters, asthma symptoms, sleep disturbance and beta-agonist use were seen for patients in both groups.

These studies demonstrate equivalent asthma control with QVAR and fluticasone in patients with symptomatic asthma. Both treatments were well tolerated and there were no clinically significant differences in the safety profiles of the two treatments.

Chemical structure of beclomethasone dipropionate:



Molecular formula: C₂₈H₃₇ClO₇, Molecular weight: 521.1, CAS Register Number 5534-09-8.

QVAR Inhalers and Autohalers contain ethanol and norflurane (HFA-134a), a propellant which does not contain chlorofluorocarbons (CFC's).

QVAR Inhalers and Autohalers are free of lactose, gluten, sugar and colourings and they do not contain materials of animal origin.

QVAR Autohaler and Inhaler are a product of technology developed by 3M Pharmaceuticals.

QVAR, Autohaler and 3M are registered trademarks

Pharmaceutical Precautions

Instructions for handling

As the canister is pressurised, no attempt should be made to puncture or dispose of it by burning.

Incompatibilities

None known

Shelf life

Shelf life is 36 months from date of manufacture, stored below 30°C.

Special precautions for storage

QVAR should be stored below 30°C. Storage in direct sunlight or heat should be avoided. Protect from frost.

Package Quantities

Inhaler or Autohaler device, 50 µg or 100 µg, containing 200 doses, 1's.

Medicine Schedule

Prescription Medicine

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