

AUSTRALIAN PRODUCT INFORMATION –
QVAR™ (BECLOMETASONE DIPROPIONATE) AUTOHALER™ and
QVAR™ (BECLOMETASONE DIPROPIONATE) INHALER

1 NAME OF THE MEDICINE

Beclometasone dipropionate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Beclometasone dipropionate (BDP) is a white to creamy white, odourless powder; it is slightly soluble in water, very soluble in chloroform and freely soluble in acetone and alcohol. QVAR also contains ethanol and norflurane (HFA-134a), a propellant which does not contain chlorofluorocarbons (CFCs).

Excipients with known effects: ethanol (alcohol) 11.85 % v/v.

QVAR 50 Inhaler and Autohaler deliver 50 µg of BDP per inhalation. QVAR 100 Inhaler and Autohaler deliver 100 µg of BDP per inhalation.

QVAR Autohaler is a breath actuated inhaler which automatically releases a metered dose of medication during inhalation through the mouthpiece and overcomes the need for patients to coordinate actuation with inspiration. QVAR Inhaler is a conventional press and breathe metered dose inhaler (P&B MDI). There are no differences in formulation between the Autohaler and the Inhaler products.

QVAR contains BDP in solution, resulting in an extra fine aerosol. The aerosol droplets of QVAR are on average much smaller (Mass Median Aerodynamic Diameter (MMAD), MMAD range 0.8 to 1.2 microns) than the particle sizes delivered by CFC-suspension formulations (MMAD range 3.5 to 4 microns) or dry powder formulations (MMAD approximately 10 microns) of BDP. The smaller particle size for QVAR results in greater deposition in the airways and less deposition in the oropharynx than beclometasone products formulated in CFCs.

Radiolabelled deposition studies demonstrated that for QVAR the majority of BDP (>55 % dose ex actuator) is deposited in the lungs and a small amount (< 35 % dose ex actuator) is deposited in the oropharynx. In contrast, approximately 4-7 % dose from the actuator of BDP formulated in chlorofluorocarbons (CFC-BDP) is deposited in the lungs and over 90 % is deposited in the oropharynx. The imaging data suggest that for QVAR, BDP is deposited widely throughout the central, intermediate and peripheral airways whereas deposition is limited to the central airways for CFC-BDP. The smaller particle size of QVAR explains the different deposition patterns compared with CFC-BDP. These delivery characteristics result in equivalent therapeutic effects being achieved at lower total daily doses of QVAR compared to CFC-BDP, and account for the recommended dosage adjustment when switching patients from CFC-BDP to QVAR (see 4.2 Dose and Method of Administration).

3 PHARMACEUTICAL FORM

Beclometasone dipropionate 50mcg per actuation pressurised inhalation aerosol can (QVAR 50 AUTOHALER) – colourless solution

Beclometasone dipropionate 50mcg per actuation pressurised inhalation aerosol can (QVAR 50 INHALER) – colourless solution

Beclometasone dipropionate 100mcg per actuation pressurised inhalation aerosol can (QVAR 100 AUTOHALER) – colourless solution

Beclometasone dipropionate 100mcg per actuation pressurised inhalation aerosol can (QVAR 100 INHALER) – colourless solution

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

QVAR is indicated for the prophylactic management of asthma.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Proper instruction 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. Patients should be advised that QVAR may have a different taste and feel than a CFC inhaler.

QVAR delivers a consistent dose of BDP:

- whether or not the canister is shaken
- without the need for the patient to wait between individual actuations
- regardless of storage orientation
- regardless of periods without use of up to 14 days (do not need to test fire)
- at temperatures as low as -10 °C.

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

Use of a Spacer

QVAR is designed to be used without a spacer. However, where a spacer is considered necessary the AeroChamber Plus is a suitable device for use with QVAR Inhaler. Use of an AeroChamber Plus spacer with QVAR Inhaler reduces the amount of BDP deposited in the oropharynx without affecting deposition in the lungs. A change in the make of spacer or a change in the formulation of QVAR may be associated with alterations in the amount of BDP delivered to the lungs, the clinical significance of which is uncertain. In these situations the patient should be monitored for any loss of asthma control.

Patients who use a spacer should be instructed to breathe in and out after each actuation of QVAR into the spacer. Any delay should be kept to a minimum. Static on the walls of the spacer may cause variability in the amount of BDP delivered. Patients should be instructed to wash the spacer in warm water and detergent and allow to air dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter.

Starting and Maintenance Dose:

The recommended dose of QVAR in adults is as follows:

- For mild to moderate asthma: 50 µg to 200 µg twice daily
- For more severe asthma: doses up to 400 µg twice daily
- Maximum recommended daily dose: 800 µg

Use in Children

In children aged five years and over the recommended dose of QVAR is 50 µg twice daily.

QVAR must be used on a regular basis even when patients are asymptomatic. When patient's symptoms remain satisfactorily controlled the dose of QVAR can be gradually reduced to the minimum effective dose to maintain control. Doses of BDP can be titrated up or down by switching between QVAR 50 and QVAR 100 as required.

Comparative clinical studies show that asthma patients achieve equivalent pulmonary function and control of symptoms with QVAR at lower total daily doses than CFC-BDP inhalers. These studies demonstrate clinical equivalence between CFC-BDP and QVAR inhalers when given in a dose ratio of 2.5 to 1.

Transferring Patients from other Inhaled Corticosteroids to QVAR:

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:

CFC-BDP	Daily Dose (µg)				
	200-250	400-500	800-1000	1200-1500	1600-2000
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

Special Patient Groups

Elderly and Patients with Hepatic or Renal Impairment

No special dosage recommendations are made.

Patients not receiving Systemic Corticosteroids

For patients who are inadequately controlled with bronchodilators and who are not receiving systemic corticosteroids, it is recommended that they continue to use a bronchodilator when treatment with QVAR commences. Any improvement in respiratory function is usually apparent in 1 to 4 weeks. Some of the patients who do not respond during this period may have excessive mucus in their bronchi so that BDP is unable to penetrate to its site of action. A short course of systemic steroids in relatively high dosage should be given to eliminate mucus and other inflammatory changes in the lungs. Continuation of treatment with QVAR usually maintains the improvement achieved with the oral steroid while it is being withdrawn gradually. Exacerbation of asthma caused by infection is usually controlled by appropriate antibiotic treatment and, if necessary, by increasing the dose of QVAR. However, it may be necessary to give a short, intensive course of systemic steroids to tide over the duration of the stress.

Steroid Dependent Patients

As recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy is slow, adrenocortical function should be monitored regularly. The patient's asthma should be in a stable state before being given inhaled steroids in addition to the usual maintenance dose of systemic steroid.

Withdrawal of systemic steroids should be gradual, starting about seven days after the introduction of QVAR therapy. For daily oral doses of prednisolone of 10 mg or less, dose reduction in 1 mg steps at intervals of not less than one week is recommended. The dose reduction scheme should be chosen to correlate with the magnitude of the maintenance systemic steroid dose.

Some patients feel unwell experiencing aches and pains, tiredness and even depression during the withdrawal phase despite maintenance or even improvement of respiratory function. These withdrawal symptoms should be treated symptomatically and the patient should be encouraged to persevere with the inhaler and withdrawal of systemic steroids. However, if there are objective signs of adrenal insufficiency, it may be necessary to resume systemic steroid treatment temporarily.

Most patients can be successfully transferred to inhaled steroids with maintenance of good respiratory function, but special care is necessary for the first months after the transfer until the hypothalamic-pituitary-adrenal (HPA) system has sufficiently recovered to enable the patient to cope with emergencies such as trauma, surgery or severe infections. It may be advisable to provide such patients with a supply of oral steroid to use in such emergencies. The dose of inhaled steroids should be increased at this time and then gradually reduced to the maintenance level after the systemic steroid has been discontinued.

Discontinuation of systemic steroids may cause exacerbation of allergic diseases such as atopic eczema and rhinitis previously controlled by the systemic BDP. These should be treated symptomatically with antihistamines and/or topical therapy

4.3 CONTRAINDICATIONS

Hypersensitivity to beclomethasone dipropionate or any other ingredient in QVAR

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Asthma Management

QVAR is not indicated for immediate relief of asthma attacks or status asthmaticus. If the prescribed dose of QVAR is no longer effective or symptoms get worse, the patient must seek medical attention for review of maintenance therapy.

Asthma management should be adjusted according to individual need based on lung function and clinical monitoring. Increasing use of a β_2 -agonist may be a sign of worsening asthma. Under these circumstances a re-assessment of the patients' therapy plan may be required and increasing glucocorticosteroid therapy should be considered. This is important since poor asthma control can result in potential life-threatening situations and increased use of β_2 -agonists may cause deterioration of asthma control.

Systemic Effects

Inhaled steroid products 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 steroids can have adverse effects, notably depression of the hypothalamic-pituitary-adrenal (HPA) axis, Cushing's syndrome, Cushingoid features, reduction of bone density, retardation of growth in children and adolescents, cataract and glaucoma and more rarely a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). In steroid-dependent patients prior systemic steroid usage may be a contributing factor, but such effects can occur amongst patients who regularly use only inhaled steroids. It is important, therefore, that the dose of inhaled steroid is titrated to the lowest dose at which effective control is maintained. Clinical studies in adult asthmatics treated with QVAR within the dose range 100-800 μg daily have demonstrated mean values for adrenal function and response within 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.

Transfer from Systemic Steroids

Patients who have received systemic steroids need special management when being transferred to inhaled steroid therapy. As recovery from impaired adrenocortical function caused by prolonged systemic steroid therapy is slow, adrenocortical function should be monitored regularly. Patients should have stable asthma before being given inhaled steroids in addition to the usual maintenance dose of systemic steroid. (See 4.2 Dose and Method of Administration).

Discontinuation of systemic steroids may cause exacerbation of allergic diseases such as atopic eczema and rhinitis. These should be treated symptomatically with antihistamines and/or topical therapy.

In patients who have been transferred from oral steroids to inhalation therapy, systemic steroid therapy may need to be reinstated rapidly during periods of stress or where airways obstruction or mucus significantly compromises the inhaled route of administration. The dose of inhaled steroids should be increased at this time and then gradually reduced to the maintenance level after the systemic steroid has been discontinued. Respiratory tract infections should be treated with appropriate antimicrobial therapy. The effect of BDP on recurrent lung infection is not known. Caution is necessary in patients with active or latent pulmonary tuberculosis.

Propellant

QVAR contains a hydrofluoroalkane propellant (norflurane). In animal studies, narcosis and sensitisation to the arrhythmogenic effects of adrenaline were observed following inhalation of norflurane at high exposure concentrations. The potency of the cardiac sensitisation was less than that of trichlorofluoromethane (CFC-11). In humans, norflurane is absorbed into the circulation following inhalational administration, although plasma concentrations are low and elimination is rapid. Excessive use of QVAR should be avoided as this carries a potential hazard from the propellant as well as from overdosage of the BDP in the formulation.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Use in the elderly

No data available

Paediatric use

To minimise the systemic effects of orally inhaled corticosteroids, the dose should be titrated down to the lowest that provides effective asthma control. The safety and efficacy of QVAR in children under the age of five has not been established.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically significant drug interactions have been associated with therapeutic doses of BDP.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The potential impairment of fertility has not been adequately investigated in animal studies of BDP.

Use in pregnancy – Pregnancy Category B3

There is inadequate clinical evidence of the safety of QVAR used during pregnancy. In animals, systemic administration of relatively high doses of BDP can cause abnormalities of foetal development including growth retardation and cleft palate. Inhalational administration of a norflurane-based formulation of BDP to pregnant rats caused retardation of foetal growth and development, and red adrenal glands. QVAR should be avoided for use in pregnancy unless the expected benefit to the patient outweighs the risk to the foetus

Use in lactation

It is probable that BDP is excreted in milk. However, given the relatively low doses used by the inhalation route, the levels are likely to be low. Studies of inhaled BDP have not been done in lactating animals. In breastfeeding mothers the therapeutic benefits of QVAR should be weighed against the potential hazards to mother and baby.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

When using 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 (see 4.4 Special Warnings and Precautions for Use).

Very rarely Qvar may cause, Cushing's syndrome, Cushingoid features, anxiety, sleeping disorders or behavioural changes including hyperactivity, aggression and irritability (predominantly in children).

Hypersensitivity reactions including rashes, urticaria, pruritis and erythema, and oedema of the eyes, face, lips and throat (angioedema) have 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 QVAR 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 %
Central & Peripheral Nervous System 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 %
Central & Peripheral Nervous System Disorders		
Headache	2 %	1 %
GI System Disorders		
Stomatitis	1 %	2 %
Respiratory System Disorders		
Pharyngitis	4 %	6 %
Rhinitis	1 %	1 %
Bronchitis	-	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

Eye Disorders: vision blurred

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

The harmful effect that follows inhalation of large amounts of QVAR over a short time period is suppression of HPA function. Specific emergency action need not be taken. Treatment with QVAR should be continued at the recommended dose to control the asthma; HPA function recovers in a day or two.

If excessive doses of BDP 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 steroid dependant and transferred to a suitable maintenance dose of a systemic steroid such as prednisolone. Regular tests of adrenal function are advised. Once the condition is stabilised, the patient should be returned to QVAR by the recommended method (see 4.2 Dose and Method of Administration).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Bronchial inflammation is known to be an important component in the pathogenesis of asthma. Inflammation occurs in both large and small airways. BDP is a synthetic glucocorticoid. 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 BDP in controlling symptoms and improving lung function in asthma although the exact mechanism of action of beclomethasone in the lungs is unknown. Inhaled BDP probably acts topically at the site of deposition in the bronchial tree after inhalation. Inhaled BDP at recommended doses reduces systemic exposure compared to oral administration, thereby minimising systemic side effects, including pituitary-adrenal suppression.

Clinical trials

A pharmacodynamic study in 43 steroid naive asthmatics given either placebo, 200, 400 or 800 µg/day of QVAR; or 800 µg/day of CFC-BDP for 14 days showed a linear correlation between reduction in 24-hour urinary free cortisol levels (24h-UFC) and dose of BDP administered, as well as between BDP dose and serum total-beclomethasone levels. The mean 24h-UFC, a sensitive marker of adrenal function, remained within the normal range for all dosing regimens. A daily dose of 800 µg QVAR caused similar reductions in 24 h-UFC levels as a daily dose of 800 µg of CFC-BDP. Results from the secondary parameters of plasma cortisol and the ACTH stimulation test supported the findings of 24 h-UFC and showed no differences to CFC-BDP and placebo at QVAR doses up to 800 µg/day.

In two 12 week trials conducted in patients with symptomatic moderate (n=347) and symptomatic moderately severe (n=233) asthma, plasma cortisol levels were monitored as a secondary safety assessment to determine HPA-axis suppression. The mean percentage change of plasma cortisol values from baseline and the number of patients with plasma cortisol values below the normal reference was similar for HFA-placebo, 800 µg/day QVAR and 800 µg/day CFC-BDP.

In a 12 month study in 473 asthmatic patients given either QVAR in a dose range of 200 to 800 µg/day or CFC-BDP in a dose range of 400 to 1600 µg/day, adrenal function was assessed by plasma cortisol levels and response to cosyntropin. No differences in mean plasma cortisol levels or clinically significant changes in cortisol levels from baseline were seen between the two treatment groups, and no significant difference in response to cosyntropin was seen between the treatment groups. The effect of QVAR on bone metabolism was assessed by serum osteocalcin concentrations. No clinically meaningful differences in serum osteocalcin levels were found between the treatment groups.

A 12 month multicentre study in 520 paediatric patients with asthma demonstrated that the effect on growth of 100-200 µg/day of QVAR from the Autohaler was comparable to those of 200-400 µg/day of CFC-BDP from a P&B MDI with spacer. The effect of QVAR on bone metabolism was assessed by serum osteocalcin levels, PICP, 1-CTP and urine deoxypyridinoline/ creatinine ratio. No treatment differences were found between the treatment groups. Analysis of adrenal function, as assessed by 24 h-UFC, plasma cortisol levels and response to low dose ACTH stimulation showed no significant differences between QVAR or CFC-BDP treatments across all doses.

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 CFC-BDP

In controlled clinical trials in adults QVAR was effective at controlling asthma at doses as low as 50 µg twice daily (100 µg/day), below the recommended dose of CFC-BDP. Comparable asthma control was achieved at lower daily doses of QVAR than with CFC-BDP (e.g. 200 µg of QVAR twice a day provided comparable asthma control as 400 µg or 500 µg 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 (see 4.2 Dosage and Method of Administration).

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 (100-200 µg/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 400 µg/day budesonide dry powder inhaler (DPI) showed that 400 µg/day QVAR delivered via the Autohaler provided equivalent control of asthma as 800 µg 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 500-1000 µg/day CFC-BDP, 800 µg/day QVAR delivered via the Autohaler provided equivalent asthma control to 1600 µg/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 200-500 µg CFC-BDP, 100-250 µg CFC-FP or 200-400 µg budesonide were randomised to receive either 400 µg/day QVAR or 400 µg/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 500 µg/day FP or 500-1000 µg/day BDP or 400-800 µg/day budesonide were switched to 800 µg/day QVAR or 1000 µg/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.

5.2 PHARMACOKINETIC PROPERTIES

BDP is hydrolysed in the lungs to beclomethasone monopropionate before reaching the systemic circulation and is further metabolised during its passage through the liver. The principal route of elimination of BDP and its metabolites is in the faeces. Between 10 % and 15 % of any orally administered dose is excreted in the urine, as both conjugated and free metabolites of BDP.

The pharmacokinetics of beclomethasone and of total-beclomethasone have been measured over 24 hours in mild asthmatics given single and multiple doses of QVAR. Total beclomethasone was obtained by hydrolysing any BDP and beclomethasone monopropionates in the serum samples to beclomethasone. The peak serum concentration for total beclomethasone is achieved within 30 minutes. The mean values of the peak serum concentrations after multiple dosing of 100 µg, 200 µg or 400 µg twice daily for 14 days are proportional to the dose. The mean peak serum concentration after the highest recommended dose of 400 µg twice daily is approximately 1 ng/mL.

Pharmacokinetic studies comparing QVAR and CFC-BDP demonstrated that a dose of 200 µg of QVAR achieved comparable total beclomethasone levels as a dose of 400 µg of CFC-BDP. This finding is consistent with the deposition results, which showed increased lung deposition and reduced oropharyngeal deposition for QVAR compared with CFC-BDP. Pharmacokinetic data in the paediatric population shows that the AUC for the dominant active metabolite 17-BMP after administration of 200 µg of QVAR from the Autohaler is similar to that of 400 µg of CFC-BDP given via an inhaler with spacer.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Avoid storage in direct sunlight or heat. Protect from frost. As the canister is pressurised no attempt should be made to puncture or dispose of it by burning.

6.5 NATURE AND CONTENTS OF CONTAINER

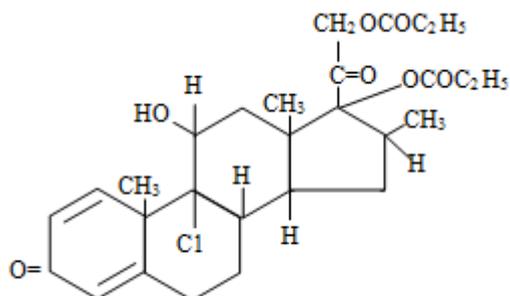
Each 200 dose canister provides 200 inhalations. 1's.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Its molecular formula is C₂₈H₃₇ClO₇ (molecular weight 521.1)

CAS number: 5534-09-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited
L10, 12 Help Street
Chatswood NSW 2067
Toll Free: 1800 630 056

9 DATE OF FIRST APPROVAL

QVAR Autohaler: 23/11/1999

QVAR 50 & 100 Inhaler: 23/11/1999

10 DATE OF REVISION

16 October 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Transfer of text from old PI format (without changes)
All 4.4 & 4.8	Reformatting of approved PI (March 2018) Addition of precautions regarding visual disturbance and CSCR as per TGA request dated 6 June 2018 (TRIM ref: D18-10542187)
4.6	15 Oct 2018: Minor editorial change in “Effects on fertility” section
5.1	Minor editorial change – relocate paragraphs “The pharmacokinetics of beclomethasone and of...” and “Pharmacokinetic studies comparing QVAR and CFC-BDP...” to section 5.2: Pharmacokinetics properties

QVAR Autohaler and QVAR Inhaler are a product technology developed by 3M Pharmaceuticals
QVAR, Autohaler and 3M are registered trademarks