NEW ZEALAND DATA SHEET

QVAR™ 50 and QVAR 100 Inhaler

1 PRODUCT NAME

QVAR 50 Inhaler 50 micrograms per actuation pressurised inhalation solution

QVAR 100 Inhaler 100 micrograms per actuation pressurised inhalation solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

QVAR 50: Beclomethasone dipropionate (BDP) 50 micrograms per metered dose.

QVAR 100: Beclomethasone dipropionate 100 micrograms per metered dose.

QVAR 50 Inhaler delivers 50 micrograms of BDP per inhalation.

QVAR 100 Inhaler delivers 100 micrograms of BDP per inhalation.

Excipients with known effects:

Ethanol

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Aerosol inhaler, solution, metered dose

A colourless solution in a pressurised aluminium canister

QVAR is a conventional press and breathe metered dose inhaler (P&B MDI).

QVAR also contains norflurane (HFA-134a), a propellant which does not contain chlorofluorocarbons (CFCs). Beclomethasone 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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

QVAR is for oral inhalation use only.

Proper instruction and good inhaler technique is necessary to get maximum benefit from QVAR Inhaler. Patients should be advised that QVAR may have a different taste and feel than a CFC inhaler. Patients should be instructed to rinse their mouth out each time after using QVAR.

Dosage

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

Adult 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.

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.

Paediatric Dose
In children aged five years and over the recommended dose of QVAR is 50 μg twice daily. In more severe cases this may be increased up to 100 μg twice daily, which is the maximum recommended dose. To minimise the systemic effects of orally inhaled steroids, the dose should be titrated down to the lowest that provides effective asthma control.

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:

	Daily Dose (μg)				
CFC-BDP	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

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.

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

<u>Method of Administration</u>

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 or periods without use of up to 14 days (do not need to test fire)

- at temperatures as low as -10°C.

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

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 dying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter.

4.3 Contraindications
Hypersensitivity to beclomethasone dipropionate or to any of the excipients listed in section 6.1.

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.

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

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 section 4.2).

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.

4.5 Interaction with other medicines and other forms of interaction
No clinically significant drug interactions have been associated with therapeutic doses of BDP.

4.6 Fertility, pregnancy and lactation
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.

Lactation

It is probable that beclomethasone 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

Not relevant.

4.8 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 Precautions).

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, pruritus 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 %
Nervous system disorders			
Headache	-	-	1 %
Respiratory, thoracic and mediastinal 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 %
Nervous system disorders		
Headache	2 %	1 %
Gastrointestinal disorders		
Stomatitis	1 %	2 %
Respiratory, thoracic and mediastinal disorders		
Pharyngitis	4 %	6 %
Rhinitis	1 %	1 %
Bronchitis	-	1 %
Increased Asthma Symptoms	1 %	-

Based on the MEDRA system organ class and frequencies, adverse events are listed in the table below according to the following frequency estimate: very common (≥ 1/10); common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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 %.

System organ class	Frequency and symptom
Application site disorders	Uncommon: cough, increased asthma symptoms
General disorders and administrative site conditions	Uncommon: chest pain, epistaxis Rare: asthenia, back pain, fatigue, oedema, pain
Respiratory, thoracic and mediastinal disorders	Uncommon: bronchitis; coughing; upper respiratory tract infection. Rare: acute asthma episode; hemoptysis;

	respiratory disorder; sinusitis.
Nervous system disorders	Uncommon: dizziness; dysphonia; migraine. Rare: neuropathy; tremor; vertigo.
Gastrointestinal disorders	Uncommon: abdominal pain; constipation. Rare: dyspepsia; GI disorders (unspecified); nausea; tongue discolouration; toothache.
Cardiac disorders	Rare: angina pectoris, palpitations
Vascular disorders	Rare: hypertension
Metabolic and nutritional disorders	Uncommon: weight increase.
Psychiatric disorders	Uncommon: increased appetite. Rare: anxiety; depression; insomnia.
Skin and subcutaneous tissue disorders	Uncommon: rash, purpura Rare: photosensitivity reaction; skin disorder; urticarial
Musculoskeletal and connective tissue disorders	Uncommon: myalgia
Infections and infestations	Uncommon: infection. Rare: infection bacterial

Post Marketing
Eye disorders: vision blurred

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 section 4.2).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Glucocorticoids, ATC Code: R03B A01

5.1 Pharmacodynamic properties

Drug delivery properties
QVAR contains BDP in solution, resulting in an extrafine 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 beclomethasone 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 section 4.2).

Pharmacodynamic effects

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.

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.

Clinical efficacy and safety

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 FEV_1 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 section 4.2).

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 has 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 BOH. 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
Potential carcinogenicity, mutagenicity and impairment of fertility 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
Ethanol
Propellant HFA-134a (Norflurane)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30°C.

Avoid storage in direct sunlight or heat. Protect from frost.

6.5 Nature and contents of container
QVAR 50 Inhaler, metered: 200 dose units providing 200 inhalations, 1s.

QVAR 100 inhaler, metered: 200 dose units providing 200 inhalations, 1s.

6.6 Special precautions for disposal and other handling
As the canister is pressurised no attempt should be made to puncture or dispose of it by burning.

7 MEDICINE SCHEDULE
Prescription

8 SPONSOR
iNova Pharmaceuticals (New Zealand) Limited
c/- Simpson Grierson
88 Shortland Street,
Auckland 1141

Toll free number: 0508 375 394

9 DATE OF FIRST APPROVAL
14 January 1999

10 DATE OF REVISION OF THE TEXT
27 July 2018

QVAR Inhaler is a product technology developed by 3M Pharmaceuticals

QVAR and 3M are registered trademarks

SUMMARY TABLE OF CHANGES

Date	Change
16 February 2018	Data sheet reformatted Reference to QVAR Autohaler deleted as this presentation is unavailable. Deletion of molecular formula, molecular weight, chemical structure and CAS number Corrected MEDRA terminology for adverse event categories New sponsor
27 July 2018	Medsafe request t update data sheet for all corticosteroid containing products