Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Qvar Autohaler 50 micrograms pressurised inhalation, solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose delivers Beclometasone Dipropionate 50 micrograms ex-valve into the mouthpiece of the actuator.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, solution.

Pressurised aluminium container closed with a metering valve containing a pressurised inhalation solution, inserted into a breath actuated beige (cap) and grey (mouthpiece) plastic actuator.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe asthma requires regular medical assessment as death may occur. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled (see dosage instructions) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Adults:
Prophylactic management in:
Mild asthma (PEF values greater than 80% predicted at baseline with less than 20% variability): Patients requiring intermittent symptomatic bronchodilator asthma medication on more than an occasional basis.

Moderate asthma (PEF values 60 - 80% predicted at baseline with 20 - 30% variability): Patients requiring regular asthma medication and patients with unstable or worsening asthma on other prophylactic therapy or bronchodilator alone.

Severe asthma (PEF values less than 60% predicted at baseline with greater than 30% variability): Patients with severe chronic asthma.

Children aged 5 years and over:
Any child aged 5 years and over who requires prophylactic asthma medication.

4.2 Posology and method of administration

NOTE: The recommended total daily dose of beclometasone dipropionate extrafine aerosol from Qvar is lower than that for current beclometasone dipropionate product and should be adjusted to the individual patient.

Qvar is for oral inhalation use only.

For optimum results, beclometasone dipropionate inhaler should be used regularly, even if the patient is asymptomatic. The initial dose of inhaled beclometasone dipropionate should be appropriate to the severity of the disease. The dose should be titrated to the lowest dose at which effective control of asthma is maintained.

When asthma symptoms remain under satisfactory control the dose may be gradually reduced to the minimum effective dose to maintain symptom control.

For normal hygiene, the mouthpiece of your autohaler device should be cleaned weekly with a clean dry tissue or cloth. Do not wash or put any part of the inhaler in water.

Adults starting and maintenance dose:

For mild to moderate asthma: 50 µg to 200 µg twice daily.

In more severe cases: doses up to 400 µg twice daily.

The maximum recommended daily dose in adults is 800 µg.

Children aged 5 years and over:

The recommended dose for Qvar in children is 50 µg twice daily.

Children with well-controlled asthma on doses of up to 400 µg per day of beclometasone dipropionate may be titrated to a dose of 50 µg twice daily of Qvar.

During periods of deterioration in asthma control, the doses may be increased to 100 µg twice daily.

The maximum recommended daily dose in children is 200 µg.

The same total daily dose in µg from either Qvar 50 or Qvar 100 aerosol provides the same clinical effect.

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

Comparative clinical studies have demonstrated that asthma patients achieve equivalent pulmonary function and control of symptoms with Qvar at lower total daily doses than CFC-beclometasone dipropionate aerosol inhalers.

Special patient groups:
No special dosage recommendations are made for elderly or patients with hepatic or renal impairment.

Using your inhaler:
Qvar Autohaler is a breath-actuated inhaler which automatically releases the metered dose of medication during a patient's inhalation through the mouthpiece and overcomes the need for patients to have good manual co-ordination.

The patient should read the instruction leaflet before use.

Before first use of the inhaler, or if the inhaler has not been used for two weeks or more, prime the inhaler by releasing two puffs into the air.

Qvar delivers 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 or periods without use of up to 14 days
- at temperatures as low as -10°C.

4.3 Contraindications

Hypersensitivity to beclometasone dipropionate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The management of asthma should follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

Increasing use of short-acting inhaled beta-2-agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.

Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. In patients considered at risk, daily flow monitoring may be instituted.

Qvar is not for use in acute attacks but for routine long-term management. Patients will require a fast- and short-acting inhaled bronchodilator to relieve acute asthmatic symptoms.

Patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the drug to the lungs.

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

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

Treatment with Qvar should not be stopped abruptly.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important therefore that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored.

As with all inhaled corticosteroids, special care is necessary in patients with active quiescent pulmonary tuberculosis.

Particular care should be taken to minimise the use of topical corticosteroids in patients with immunosuppression.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Qvar inhaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

Steroid-dependent patients:

The transfer of steroid-dependent patients to Qvar and their subsequent management, needs special care mainly because recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, is slow.

- The patient should be in a reasonably stable state before being given Qvar in addition to his usual maintenance dose of systemic steroid.
- After about a week, gradual withdrawal of the systemic steroid is started by reducing the daily dose by l mg prednisolone, or its equivalent of other corticosteroids, at not less than weekly intervals.
- Patients treated with systemic steroids for long periods of time, or who have received high doses may have adrenocortical suppression. In these patients, adrenocortical function should be monitored regularly and their

dose of systemic steroid reduced cautiously.
- Most patients can be successfully transferred to Qvar with maintenance of good respiratory function, but special care is necessary for the first months after the transfer until the pituitary-adrenal system has sufficiently recovered to enable the patient to cope with emergencies such as trauma, surgery or infections.

Transferred patients whose adrenocortical function is impaired should carry a warning card indicating that they need supplementary systemic steroids during periods of stress or elective surgery. They should also be given a supply of oral steroid to use in emergency, for example when the asthma worsens as a result of a chest infection. The dose of beclometasone dipropionate should be increased at this time and then reduced to the maintenance level after the systemic steroid has been discontinued.

Patients with high blood levels of *Candida precipitins*, indicating a previous infection, are more likely to develop candidiasis of the mouth and throat (thrush). All patients may find it helpful to rinse their mouth with water after using the inhaler.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

Patients should be advised that this product contains small amounts of ethanol. At the normal doses the amounts of ethanol are negligible and do not pose a risk to patients.

4.5 Interaction with other medicinal products and other forms of interaction

Beclometasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

Qvar Autohaler contains a small amount of ethanol. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronizadole.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is inadequate evidence of the safety of beclometasone dipropionate or Norflurane (HFA 134a or Tetrafluoroethane) propellant in human pregnancy.

In animal reproduction studies with beclometasone dipropionate, adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; direct inhaled application ensures minimal systemic exposure.

Studies of the effect of Norflurane (HFA 134a) on reproductive function and embryo-foetal development in animals have revealed no clinically relevant adverse events.

No clinically relevant adverse events have been associated with the administration of Norflurane (HFA 134a) propellant. Thus, it is unlikely that there will be any adverse effects in humans.

Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Breast-feeding
The excretion of beclometasone dipropionate in milk has not been studied in animals. It is reasonable to assume that beclometasone dipropionate is secreted in milk but at the dosage used for direct inhalation, there is low potential for significant levels in breast milk. Beclometasone dipropionate should only be used in a nursing mother if the expected benefit justifies the risk to the newborn/infant.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo and comparator group has not been taken into account in estimation of these frequencies. Rare and very rare events were generally determined from spontaneous data.

Infections and infestations	
Very common:	Candidiasis of the mouth and throat.
Immune system disorders	
Hypersensitivity reactions with the following manifestations have been reported:	
Uncommon:	Rash, urticaria, pruritus, erythema.
Very rare:	Angioedema of the eyes, face, lips and throat, respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactoid/anaphylactic reactions.
Endocrine disorders	
Possible systemic effects include (see section 4.4 *Special Warnings and Precautions for Use*):	
Very rare:	Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, and glaucoma.
Psychiatric disorders	
Very rare:	Anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children).
Unknown:	Depression, aggression (predominantly in children).
Respiratory, thoracic and mediastinal disorders	
Common:	Hoarseness, throat irritation.
Very rare:	Paradoxical bronchospasm.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Qvar inhaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

For beclometasone dipropionate extrafine aerosol, a rare incidence of nausea has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

There is no specific treatment for an overdose of beclometasone dipropionate. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Acute inhalation of beclometasone dipropionate doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not need emergency action as adrenal function is recovered in a few days, as verified by plasma cortisol measurements.

However if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression may result. Monitoring of adrenal reserve may be necessary. In cases of beclometasone dipropionate overdose, therapy may still be continued at clinically appropriate dosage (within the approved range) for symptom control.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: R03B A01

Qvar contains beclometasone dipropionate in solution in HFA-134a propellant resulting in an extrafine aerosol. The aerosol droplets are on average much smaller than the beclometasone dipropionate particles delivered by CFC-suspension formulations or dry powder formulations of beclometasone dipropionate. The extrafine particle fraction will be 60% ± 20% of the drug particles £3.3 microns per shot, ex-actuator.

Radio-labelled deposition studies have demonstrated that the majority of drug (>55% ex-actuator) is deposited in the lung and <35% ex-actuator is deposited in the oropharynx. These delivery characteristics result in equivalent therapeutic effects at lower total daily doses of Qvar, compared with CFC beclometasone dipropionate formulations.

Inhaled beclometasone dipropionate is now well established in the management of asthma. It is a synthetic glucocorticoid and at up to the maximum recommended daily dose exerts a topical, anti-inflammatory effect on the lungs, without significant systemic activity.

5.2 Pharmacokinetic properties

The Pharmacokinetic profile of Qvar shows that the peak serum concentration for total BOH (total of any Beclometasone dipropionate or monopropionate) after single and multiple doses is achieved after 30 minutes. The value at the peak is approximately 2ng/ml after the highest recommended dose of 800 µg and the serum levels after 100, 200 and 400 µg are proportional.

In both single dose and multiple dose pharmacokinetic studies, a dose of 200µg of Qvar achieved comparable total-BOH levels, as a dose of 400µg of CFC beclometasone dipropionate aerosol. This provided the scientific rationale for investigating lower total daily doses of Qvar to achieve the same clinical effect.

In a single dose Pharmacokinetic study in children, a dose of 200µg of Qvar delivered without a spacer achieved comparable AUC (17-BMP) levels as a dose of 400µg of a CFC aerosol via a spacer.

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

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

The principal route of elimination of Beclometasone 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.

5.3 Preclinical safety data

Hydrofluoroalkane 134a

Statements from CPMP:

1. In animal studies, HFA-134a has been shown to have no significant pharmacological effects other than at very high exposure concentrations, then narcosis and a relatively weak cardiac sensitising effect were found. The potency of the cardiac sensitisation was less than that of CFC-11 (trichlorofluoromethane).

2. In studies to detect toxicity, repeated high dose levels of HFA-134a indicated that safety margins based on systemic exposure would be of the order 2200, 1314 and 381 for mouse, rat and dog with respect to humans.

3. There are no reasons to consider HFA-134a as a potential mutagen, clastogen or carcinogen judged from *in vitro* and *in vivo* studies including long-term administration by inhalation in rodents.

Qvar

Safety studies with this product in rat and dog showed few, if any, adverse effects other than those normally associated with general steroid exposure including lymphoid tissue alterations such as reduction in thymus, adrenal and spleen weights.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (hydrofluoroalkane 134a)
Ethanol Anhydrous

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.
Storage in direct sunlight or heat should be avoided.
Do not refrigerate or freeze.
The canister contains a pressurised liquid.
Do not expose to temperatures higher than 50ºC.
Do not pierce canister.

6.5 Nature and contents of container

Pressurised aluminium container closed with a metering valve containing either 100 or 200 doses and supplied with a plastic actuator.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Norton Waterford Limited
Trading as: IVAX Pharmaceuticals Ireland
Unit 301
Industrial Park
Waterford

8 MARKETING AUTHORISATION NUMBER

PA0436/035/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first autorisation: 26 July 1999

Date of last renewal: 26 July 2009

10 DATE OF REVISION OF THE TEXT

May 2017