Qvar 50
Qvar 100

1. NAME OF THE MEDICINAL PRODUCT

Qvar 50
Qvar 100

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qvar 50 Solution for Inhalation – Pressurised Metered Dose Inhaler/ Autohaler-
Beclometasone Dipropionate 50 micrograms per metered (ex-valve) dose.

Qvar 100 Solution for Inhalation - Pressurised Metered Dose Inhaler/Autohaler-
Beclometasone Dipropionate 100 micrograms per metered (ex-valve) dose.

Excipient with known effect:
This medicine contains 4.74 mg of alcohol (ethanol) in each puff. The amount in one puff of this medicine is equivalent to less than 1ml beer or 1 ml wine.
The small amount of alcohol in this medicine will not have any noticeable effects.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation, solution.

A colourless solution in a pressurised aluminium canister fitted with a metering valve and an actuator.

Qvar contains a propellant, which does not contain any chlorofluorocarbons (CFCs).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and treatment of bronchial asthma in adults and children 5 years of age and above.

4.2 Posology and method of administration

Qvar is for inhalation use only.

Patients should be instructed in the proper use of their inhaler, including rinsing out their mouth with water after use. Patients should be advised that Qvar may have a different taste and feel than a CFC inhaler.

NOTE: The recommended total daily dose of Qvar is lower than that for current beclometasone dipropionate CFC containing products and should be adjusted to the needs of the individual patient.

ADULT STARTING AND MAINTENANCE DOSE:
It is important to gain control of asthma symptoms and optimise pulmonary function as soon as possible. When patients' symptoms remain under satisfactory control, the dose should be titrated to the lowest dose at which effective control of asthma is maintained.

To be effective, inhaled Qvar must be used on a regular basis even when patients are asymptomatic.

Therapy in new patients should be initiated at the following dosages

Mild asthma:	100 to 200 micrograms per day in two divided doses.
Moderate asthma:	200 to 400 micrograms per day in two divided doses.
Severe asthma:	400 to 800 micrograms per day in two divided doses.

TRANSFERRING PATIENTS TO QVAR FROM A CFC-CONTAINING INHALER

The general approach to switching patients to Qvar involves two steps as detailed below. Specific guidance on switching well-controlled and poorly-controlled (symptomatic) patients is given below the table.

Step 1: Consider the dose of CFC containing beclometasone dipropionate product appropriate to the patient's current condition.

Step 2: Convert the CFC containing beclometasone dipropionate dose to the Qvar dose according to the table below.

Total Daily Dose (mcg/day)								
CFC BDP*	200-250	300	400-500	600-750	800-1000	1100	1200-1500	1600-2000
QVAR	100	150	200	300	400	500	600	800

*CFC-BDP = CFC beclometasone dipropionate

1. Dosing in well-controlled patients with asthma

Patients with well-controlled asthma using beclometasone dipropionate CFC containing product should be switched to Qvar at a dose in accordance with the table above.

For example:

Patients on 2 puffs twice daily of CFC beclometasone dipropionate 100 micrograms would change to 2 puffs twice daily of Qvar 50 micrograms.

Patients on 2 puffs twice daily of CFC beclometasone dipropionate 200 micrograms would change to 2 puffs twice daily of Qvar 100 micrograms.

2. Dosing in poorly-controlled (symptomatic) patients with asthma

Patients with poorly-controlled asthma may be switched from CFC containing beclometasone dipropionate products to Qvar at the same microgram for microgram dose up to 800 micrograms daily. Comparative clinical studies have demonstrated that asthma patients

achieve equivalent pulmonary function and control of symptoms with Qvar at lower total daily doses than with CFC containing beclometasone dipropionate products.

Alternatively the patient's current CFC containing beclometasone dipropionate dose can be doubled and this dose can be converted to the Qvar dose according to the table above.

Patients on budesonide inhalers may be transferred to Qvar as described for CFC containing beclometasone dipropionate products.

Patients on fluticasone inhalers may be transferred to the same total daily dose of Qvar up to 800 micrograms.

Once transferred to Qvar the dose should be adjusted to meet the needs of the individual patient.

The maximum recommended dose is 800 micrograms per day in divided doses.

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

CHILDREN 5 YEARS OF AGE AND OLDER

With mild persistent or moderate asthma: 50 micrograms two times per day.
In severe cases: 100 micrograms two times per day.

The maximum recommended daily dose in children is 100 micrograms two times per day.
As the use of a spacing device might be needed, certain spacing devices can be used with this product.

SPECIAL PATIENT GROUPS

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

INSTRUCTIONS FOR USE
Qvar pMDI is recommended for those patients who have demonstrated consistent good technique with co-ordinating actuation and inhalation.

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.

Where a spacer is considered necessary for specific patient needs, Qvar with AeroChamber Plus™ holding chamber, as the extrafine particle fraction is maintained.

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

Patients should be properly instructed on the use of the inhaler to ensure that the drug reaches the target areas within the lungs. To be effective, Qvar must be used by patients on a regular basis, even when patients do not have asthma symptoms. When symptoms are controlled, maintenance Qvar therapy should be reduced in a stepwise manner to the minimum effective dose. Inhaled steroid treatment should not be stopped abruptly.

Patients with asthma are at risk of acute attacks and should have regular assessments of their asthma control including pulmonary function tests.

Qvar is not indicated for the immediate relief of asthma attacks. Patients therefore need to have relief medication (inhaled short-acting bronchodilator) available for such circumstances.

Severe asthma exacerbations should be managed in the usual way.
Subsequently, it may be necessary to increase the dose of extrafine beclometasone dipropionate up to the maximum daily dose. Systemic steroid treatment may be needed and/or an antibiotic, if there is an infection, together with β-agonist therapy, as needed.

Severe asthma requires regular medical assessment, including lung-function testing, as there is a risk of severe attacks and even death. Patients should be instructed to seek medical attention as soon as possible for review of beclometasone dipropionate therapy, if their peak flow falls, if symptoms persist or worsen or if their short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required, this may indicate deterioration of asthma control. If this occurs, patients should be assessed and the need for increased anti-inflammatory therapy considered (eg. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Treatment with Qvar should not be stopped abruptly.

Patients who have received systemic steroids for long periods of time or at high doses, or both, need special care and subsequent management when being transferred to inhaled steroid therapy. Patients should have stable asthma 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 inhaled steroid therapy. For daily oral doses of prednisolone of 10mg or less, dose reduction in 1mg steps, at intervals of not less than one week is recommended. For patients on daily maintenance doses of oral prednisolone greater than 10mg, larger weekly reductions in the dose might be acceptable. The dose reduction scheme should be chosen to correlate with the magnitude of the maintenance systemic steroid dose.

Most patients can be successfully transferred to inhaled steroids with maintenance of good respiratory function, but special care is necessary for the first few months after the transfer, until the hypothalamic-pituitary-adrenal (HPA) axis has sufficiently recovered to enable the patient to cope with stressful emergencies such as trauma, surgery or serious infections. In addition, it may be advisable to provide such patients with a supply of corticosteroid tablets to use in these circumstances. 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. As recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy is slow, adrenocortical function should be monitored regularly.

Patients should be advised that they may feel unwell in a non-specific way during systemic steroid withdrawal despite maintenance of, or even improved respiratory function. Patients should be advised to persevere with their inhaled product and to continue withdrawal of systemic steroids, even if feeling unwell, unless there is evidence of HPA axis suppression.

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

Beclometasone dipropionate, like other inhaled steroids, is absorbed into the systemic circulation from the lungs. Beclometasone dipropionate and its metabolites may exert detectable suppression of adrenal function. Within the dose range 100-800 micrograms daily, clinical studies with Qvar have demonstrated mean values for adrenal function and responsiveness within the normal range.

However, 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, blurred vision, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Therefore, it is important that the dose of inhaled corticosteroid is reviewed regularly and 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. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than the recommended doses, may result in clinically significant adrenal suppression and acute adrenal crisis. Situations that could potentially trigger acute adrenal crisis include trauma, surgery, infection or any rapid reduction in dose. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, hypotension, hypoglycaemia and seizures. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Like other corticosteroids, caution is necessary in patients with active or latent pulmonary tuberculosis.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a fast-acting bronchodilator and should be treated straightaway. Beclometasone dipropionate should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary.

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.

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 (see section 4.5).

Excipients
Ethanol
The small amount of alcohol in this medicine will not have any noticeable effects.

4.5. Interactions with other medicinal products and other forms of interaction

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

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.

4.6. Fertility, pregnancy and lactation

The potential risk of this product for humans is unknown.

Qvar

There is no experience of this product in pregnancy and lactation in humans, therefore the product should only be used if the expected benefits to the mother are thought to outweigh any potential risk to the foetus or neonate.

Beclometasone dipropionate

Pregnancy

There is inadequate evidence of safety in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate and intra-uterine growth retardation. There may therefore, be a risk of such effects in the human foetus. It should be noted, however, that the foetal changes in animals occur after relatively high systemic exposure. Beclometasone dipropionate is delivered directly to the lungs by the inhaled route and so avoids the high level of exposure that occurs when corticosteroids are given by systemic routes.

The use of beclometasone dipropionate in pregnancy requires that the possible benefits of the drug be weighed against the possible hazards. The drug has been in widespread use for many years without apparent ill consequence.

Breast-feeding
No specific studies examining the transfer of beclometasone dipropionate into the milk of lactating animals have been performed.It is probable that beclometasone dipropionate is excreted in milk. However, given the relatively low doses used by the inhalation route, the levels are likely to be low. In mothers breast feeding their baby the therapeutic benefits of the drug should be weighed against the potential hazards to mother and baby.
There is no experience with or evidence of safety of propellant HFA 134a in human pregnancy or lactation. However, studies on the effect of HFA 134a on reproductive function and embryofoetal development in animals have revealed no clinically relevant adverse effects.

4.7. Effects on ability to drive and use machines

Not relevant.

4.8. Undesirable effects

A serious hypersensitivity reaction including oedema of the eye, face, lips and throat (angioedema) has been reported rarely.

As with other inhalation therapy, paradoxical bronchospasm may occur after dosing. Immediate treatment with a short-acting bronchodilator should be initiated, Qvar should be discontinued immediately and an alternative prophylactic treatment introduced.

Systemic effects of inhaled corticosteroids may occur, particularly with high doses prescribed for prolonged periods. These include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density and the occurrence of cataract and glaucoma.

Commonly, when taking Qvar, hoarseness and candidiasis of the throat and mouth may occur. To reduce the risk of hoarseness and candida infection, patients are advised to rinse their mouth after using their inhaler.

Based on the MedDra 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).

MedDra – system organ class	**Frequency and Symptom**
Infections and infestations	*Common*: Candidiasis in mouth and throat
Immune system disorders	*Rare*: Allergic reactions, angioedema in eyes, throat, lips and face
Endocrine disorders	*Very rare*: Cushing's syndrome, cushingoid features, adrenal suppression*, growth retardation * (in children and

	adolescents), bone density decreased*
Psychiatric Disorders	*Unknown*: Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)
Nervous system disorders	*Uncommon:* Headache, vertigo, tremor
Eye disorders	*Uncommon:* Vision, blurred (see also section 4.4) *Very rare*: Cataract,* glaucoma* *Not known: C*entral serous retinopathy
Respiratory, thoracic and mediastinal disorders	*Common*: Hoarseness, pharyngitis *Uncommon*: Cough, increased asthma symptoms *Rare*: Paradoxical bronchospasm
Gastrointestinal disorders	*Common*: Taste disturbances *Uncommon*: Nausea
Skin and subcutaneous tissue disorders	*Uncommon*: Urticaria, rash, pruritus, erythema, purpura
Musculoskeletal and connective tissue disorders	*Very rare*: Decrease bone mineral density

*Systemic reactions are a possible response to inhaled corticosteroids, especially when a high dose is prescribed for a prolonged time (see section 4.4 Special warnings and precautions for use).

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9. Overdose

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

If excessive doses of beclometasone dipropionate were taken over a prolonged period a degree of atrophy of the adrenal cortex could occur in addition to HPA axis suppression. In this event the patient should be treated as steroid dependent and transferred to a suitable maintenance dose of a systemic steroid such as prednisolone. Once the condition is stabilised, the patient should be returned to Qvar by the method described above in section 4.4.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC Code: R03B A01

Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity. It is extensively hydrolysed via esterase enzymes to the active metabolite beclometasone 17-monohydrate, which is a potent topical anti-inflammatory agent.

Qvar contains beclometasone dipropionate in solution with propellant HFA-134a resulting in an extrafine aerosol. The aerosol droplets are on average much smaller than the beclometasone dipropionate particles delivered by CFC-containing 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 in adults with mild asthma have demonstrated that the majority of drug (>55% ex-actuator) is deposited in the lung and a small amount (< 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. These studies were performed with Qvar pMDI. Qvar pMDI is a 'press and breathe' inhaler, whereas Qvar Autohaler is a breath-activated inhaler.

Inhaled beclometasone dipropionate is well established in the management of asthma. It is a synthetic glucocorticoid and exerts a topical, anti-inflammatory effect on the lungs, with fewer systemic effects than oral corticosteroids.

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 containing beclometasone dipropionate aerosol inhalers.

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-beclometasone levels obtained. At a daily dose of 800 micrograms Qvar, suppression of urinary free cortisol was comparable with that observed with the same daily dose of CFC containing beclometasone dipropionate, indicating a wider safety margin, as Qvar is administered at lower doses than the CFC-containing product.

5.2. Pharmacokinetic properties

The pharmacokinetic profile of Qvar shows that the peak serum concentration for total-beclometasone (BOH) (total of any beclometasone OH and beclometasone dipropionate or monopropionate hydrolysed to beclometasone OH) after single and multiple doses is achieved after 30 minutes.

The value at the peak is approximately 2 nanograms/ml after a total daily dose of 800 micrograms and the serum levels after 100, 200 and 400 micrograms are proportional. 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.

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

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

In a single dose pharmacokinetic study in children, a dose of 200 micrograms of extrafine beclometasone dipropionate delivered without a spacer achieved comparable AUC (beclometasone 17 monopropionate) levels as a dose of 400 micrograms of a CFC-containing beclometasone dipropionate product delivered via a spacer.

5.3. Preclinical safety data

In animal studies, propellant 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).

In studies to detect toxicity, repeated high dose levels of propellant 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.

There are no reasons to consider propellant 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.

Studies of propellant HFA-134a administered to pregnant and lactating rats and rabbits have not revealed any special hazard.

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 very small risk of such effects in the human foetus. However, inhalation of beclometasone dipropionate into the lungs avoids the high level of exposure that occurs with administration by systemic routes.

Safety studies with Qvar 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. An inhalation reproductive study with Qvar (an equivalent inhaler) this product in rats did not exhibit any teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propellant HFA-134a (Norflurane)
Ethanol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C. Storage in direct sunlight or heat should be avoided.
Protect from frost.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C.
Do not pierce the canister.

6.5 Nature and contents of container

Qvar 50 Autohaler: pressurized aluminium canister closed with metering valve, containing 200 actuations.

Qvar 100 Autohaler: pressurized aluminium canister closed with metering valve, containing 200 actuations.

Qvar 50 pMDI: pressurized aluminium canister closed with a metering valve, containing 200 actuations.

Qvar 100 pMDI: pressurized aluminium canister closed with a metering valve, containing 200 actuations.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7 Licence Holder and Manufacturer

Manufacturer:
Kindeva Drug Delivery Limied
Derby Road, Loughborough, Leicestershire, UK.

Licence Holder:
TEVA ISRAEL LTD
124 Dvora HaNevi'a St., Tel Aviv 6944020 Israel

8. Registration Numbers

Qvar 50 - Pressurised Metered Dose Inhaler/ Autohaler: 139.28.30660
Qvar 100 - Pressurised Metered Dose Inhaler/ Autohaler: 139.29.30661

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