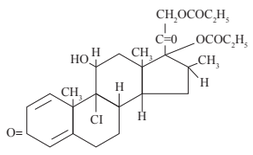
315 mm

180 mm

PRODUCT INFORMATION
QVAR® AUTOHALER®

NAME OF DRUG
The active ingredient in QVAR is beclomethasone dipropionate. Beclomethasone dipropionate 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. Its molecular formular is $C_{28}H_{37}ClO_7$ (molecular weight 521.1).
Its chemical structure is:



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

DESCRIPTION
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. There are no differences in formulation between the Autohaler and the Inhaler products.

QVAR contains beclomethasone dipropionate in solution, resulting in an extrafine aerosol. The aerosol droplets of QVAR are on average much smaller (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 beclomethasone dipropionate. 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 beclomethasone dipropionate (>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 beclomethasone dipropionate 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 the drug 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 Dosage and Administration).

PHARMACOLOGY
Pharmacodynamics
Bronchial inflammation is know to be an important component in the pathogenesis of asthma. Inflammation occurs in both large and small airways. Beclomethasone dipropionate 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 beclomethasone dipropionate in controlling symptoms and improving lung function in asthma although the exact mechanism of action of beclomethasone in the lungs is unknown. Inhaled beclomethasone dipropionate probably acts topically at the site of deposition in the bronchial tree after inhalation. Inhaled beclomethasone dipropionate 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 800µg/day of QVAR; or 800µg/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-BOH levels. The mean 24h-UFC, a sensitive marker of adrenal function, remained within the normal range for all dosing regimens. A daily dose of 800µg QVAR caused similar reductions in 24h-UFC levels as a daily dose of 800µg of CFC-BDP. Results from the secondary parameters of plasma cortisol and the ACTH stimulation test supported the findings of 24h-UFC and showed no differences to CFC-BDP and placebo at QVAR doses up to 800µg/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, 800µg/day QVAR and 800µg/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 100-200µg/day of QVAR from the Autohaler was comparable to those of 200-400µg/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 24h-UFC, plasma cortisol levels and response to low dose ACTH simulation 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.

Pharmacokinetics
Beclomethasone dipropionate 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 beclomethasone dipropionate 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 the drug.

The pharmacokinetics of beclomethasone (BOH) and of total-BOH have been measured over 24 hours in mild asthmatics given single and multiple doses of QVAR. Total BOH was obtained by hydrolyzing any beclomethasone dipropionate and monopropionates in the serum samples to BOH. The peak serum concentration for total BOH is achieved within 30 minutes. The mean values of the peak serum concentrations after multiple dosing of 100µg, 200µg or 400µg twice daily for 14 days are proportional to the dose. The mean peak serum concentration after the highest recommended dose of 400µg twice daily is approximately 1ng/ml. Pharmacokinetic studies comparing QVAR and CFC-BDP demonstrated that a dose of 200µg of QVAR achieved comparable total BOH levels as a dose of 400µg 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 200µg of QVAR from the Autohaler is similar to that of 400µg of CFC-BDP given via an inhaler with spacer.

INDICATIONS
QVAR is indicated for the prophylactic management of asthma.

CONTRAINDICATIONS
Hypersensitivity to beclomethasone dipropionate or any other ingredient in QVAR.

PRECAUTIONS
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.

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, reduction of bone density and retardation of growth in children. In steroid-dependent patients prior systemic steroid usage may be a contributing factor, but such effects can occur amongst patients who use only inhaled steroids regularly. Clinical studies in adult asthmatics treated with QVAR within the dose range 100-800µg 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.

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 Dosage and 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 beclomethasone dipropionate on recurrent lung infection is not known. Caution is necessary in patients with active or latent pulmonary tuberculosis.

QVAR contains a hydrofluoroalkane propellant (norflurane). In animal studies, narcosis and sensitisation to the arrhythmogenic effects of adrenaline were observed following inhalation of nortlurane 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 avoded as this carries a potential hazard from the propellant as well as from overdosage of the active drug in the formulation.

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

Beclomethasone 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. cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

Use in Children
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.

Use in 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 beclomethasone dipropionate can cause abnormalities of foetal development including growth retardation and cleft palate. Inhalational administration of a norflurane-based formulation of beclomethasone di propionate 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 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 bedomethasone dipropionate have not been done in lactating animals. In breastfeeding mothers the therapeutic benefits of the drug should be weighed against the potential hazards to mother and baby.

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

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ADVERSE REACTIONS
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.

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 resp 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.

DOSAGE AND 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 beclomethasone dipropionate
- 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.

Where a spacer is considered necessary the Aerochamber is a suitable device for use with QVAR inhalers. Use of a spacer with QVAR inhalers reduces the amount of drug deposited in the oropharynx without affecting drug deposition in the lungs.

Starting and Maintenance Dose:
The recommended dose of QVAR in adults is as follows:

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

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

Transfering Patients from a CFC-BDP Inhaler to QVAR:
Step 1 - Consider the dose of CFC-BDP appropriate to the patients' current condition. Symptomatic patients may require an increased dose of CFC-BDP and this increased dose should be considered in transferring patients to QVAR.
Step 2 - Convert the appropriate CFC-BOP dose to the QVAR dose according to the table below:

	Daily Dose of Beclomethasone Dipropionate (µg)						
CFC-BDP	200-250	300	400-500	600-750	800-1000	1200-1500	1600-2000
QVAR	100	150	200	300	400	600	800

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 the drug 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 Dependant 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 sysremic 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 10mg 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 drug. These should be treated symptomatically with antihistamines and/or topical therapy.

OVERDOSAGE
The harmful effect that follows inhalation of large amounts of the drug 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 beclomethasone dipropionate 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 Dosage and Administration).

PRESENTATION
QVAR 50µg Autohaler delivers 50µg of beclomethasone dipropionate per inhalation.
QVAR 100g Autohaler delivers 100µg of beclomethasone dipropionate per inhalation.
Each 200 dose canister provides 200 inhalations.

STORAGE
Store below 30°C. Avoid storage in direct sunlight or heat. Protect from frost.

MANUFACTURER
Kindeva Drug Delivery Limited
Derby Road, Loughborough LE11 5SF,
United Kingdom.

Revision date: Jan 2021

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GROUP 24|7 WORLDWIDE™ inova pharmaceuticals

SUBMISSION ARTWORK

Job No. : JB-02383 V0
UIC : A4381
SKU : 00000

30.10.20 - V0 - Artwork build - Sunny

A4381_NOT MARKETED_QVAR AUTOHALER 200D
Component : LEAFLET
Country : MY

Dieline Ref: Xxxxxx xxxxxx
EMO: KINDEVA
Printer: Xxxxxx Xxxxxxxxxxx

G247 File Name: 91472_A4381_NOT MARKETED_QVAR AUTOHALER 200D_MY_LT_V0

Colour 100% Black

Guide

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Any additonal information and technical check required by EMO on the Artwork BEFORE APPROVING.

1.955mm **PRODUCT INFORMATION** — Font Type: Times New Roman Bold, Font Size: 8 pt
1.955mm **QVAR® AUTOHALER®**

NAME OF DRUG — Font Type: Times New Roman Bold, Font Size: 6 pt
1.502mm The active ingredient in QVAR is beclomethasone dipropionate. Beclomethasone dipropionate 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. Its molecular formular is $C_{28}H_{37}ClO_7$ (molecular weight 521.1). — Font Type: Times New Roman Regular, Font Size: 6 pt

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