Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Arquist 125 microgram per actuation pressurised inhalation, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose (ex-valve) contains 125 micrograms of fluticasone propionate. This is equivalent to a delivered dose (ex-actuator) of 110 micrograms fluticasone propionate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation suspension (pressurised inhalation).
Arquist is a white homogeneous suspension, filled in an aluminum container fitted with a suitable metering valve and a plastic actuator. White coloured body with yellow cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Arquist is indicated for the treatment of asthma in adults and adolescents over 16 years of age. Arquist is also indicated for the treatment of severe COPD in conjunction with a long-acting beta agonist (such as salmeterol) for use in adults.

4.2 Posology and method of administration

Arquist is for inhalation by oral inhalation only.

Patients should be made aware of the prophylactic nature of therapy with inhaled fluticasone propionate and that it should be taken regularly even when they are asymptomatic. The onset of therapeutic effect is 4 to 7 days, although some benefit may be apparent as soon as 24 hours for patients who have not previously received inhaled steroids.

If patients find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought.

It is intended that each prescribed dose is given by a minimum of 2 inhalations.

In patients who find co-ordination of a pressurised metered-dose inhaler difficult a volumatic spacer may be used with Arquist inhaler.

Posology
Asthma
The dosage of fluticasone propionate should be adjusted according to the individual response.

Adults and adolescents over 16 years of age

100 to1000 micrograms twice daily.

Patients should be given a starting dose of inhaled fluticasone propionate which is appropriate for the severity of their disease:

Mild asthma: up to 250 micrograms twice daily Moderate asthma: 250 to 500 micrograms twice daily. Severe asthma: 500 to 1000 micrograms twice daily
The dose may then be adjusted until control is achieved or reduced to the minimum effective dose, according to the individual response.

Alternatively, the starting dose of fluticasone propionate may be gauged at half the total daily dose of beclomethasone dipropionate or equivalent as administered by metered-dose inhaler.

Chronic obstructive pulmonary disease(COPD)
Adults
500 micrograms twice daily, in conjunction with a long-acting beta agonist (such as salmeterol).

Medication must be used daily for optimum benefit which may take three to six months. If there is no improvement after three to six months then the patient should undergo medical assessment.

Only the 250 microgram device is suitable for the administration of this dose.

Special patient groups
There is no need to adjust the dose in elderly patients or in those with hepatic or renal impairment.

Paediatric population
Arquist are recommended for asthma in adults and adolescents over 16 years of age and Chronic Obstructive Pulmonary Disease (COPD) in adults only.

Method of Administration:
It is important to instruct the patient about correct inhalation technique (see package leaflet and instructions for use).

Testing your inhaler
1. When using your inhaler for the first time, test it to ensure that it is working. Remove the mouthpiece cover by gently squeezing the sides with your thumb and forefinger and pull apart.

2. To make sure that it works, shake the inhaler well, point the mouthpiece away from you and press the canister to release four puffs into the air. If you have not used the inhaler for five days or more, release two puffs of medicine into the air.

Using your inhaler
It is important to start to breathe as slowly as possible just before using your inhaler.

1. Stand up or sit upright when using your inhaler.
2. Remove the mouth piece cover. Check inside and outside to make sure that the mouthpiece is clean and free of objects.
3. Shake the inhaler 4 or 5 times to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.
4. Hold the inhaler upright with your thumb on the base, below the mouthpiece. Breathe out as far as is comfortable. Do not breathe in again yet.
5. Place the mouthpiece in your mouth between your teeth. Close your lips around it. Do not bite.
6. Breathe in through your mouth. Just after starting to breathe in, press down on the top of the canister to release a puff of medicine. Do this while still breathing in steadily and deeply.
7. Hold your breath, take the inhaler from your mouth and your finger from the top of the inhaler. Continue holding your breath for a few seconds, or as long as is comfortable.
8. If your doctor has told you to take two puffs, wait about half a minute before you take another puff by repeating steps 3 to 7.
9. Afterwards, rinse your mouth with water and spit it out.
10. After use always replace the mouthpiece cover straight away to keep out dust. Replace the cover by firmly pushing and clicking into position.
11. Practise in front of a mirror for the first few times. If you see'mist'coming from the top of your inhaler or the sides of your mouth you should start again.
12. Older children or people with weak hands may find it easier to hold the inhaler with both hands. Put the two forefingers on top of the inhaler and both thumbs on the bottom below the mouthpiece. If this does not help, Volumatic spacer device may make it easier. Your doctor, nurse or pharmacist will be able to advise you.

Cleaning your inhaler:
To prevent your inhaler blocking, it is important to clean it at least once a week.

To clean your inhaler:

- Remove the mouthpiece cover.
- Do not remove the metalcanister from the plastic casing at any time.
- Wipe the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.
- Replace the mouthpiece cover.

DO NOT PUT THE METAL CANISTER IN WATER.

4.3 Contraindications

Hypersensitivity to the fluticasone 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 β2-agonists to control asthma 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 peak flow monitoring may be instituted.

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

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

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

Pneumonia in patients with COPD
An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

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

Because of the possibility of impaired adrenal response, patients transferring from oral steroid therapy to inhaled fluticasone propionate therapy should be treated with special care, and adrenocortical function regularly monitored.

Following introduction of inhaled fluticasone propionate, withdrawal of systemic therapy should be gradual and patients are encouraged to carry a steroid warning card indicating the possible need for additional therapy in times of stress.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids (see section 4.9). Possibles ystemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral

density, 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). It is important, therefore, that the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained (seesection 4.8).

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

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

Similarly replacement of systemic steroid treatment with inhaled therapy may unmask allergies suchas allergic rhinitis or eczema previously controlled by the systemic drug. These allergies should be symptomatically treated with antihistamine and/ortopical preparations, including topical steroids.

Treatment with fluticasone propionate should not be stopped abruptly.

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

Prolonged treatment with high doses of inhaled corticosteroids may result in adrenal suppression and acute adrenal crisis. Situations, which could potentially trigger acute adrenal crisis, include trauma, surgery, infection or any rapid reduction in dosage. Presenting symptoms are typically vague and may include anorexia, abdominal pain, weight loss,tiredness, headache, nausea, vomiting, decreased level of consciousness, hypoglycaemia, and seizures. The possibility of residual impaired adrenal response should always be considered in emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered (see section 4.9).

Adrenal function and adrenal reserve usually remain within the normal range on recommended doses of fluticasone propionat e therapy. The benefits of inhaled fluticasone propionate therapy should minimise the need for oral steroids. However, the possibility of adverse effects in patients, resulting from prior or intermittent administration of oral steroids, may persist for some time. The extent of the adrenal impairment may require specialist advice before elective procedures.

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient out weighs the risk of systemic corticosteroid side-effects (see section 4.5).

There have been very rare reports of increases in blood glucose levels (see section 4.8) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Visual disturbance
Visual disturbance may be reported with systemic and topical cortico steroid 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 o f 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.

4.5 Interaction with other medicinal products and other forms of interaction

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after inhaled dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochromne P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Studies have shown that other inhibitors of cytochromne P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochromne P450 3A4 inhibitors (e.g. ketoconazole) as there is potential for increased systemic exposure to fluticasone propionate.

In a small study in healthy volunteers, the slightly less potent CYP3A inhibitor ketoconazole increased the exposure of fluticasone propionate after a single inhalation by 150%. This resulted in a greater reduction of plasma cortisol as compared with fluticasone propionate alone. Co-treatment with other potent CYP3A inhibitors, such as itraconazole, is also expected to increase the systemic fluticasone propionate exposure and the risk of systemic side-effects. Caution is recommended and long-term treatment with such drugs should, if possible, be avoided.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data on human fertility. Animal studies indicates no effects of fluticasone propionate on male or female fertility.

Pregnancy

There are limited data in pregnant women. Administration of fluticasone propionate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. It is important, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained. Treatment with fluticasone propionate should not be stopped abruptly.

Results from a retrospective epidemiological study did not find an increased risk of major congenital malformations following exposure to fluticasone propionate when compared to other inhaled corticosteroids, during the first trimester of pregnancy (see section 5.1).

Reproductive studies in animals have shown only those effects characteristic of glucocorticosteroids at systemic exposures in excess of those seen at the recommended inhaled therapeutic dose. There is inadequate evidence of safety of fluticasone propionate in human pregnancy. Data on a limited number (200) of exposed pregnancies indicate no adverse effects of fluticasone propionate on pregnancy or the health of the foetus/new born child. To date no other relevant epidemological data are available. Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development, including cleft palate and intra-uterine growth retardation. There may therefore be a very small risk of such effects in the human fetus. It should be noted, however, that the fetal changes in animals occur after relatively high systemic exposure. Because fluticasone propionate delivers fluticasone propionate
directly to the lungs by the inhaled route it avoids the high level of exposure that occurs when corticosteroids are given by systemic routes. Administration of fluticasone propionate during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus (see section 5.3).

Breast-feeding

The excretion of fluticasone propionate into human breast milk has not been investigated. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the breast milk. However, plasma levels in patients following inhaled application of fluticasone propionate at recommended doses are likely to be low. A risk to the newborns/infants cannot be excluded.

Administration during lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

4.7 Effects on ability to drive and use machines

Fluticasone propionate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (> 1/10), common(> 1/100to <1/10), uncommon (> 1/1000to <1/100),rare (>1/10,000to <1/1000)and veryrare (<1/10,000) including isolated reports and not known (cannot be estimated from the available data). Very common, common and uncommon events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data.

Infections and infestations
Very common: Candidiasis of mouth and throat.

Candidiasis (thrush) of the mouth and throat occurs in some patients. Such patients may find it helpful to rinse out their mouth with water after using their medication. Symptomatic candidiasis can be treated with topical anti-fungal therapy whilst still continuing with the fluticasone propionate.
Common: Pneumonia (in COPD patients).
Rare: Oesophageal candidiasis

Immune system disorders
Hyper sensitivity reactions with the following manifestations have been reported:
Uncommon: Cutaneous hyper sensitivity reactions.
Very rare: Angioedema (mainly facial and oropharyngeal oedema), respiratory symptoms (dyspnoea and/or bronchospasm) and anaphylactic reactions.

Endocrine disorders
Possible systemic effects (see section 4.4 *)* include:
Very rare: Cushing's syndrome, Cushingoid features (such as adrenal suppression, growth retardation, decreased bone mineral density, cataract, glaucoma).

Metabolism and nutrition disorders
Very rare: Hyperglycaemia.

Psychiatric disorders
Very rare: Anxiety, sleep disorders and behavioural changes, including hyperactivity and irritability (predominantly in children).
Not known: Depression, aggression(predominantly in children)

Eye disorders
Not known: vision, blurred (see section 4.4)

Respiratory, thoracic and mediastinal disorders
Common: Hoarseness/ Dysphonia.
Not known: Epistaxis
In some patients inhaled fluticasone propionate may cause hoarseness. It maybe helpful to rinse out the mouth with water immediately after inhalation.
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. Fluticasone propionate should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

Gastrointestinal Disorders
Very rare: Dyspepsia

Skin and subcutaneous tissue disorders
Common: Contusions

Musculoskeletal & Connective Tissue Disorders
Very rare: Arthralgia

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: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
Acute inhalation of fluticasone propionate doses in excess of those approved may lead to temporary suppression of the hypothalamic-pituitary-adrenal axis. This does not usually require emergency action, as normal adrenal function typically

recovers within a few days.

If higher than approved doses are continued over prolonged periods, significant adrenocortical suppression is possible. There have been very rare reports of acute adrenal crisis occurring in children exposed to higher than approved doses (typically 1000 micrograms daily and above), over prolonged periods (several months or years) observed features included hypoglycaemia and sequelae of decreased consciousness and/or convulsions. Situations which could potentially trigger acute adrenal crisis include exposure to trauma, surgery, infection or any rapid reduction in dosage.

Management
Patients receiving higher than approved doses should be managed closely and the dose reduced gradually.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other drugs for obstructive airway diseases, inhalants, glucocorticoids. ATC code: R03B A05

Pharmacodynamic effects
Fluticasone propionate given by inhalation at recommended doses has a glucocorticoidanti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma, without the adverse effects observed when corticosteroids are administered systemically.

Fluticasone propionate containing medications in asthma during pregnancy
An observational retrospective epidemiological cohort study utilising electronic health records from the United Kingdom was conducted to evaluate the risk of MCMs following first trimester exposure to inhaled FP alone and salmeterol-FP combination relative to non-FP containing ICS. No placebo comparator was included in this study.

Within the asthma cohort of 5362 first trimester ICS-exposed pregnancies, 131 diagnosed MCMs were identified; 1612 (30%) were exposed to FP or salmeterol-FP of which 42 diagnosed MCMs were identified. The adjusted odds ratio for MCMs diagnosed by 1 year was 1.1(95%CI:0.5– 2.3) for FP exposed vs non-FPICS exposed women with moderate asthma and 1.2 (95%CI:0.7– 2.0)for women with considerable to severe asthma. No differencein the risk of MCMs was identified following first trimester exposure to FP alone versus salmeterol-FP combination. Absolute risks of MCM across the asthma severity strata ranged from 2.0 to 2.9 per 100 FP-exposed pregnancies which is comparable to results from a study of 15,840 pregnancies unexposed to asthma therapies in the General Practice Research Database (2.8 MCM events per 100 pregnancies).

Clinical efficacy and safety
COPD
TORCH wasa 3-year study to assess the effect of treatment with Seretide Diskus50/500 mcgbd, salmeterol Diskus 50mcgbd, fluticasone propionate(FP) Diskus 500mcgbd or placebo on all-cause mortality in patients with COPD. COPD patients with a baseline (pre-bronchodilator) FEV1<60% of predicted normal were randomised to double-blind medication. During the study, patients were permitted usual COPD therapy with the exception of other inhaled corticosteroids, long-acting bronchodilators and long-termsystemic corticosteroids. Survival status at 3 years was determined for all patients regardless of withdrawal from study medication. The primary endpoint was reduction in all cause mortality at 3 years for Seretide vs Placebo.

	Placebo N=1524	**Salmeterol50 N=1521**	**FP500 N=1534**	**Seretide50/500**
All cause mortality at 3 years				
Number of deaths	231 (15.2%)	205 (13.5%)	246 (16.0%)	193 (12.6%)
Hazard Ratio vs Placebo (CIs)	N/A	0.879 (0.73, 1.06)	1.060 (0.89, 1.27)	0.825 (0.68, 1.00)
p value		0.180	0.525	0.05211
Hazard Ratio Seretide 50/500 vs components	N/A	0.932 (0.77, 1.13) 0.481	0.774 (0.64, 0.93) 0.007	N/A
1. Non significant P value after				

adjustment for 2 interim analyses on the primary efficacy comparison				

There was a trend towards improved survival in subjects treated with Seretide compared with placebo over 3 years however this did not achieve the statistical significance level p≤0.05.

The mean number of moderate to severe exacerbations per year was significantly reduced with Seretide as compared with treatment with salmeterol, FP and placebo (mean rate in the Seretide group 0.85 compared with 0.97 in the salmeterol group, 0.93 in the FP group and 1.13 in the placebo). This translates to a reduction in the rate of moderate to severe exacerbations of 25% (95% CI:19% to31%; p<0.001) compared with placebo, 12% compared with salmeterol (95%CI:5% to19%, p=0.002) and 9% compared with FP (95%CI:1% to 16%,p=0.024). Salmeterol and FP significantly reduced exacerbation rates compared with placebo by15% (95%CI:7% to 22%;p<0.001)and 18%(95%CI: 11%to 24%;p<0.00l) respectively.

Health Related Quality of life, as measured by the St George's Respiratory Questionnaire (SGRQ) was improved by all active treatments in comparison with placebo. The average improvement over three years for Seretide compared with placebo was -3.1 units (95%CI:-4.1 to-2.1;p<0.001), compared with salmeterol was -2.2 units (p<0.001) and compared with FP was-1.2 units(p=0.017). A4-unit decrease is considered clinically relevant.

The estimated 3-year probability of having pneumonia reported as an adverse event was 12.3% for placebo, 13.3% for salmeterol, 18.3% for FP and 19.6% for Seretide (Hazard ratio for Seretide vs placebo: 1.64, 95%CI: 1.33 to 2.01, p<0.001). There was no significant difference in probability of bone fracture (5.1% placebo, 5.1% salmeterol, 5.4% FP and 6.3% Seretide; Hazard ratio for Seretide vs placebo:1.22, 95% CI: 0.87 to 1.72, p=0.248).

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of fluticasone propionate for each of the available inhaler devices has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data. In healthy adult subjects the absolute bioavailability of fluticasone propionate inhaler is (10.9%). In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed.

Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. The remainder of the inhaled dose may be swallowed but contributes minimally to systemic exposure due to the low aqueous solubility and pres systemic metabolism, resulting in oral availability of less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose.

Distribution
Fluticasone propionate has a large volume of distribution at steady-state (approximately 300l).Plasma proteinbinding ismoderately high(91%).

Biotransformation
Fluticasone propionate is cleared very rapidly from the systemic circulation. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Other unidentified metabolites are also found in the faeces.

Elimination
The disposition of fluticasone propionate is characterised by high plasma clearance (1150ml/min) and a terminal half-life of approximately 8 hours.

The renal clearance of fluticasone propionate is negligible. Less than 5% of the dose is excreted in urine, mainly as metabolites. The main part of the dose is excreted in faeces as metabolites and unchanged drug.

5.3 Preclinical safety data

Toxicology has shown only those class effects typical of potent corticosteroids, and these only at doses in excess of that proposed for therapeutic use. No novel effects were identified in repeat dose toxicity tests, reproductive studies or teratology studies. Fluticasone propionate is devoid of mutagenic activity in-vitro and in-vivo and showed no tumorigenic potential in

rodents. It is both non-irritant and nonsensitizing in animal models.

Subcutaneous embryofetal development studies in mouse and rat at 45 and 100 mcg/kg, respectively (approximately equivalent to 4 and 6 times the maximum recommended daily inhaled dose of 500 mcg twice daily in adults based on mouse and rat plasma levels of 486 and 710 pg/mL, respectively) resulted in fetal developmental toxicity characteristic of a potent corticosteroid, including cleft palate and embryonic fetal growth retardation, at doses that caused maternal toxicity. The no effect level for these finding in rat were associated with systemic exposures approximately 3 times the highest clinical exposure based on rat plasma level of 310 pg/mL. In the rabbit, fetal weight reduction and cleft palate occurred at a maternally toxic subcutaneous dose of 4 mcg/kg (less than 1.4 times the maximum recommended inhaled dose of 500 mcg twice daily based on rabbit plasma level of 149 pg/mL). However, fluticasone propionate administered via inhalation to rats did not induce teratogenicity at maternal toxic doses associated with exposures 13 times the human exposure achieved with the maximum recommended daily inhaled dose based on rat plasma level of 1430 pg/mL.

The non-CFC propellant, HFA134a, has been shown to have no toxic effect at very high vapor concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years

The use of HFA 134a as a propellant has not altered the toxicity profile of fluticasone propionate compared to that using the conventional CFC propellant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Do not refrigerate or freeze.
Protect from direct sunlight.

As with most medicines in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold. If the inhaler gets very cold, take the metal canister out of the plastic case and warm it in your hands for a few minutes before use. Never use anything else to warm it up. Replace the mouth piece cover firmly and snap into position.

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

6.5 Nature and contents of container

An inhaler comprising an aluminium alloy canister sealed with a metering valve, actuator and cap. Each canister contains 120 metered actuations.

Pack sizes:

1 or 2 canisters. Each canister contains 120 metered actuations.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Patients should be carefully instructed **in the correct** use of the inhaler (see section 4.2).

7 MARKETING AUTHORISATION HOLDER

Cipla Europe NV
De Keyserlei 58-60, Box-19
2018 Antwerp
Belgium

8 MARKETING AUTHORISATION NUMBER

PA1963/012/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd October 2015
Date of last renewal: 17th July 2019

10 DATE OF REVISION OF THE TEXT

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