Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clenil Modulite 200 micrograms per metered dose Pressurised Inhalation Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 50 micrograms of beclometasone dipropionate.
Each metered dose contains 100 micrograms of beclometasone dipropionate.
Each metered dose contains 200 micrograms of beclometasone dipropionate.
Each metered dose contains 250 micrograms of beclometasone dipropionate.

Excipient with known effect
Clenil Modulite 50 micrograms per metered dose contains 7.683 mg ethanol.
Clenil Modulite 100 micrograms per metered dose contains 7.638 mg ethanol.
Clenil Modulite 200 micrograms per metered dose contains 8.267 mg ethanol.
Clenil Modulite 250 micrograms per metered dose contains 8.929 mg ethanol.

3 PHARMACEUTICAL FORM

Pressurised inhalation, solution.
The solution is clear and colourless.

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 Peak Expiratory Flow (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 or oral corticosteroid therapy. Sudden worsening of symptoms, which may be potentially life-threatening, may require increased corticosteroid dosage, which should be administered under urgent medical supervision.

Clenil Moduilte is indicated for the prophylactic management of mild, moderate, or severe asthma in:

Adults
Mild asthma (PEF valves greater than 80 % predicted at baseline with less than 20 % variability): Patients requiring intermittent symptomatic bronchodilator asthma medication on a regular basis.

Moderate asthma (PEF valves 60 % to 80 % predicted at baseline with 20 % to 30 % variability): Patients with unstable or worsening asthma despite prophylactic therapy or bronchodilator alone.

Severe asthma (PEF valves greater than 60 % predicted at baseline with greater than 30 % variability): Patients with severe chronic asthma and those who are dependent on systemic corticosteroids for adequate control of symptoms.

Children
Any child who requires prophylactic asthma medication.

4.2 Posology and method of administration

Posology

Clenil Moduliteis for oral inhalation use only. A spacer device may be used with ClenilModulite in patients who have difficulty synchronising aerosol actuation with inspiration of breath.

The dosage of beclometasone dipropionate should be adjusted according to the individual response.

The starting dose of inhaled beclometasone dipropionate should be adjusted to the severity of the disease. The dose may then be adjusted until control is achieved and then should be titrated to the lowest dose at which effective control of asthma is maintained.

Adults (including the elderly) and adolescents 12 years of age and older
Mild asthma: 200 micrograms to 600 micrograms per day, in divided doses

Moderate asthma: 600 micrograms to 1000 micrograms per day, in divided doses

Severe asthma: 1000 micrograms to 2000 micrograms per day, in divided doses

The spacer device must always be used when Clenil Modulite is administered to adults and adolescents taking total daily doses of 1000 micrograms or greater.

Children over 4 years of age
Up to 400 micrograms per day, in divided doses

Patients with hepatic or renal impairment
No dosage adjustment is needed in patients with hepatic or renal impairment.

Method of Administration
The aerosol spray is inhaled through the mouth into the lungs. The correct administration is essential for successful therapy. The patient must be instructed on how to use Clenil Modulite correctly and advised to read and follow the instructions printed on the Patient Information Leaflet carefully.

Instructions for Use
Patients should be instructed in the proper use of their inhaler (see patient information leaflet). During inhalation, the patient should preferably sit or stand. The inhaler has been designed for use in a vertical position.

Testing the inhaler:
If the inhaler is new or has not been used for three days or more, one puff should be released into the air. It is not necessary to shake the inhaler before use because this is a solution aerosol.

Instruct the patient to remove the mouthpiece cover and check that it is clean and free from foreign objects. The patient should then be instructed to breathe out before placing the inhaler into their mouth. They should then close their lips around the mouthpiece and breathe in steadily and deeply. They must not bite the mouthpiece. After starting to breathe in through the mouth, the top of the inhaler should be pressed down. Whilst the patient is still breathing in, the patient should then remove the inhaler from their mouth and hold their breath for about 5 to 10 seconds, or as long as is comfortable, and then breathe out slowly. The patient must not breathe out into the inhaler. If another dose is required the patient should be advised to wait 30 seconds before repeating the procedure just described. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The patient should be told not to rush the procedure described. It is important that the patient breathes in as slowly as possible prior to actuation. Inform the patient that if a mist appears on inhalation, the procedure should be repeated.

There is a dose indicator on the back of the inhaler which tells you how many puffs are left, the dose indicator rotates by a small amount when a puff is delivered. The number of puffs remaining is displayed in intervals of 20.

Patients should consider getting a replacement when the indicator shows the number 20. The indicator will stop at 0 when all the recommended puffs have been used. Replace the inhaler when the indicator reads 0.

It may be helpful to advise children and patients with weak hands to hold the inhaler with two hands, by placing both forefingers on top of the inhaler and both thumbs at the bottom of the device.

Patients who find it difficult to co-ordinate actuation with inspiration of breath should be told to use a spacer device to ensure proper administration of the product.

Young children may find it difficult to use the inhaler properly and will require help. Using the inhaler with a spacer device with a face mask may help in young children.
Advise the patient to thoroughly rinse the mouth or gargle with water or brush the teeth immediately after using the inhaler.

The patient should be told of the importance of cleaning the inhaler at least weekly to prevent any blockage and to carefully follow the instructions on cleaning the inhaler printed on the Patient Information Leaflet. The inhaler must not be washed or put in water.

The patient should be told also to refer to the Patient Information Leaflet accompanying the spacer device for the correct instructions on its use and cleaning.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 if short-acting relief bronchodilator treatment becomes less effective, or more inhalations than usual are required as 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).

Clenil Modulite does not provide relief of acute asthma symptoms, which require a short-acting inhaled bronchodilator. Patients should have relief medication available.

Patients should be properly instructed on the use of the inhaler to ensure that the drug reaches the target areas within the lungs.

Patients should also be informed of the prophylactic nature of that Clenil Moduliteand that it should be used on a regular basis, even when they are asymptomatic.

Severe exacerbations of asthma must be treated in the usual way, ie. by increasing the dose of inhaled beclometasone dipropionate, giving a systemic steroid if necessary, and/or an appropriate antibiotic if there is an infection, together with b-agonist therapy.

Systemic effects of inhaled corticosteroids may occur, particularly when prescribed at high doses 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 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. If growth is slowed, therapy should be reviewedwith the aim of reducing the dose of inhaled corticosteroids, if possible, to the lowest dose at which effective control of asthma is maintained. In addition, considerationshould also be given to referring the patient to a paediatric respiratory specialist.

Certain individuals may show greater susceptibility to the effects of inhaled corticosteroids. Prolonged treatment with high doses of inhaled corticosteroids may result in clinically significant adrenal suppression.

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.
The transfer to Clenil Moduliteof patients, who have been treated with systemic steroids for long periods of time or at high doses, needs special care, since recovery from possible adrenocortical suppression may take considerable time. Reduction of the dose of systemic steroid can be commenced approximately one week after initiating treatment with Clenil Modulite. The

size of the reduction should correspond to the maintenance dose of systemic steroid. For patients receiving maintenance doses of 10 mg daily or less of prednisolone (or equivalent) reductions in dose of not more than 1 mg are suitable. For higher maintenance doses, larger reductions in dose may be appropriate. These oral dosage reductions should be introduced at not less than weekly intervals.

Adrenocortical function should be monitored regularly as the dose of systemic steroid is gradually reduced.

Some patients feel unwell during withdrawal of systemic steroids despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled beclometasone dipropionate and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients weaned off oral steroids whose adrenocortical function is impaired should carry a steroid warning card indicating that they may need supplementary systemic steroids during periods of stress, eg. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc.

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.

Treatment with Clenil Moduliteshould not be stopped abruptly.

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

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Clenil Modulite contains less than 9 mg of alcohol (ethanol) in each actuation. which is equivalent to 0.88 mg/kg per dose in adults and 1,54 mg/kg per dose in children. The maximum amount of ethanol per dose in this medicine is equivalent to less than 2 ml of wine or beer. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

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

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. 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

There is inadequate evidence of safety of beclometasone dipropionate or norflurane (HFA-134a) propellant in human pregnancy.

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 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. 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.

There is no experience with or evidence of safety of norflurane (HFA-134a) propellant in human pregnancy or lactation. However, studies of the effect of norflurane on reproductive function and embryo-fetal development in animals have revealed no clinically relevant adverse effects.

No specific studies examining the transfer of beclometasone dipropionate into the milk of lactating animals have been performed.

It is reasonable to assume that beclometasone dipropionate is secreted in milk, but at the dosages used for direct inhalation, there is low potential for significant levels in breast milk.

The use of beclometasone dipropionate during pregnancy or in breast-feeding mothers requires that the expected therapeutic benefits of the drug outweigh any potential risks to the mother, fetus or neonate.

4.7 Effects on ability to drive and use machines

Clenil Modulite is unlikely to affect the ability to drive or operate machinery.

4.8 Undesirable effects

The frequency of Adverse Reactions has been classified as follows :
Very common (≥ 1/10)
Common (≥ 1/100 < 1/10)
Uncommon (≥ 1/1,000 < 1/100)
Rare (≥ 1/10,000 < 1/1,000)
Very rare (< 1/10,000) including isolated reports

Common, uncommon and very common adverse events were 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 adverse events were determined from spontaneous data.

System organ Class	Adverse Reaction	Frequency
Infections and Infestations	Oral candidiasis (of the mouth and throat)	Very Common
Immune System Disorders	Hypersensitivity reaction with the following manifestations:	
	Rash, urticaria, pruritus, erythema	Uncommon
	Oedema of the eyes, face, lips and throat	Very Rare
Endocrine Disorders	Adrenal suppression*, growth retardation* (in children and adolescents), bone density decreased*, Cushing's syndrome, Cushingoid features	Very Rare
Psychiatric Disorders (see section 4.4 Special warnings and precautions for use)	Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural disorders (predominantly in children)	Unknown
Nervous System Disorders	Headache	Unknown
Eye Disorders	Cataract*, glaucoma*	Very Rare
	Vision, blurred (see also section 4.4)	Unknown
Respiratory, Thoracic and Mediastinal Disorders	Hoarseness, throat irritation	Common
	Paradoxial bronchospasm, wheezing, dyspnoea, cough	Very Rare
Gastrointestinal Disorders	Nausea	Unknown

*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).

Candidiasis of the mouth and throat (thrush) occurs in some patients, the incidence increasing with doses greater than 400 micrograms beclometasone dipropionate per day. Patients with high blood levels of *Candida precipitins,* indicating a previous infection, are most likely to develop this complication. Patients may find it helpful to rinse their mouth thoroughly with water after inhalation. Symptomatic oral candidiasis can be treated with topical antifungal therapy while continuing with Clenil Modulite.

Hoarseness or throat irritation may occur in some patients. These patients should be advised to rinse the mouth out with water immediately after inhalation. The use of a large volume spacer device may be considered.

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

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, Website: www.hpra.ie

4.9 Overdose

Acute: Inhalation of doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action. In these patients treatment should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol.

Chronic: Use of inhaled beclometasone dipropionate in daily doses in excess of 1,500 micrograms over prolonged periods may lead to adrenal suppression. Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Glucocorticoid
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-monopropionate" (B--17--MP), which has potent topical anti-inflammatory activity.

5.2 Pharmacokinetic properties

Absorption
When administered via inhalation by a metered dose inhaler (MDI), systemic absorption of unchanged beclometasone dipropionate (BDP) occurs through the lungs. There is negligible oral absorption of the swallowed dose of unchanged BDP. Prior to absorption there is extensive conversion of BDP to its active metabolite B--17--MP. The systemic absorption of B--17--MP arises from both lung deposition and oral absorption of the swallowed dose. The absolute bioavailability following inhalation is approximately 60 % of the nominal dose for B--17--MP. BDP is absorbed rapidly with peak plasma concentrations observed (tmax) at 0.3 hour. B--17--MP appears more slowly with a tmax of 1 hour. There is an approximately linear increase in systemic exposure with increasing inhaled dose. When administered orally the bioavailability of BDP is negligible but pre-systemic conversion to B--17--MP results in 40 % of the dose being absorbed as B--17--MP.

Distribution
The tissue distribution at steady-state for BDP is moderate (20 L) but more extensive for B--17--MP (424 L). Plasma protein binding is moderately high (87 %).

Metabolism
BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The main product of metabolism is the active metabolite (B--17--MP). Minor inactive metabolites, beclometasone-21-monopropionate (B--21--MP) and beclometasone (BOH), are also formed but these contribute little to the systemic exposure.

Elimination
The elimination of BDP and B--17--MP are characterised by high plasma clearance (150 L / hour and 120 L / hour) with corresponding terminal elimination half-lives of 0.5 hour and 2.7 hour. Following oral administration of tritiated BDP, approximately 60 % of the dose was excreted in the faeces within 96 hours mainly as free and conjugated polar metabolites.

Approximately 12 % of the dose was excreted as free and conjugated polar metabolites in the urine. The renal clearance of BDP and its metabolites is negligible.

5.3 Preclinical safety data

Preclinical safety studies indicate that beclometasone dipropionate shows negligible systemic toxicity when administered by inhalation.

The non-CFC norflurane (HFA-134a) propellant has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (Hydrofluoroalkane, HFA-134a)
Ethanol, anhydrous
Glycerol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

As with most inhaled medicines in aerosol canisters, the therapeutic effect may decrease when the canister is cold.

6.5 Nature and contents of container

A pressurised, aluminium canister fitted with a metering valve, actuator and dust cap.

Each canister contains 200 metered doses.

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

Patients should be carefully monitored in the proper use of their inhaler.

7 MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
26A via Palermo
43122 Parma
Italy

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th September 2005
Date of last renewal: 30th September 2010

10 DATE OF REVISION OF THE TEXT

March 2023