Module 1.3.1.1: PACKAGE INSERT FOR

CICLOVENT 80 / 160 (Pressurised inhalation solution)

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

CICLOVENT 80 (Pressurised inhalation solution)

CICLOVENT 160 (Pressurised inhalation solution)

COMPOSITION:

CICLOVENT 80: 1 puff delivers 80 µg ciclesonide (ex actuator).

CICLOVENT 160: 1 puff delivers 160 µg ciclesonide (ex actuator).

Inactive ingredients are anhydrous ethanol, lecithin and tetrafluoroethane (HFA-134a propellant).

PHARMACOLOGICAL CLASSIFICATION:

A 21.5.1 Corticosteroids and analogues.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Ciclesonide, an inhaled topical corticosteroid, displays a low affinity for binding to the glucocorticoid receptor. After oral inhalation, the enzymatic conversion of ciclesonide to the principal metabolite (C21-des-isobutyryl-ciclesonide) occurs in the lungs. The

metabolite is considered to be the active principle, since it has prominent anti-inflammatory activity.

Pharmacokinetic properties:

Ciclesonide is presented as a solution aerosol in ethanol and HFA-134a propellant. Between different doses, inhaler strengths and systemic exposure, a linear relationship is displayed.

Absorption:

Both ciclesonide and its active principle have an insignificant oral bioavailability (< 0,5 % and < 1 %, respectively). In healthy subjects lung deposition is 52 % and, in keeping with this percentage, systemic bioavailability of the active principle when using the ciclesonide metered dose inhaler, is > 50 %. The swallowed portion of inhaled ciclesonide does not add to systemic absorption, due to the active principle's low oral bioavailability (< 1 %).

Distribution:

The volume of distribution of ciclesonide following intravenous administration is 2,9 ℓ/kg on average. A high hepatic extraction is indicated by the high (average 2,0 ℓ/h/kg) total serum clearance of ciclesonide. The plasma protein binding of ciclesonide and its active principle (on average 99 % and 98 – 99 %, respectively), indicates near complete binding to human plasma proteins. As a result, only the unbound ciclesonide fraction (< 1 %) is available for further systemic pharmacodynamic effects.

Metabolism:

In the lung, ciclesonide is mainly hydrolysed by esterase enzymes to its biologically active metabolite. Examination of further enzymatic metabolism by human hepatic microsomes indicates that this compound is primarily metabolised by CYP3A4 to inactive hydroxylated metabolites.

Excretion:

Following intravenous and oral administration, ciclesonide is mainly excreted via the faeces, demonstrating that the main route of elimination is excretion via the bile.

INDICATIONS:

CICLOVENT is indicated as prophylactic treatment of asthma in adults, adolescents and children 6 years of age and older.

CONTRAINDICATIONS:

CICLOVENT is contraindicated:

- In patients with known hypersensitivity to ciclesonide or any of the ingredients of **CICLOVENT**.
- In children under 6 years of age, as safety and efficacy have not been established (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

WARNINGS AND SPECIAL PRECAUTIONS:

There is insufficient data available in children under 6 years of age. Therefore, the use of **CICLOVENT** in this age group is not recommended (see **"CONTRAINDICATIONS"**).

In patients with severe hepatic impairment, no data are available, and an increased exposure is anticipated in these patients. Therefore, patients with severe hepatic impairment should be monitored for potential systemic effects.

To decrease the risk of developing systemic corticosteroid effects, e.g. adrenal suppression, decreased bone mineral density, growth retardation in adolescents, glaucoma and cataract, the **CICLOVENT** dose should be titrated to the lowest effective dose at which asthma control is maintained (see **"SIDE-EFFECTS"**).
In patients with pulmonary tuberculosis **CICLOVENT** must be used with caution.

Treatment with **CICLOVENT** is not indicated in status asthmaticus or in cases where intensive measures are necessary to treat acute episodes of asthma.

CICLOVENT is not intended to relieve symptoms of acute asthma; an inhaled short-acting bronchodilator is necessary to relieve such symptoms. Patients should be advised to have their rescue medication available.

In patients with severe asthma regular assessments of asthma control, including pulmonary function tests, are needed, since these patients are at risk of acute asthma attacks.

Deterioration of asthma control is indicated by increasing use of short-acting bronchodilators to relieve symptoms of asthma. Advise patients to seek medical attention if they require more inhalations of their short-acting relief bronchodilator than usual, or if it becomes less effective. In this case, patients must be reassessed.

If increased anti-inflammatory therapy is required, a higher dose of **CICLOVENT** or a course of oral corticosteroids should be considered. Severe exacerbations of asthma must be managed in the usual way.

When transferring a patient from oral steroids to **CICLOVENT** the risk of impaired adrenal reserve may continue for a significant period of time. Therefore, the possibility of experiencing unwanted effects may continue for some time. To establish the degree of adrenal impairment, these patients may need specialised advice before elective procedures. In elective and emergency (medical or surgical) situations expected to cause stress, the possibility of impairment of adrenal response must always be taken into account and consideration given to the use of suitable oral or parenteral corticosteroid treatment.

Paradoxical bronchospasm after dosing, with an immediate increase in symptoms of bronchoconstriction or wheezing, must be treated with an inhaled short-acting bronchodilator, which usually causes rapid relief. Treatment with **CICLOVENT** may only be continued after assessment of the patient, and if after careful consideration the expected benefit is considered to outweigh the potential risk. The association between the severity of asthma and the general susceptibility to acute bronchial reactions have to be taken into account (see **"SIDE-EFFECTS"**).

Patients must be advised not to stop treatment with **CICLOVENT** abruptly.

In order to ensure optimal delivery to the lungs, patient inhaler technique should be evaluated on a regular basis to ensure that inspiration is coordinated with inhaler actuation.

Effects on ability to drive and use machines:

CICLOVENT has no or an insignificant effect on the patient's ability to drive or use machines.

INTERACTIONS:

Clinically relevant interactions are unlikely, as the serum levels of both ciclesonide and its active principle, the metabolite M1, are low.

Concurrent use of **CICLOVENT** and a potent cytochrome P450 3A4 inhibitor (such as ketoconazole, ritonavir, itraconazole or nelfinavir) should be avoided, as there may be an increase in serum levels of ciclesonide / metabolite M1.

No mutual interaction has been demonstrated between ciclesonide and erythromycin (a CYP3A4 probe substrate).

PREGNANCY AND LACTATION:

The use of **CICLOVENT** during pregnancy and lactation is not recommended as safety and efficacy have not been established.

DOSAGE AND DIRECTIONS FOR USE:

CICLOVENT is for inhalation use only.

Adults and adolescents:

The total daily dose of **CICLOVENT** ranges from 80 µg (ex actuator) to 320 µg (ex actuator) and may be administered as a single daily inhalation in the morning or evening, or in 2 divided doses.

Children 6 years and older:

The recommended daily dose of **CICLOVENT** ranges from 80 µg (ex actuator) to 160 µg (ex actuator) and may be administered as a single daily inhalation in the morning or evening, or in 2 divided doses.

The **CICLOVENT** dose must be individualised and titrated to the lowest effective dose required to control asthma.

No information is available on the use of **CICLOVENT** with a spacer.

The patient must be in a stable phase when transferring from an oral steroid to **CICLOVENT**. The oral steroid should be administered concurrently with a high dose of **CICLOVENT** for approximately 10 days. After this period of time, the oral steroid dose may be decreased slowly to the lowest level at which asthma control is maintained. Eventually, it may be possible in many patients to completely withdraw the oral steroid with **CICLOVENT** treatment; however other patients may require maintenance of a low dose of oral steroid. These patients continue to be at risk of adrenal reserve impairment for a significant period of time after transferring to **CICLOVENT**.

Elderly and patients with hepatic or renal impairment:

No dosage adjustment is required in the elderly or in patients with renal or hepatic impairment.

Children under 6 years of age:

There is insufficient data available in children under 6 years of age. Therefore, the use of **CICLOVENT** in this age group is not recommended (see **"CONTRAINDICATIONS"**).

Instructions for use / handling:

Patients should be instructed on the correct use of the **CICLOVENT** inhaler.

Three puffs should be released into the air before using the **CICLOVENT** inhaler for the first time, or if it has not been used for a week or longer. As **CICLOVENT** is a solution aerosol it is not necessary to shake the inhaler.

The mouthpiece cover should be removed and the mouthpiece of the inhaler placed into the patient’s mouth. The lips should be closed around the mouthpiece.

The patient should start to breathe in slowly and deeply through the mouth and the top of the inhaler should be pressed down after the patient has started to breathe in.

After inhalation, the inhaler should be removed from the patient’s mouth and the breath held for approximately 10 seconds, or as long as is comfortable. The patient should be instructed to breathe out slowly and to replace the cover of the mouthpiece. The patient should not exhale into the **CICLOVENT** inhaler.

The **CICLOVENT** inhaler should be cleaned on a weekly basis by wiping the mouthpiece with a clean, dry cloth or tissue. The patient should not wash or place the **CICLOVENT** inhaler in water.

SIDE-EFFECTS:

The following side-effects may occur with the use of **CICLOVENT**:

Infections and infestations:

Less frequent: Oropharyngeal candidiasis.

Immune system disorders:

Less frequent: Immediate or delayed hypersensitivity reactions, such as angioedema with swelling of lips, tongue and pharynx.

Respiratory, thoracic and mediastinal disorders:

Frequent: Paradoxical bronchospasm (immediately after dosing), hoarseness.

Less frequent: Cough after inhalation.

Gastrointestinal disorders:

Less frequent: Unpleasant (bad) taste.

Skin and subcutaneous tissue disorders:

Less frequent: Rash and eczema.

General disorders and administrative site conditions:

Less frequent: Application site reactions, including inflammation, irritation, burning and application site dryness.

CICLOVENT may cause systemic corticosteroid effects, especially when used at high doses and for extended periods (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Acute overdose:

After overdose of inhaled ciclesonide, the potential for developing acute toxic effects is low. No specific treatment is required following acute overdosage.

Chronic overdose:

Adrenal suppression may develop to some extent; therefore the adrenal reserve may need to be monitored. Treatment of chronic overdosage is symptomatic and supportive.

IDENTIFICATION:

Clear solution free from visible particles.

PRESENTATION:

CICLOVENT 80: Carton containing a metered dose inhaler, of 60 or 120 doses, consisting of plain silver aluminium container without any

coating, fitted with a silver metallic metering valve and a plastic actuator having a maroon body and buff cap.

CICLOVENT 160: Carton containing a metered dose inhaler, of 60 or 120 doses, consisting of plain silver aluminium container without any coating, fitted with a silver metallic metering valve and a plastic actuator having a maroon body and grey cap.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

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

REGISTRATION NUMBERS:

CICLOVENT 80: 43/21.5.1/1168

CICLOVENT 160: 43/21.5.1/1169

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD

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RSA

DATE OF PUBLICATION OF THE PACKAGE INSERT:

First published: 05 June 2014

Revised: 26 May 2020