SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LASECON 160 mcg/actuation Inhalation Aerosol, Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single actuation (delivered dose from the mouthpiece):
Active substance:
Ciclesonide 160 micrograms

Excipients:
Anhydrous ethanol 4.74 mg

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Inhalation aerosol
Concave bottom metal tube with plastic activator and dosing valve

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is used in all stages of asthma to reduce the need for anti-inflammatory, bronchodilator, symptom control and oral steroids.

It is not recommended to be used alone in COPD.

4.2 Posology and method of administration

Posology:
Adults:
The recommended initial dose of LASECON is 160 micrograms once daily. However, in a 12-week study, in severe asthma patients, a dose of 640 mcg/day (given as 320 mcg twice daily) reduced the frequency of exacerbations but did not improve lung function (see section 5.1). For some patients, 80 micrograms once daily may also be preferred as an effective maintenance dose.

For pediatric patients aged 6-11 years:
80-160 mcg may be used once daily, depending on the patient's clinical condition.

Frequency and duration of administration:
LASECON is used once a day in the evening or morning. The final decision on what time of day (evening or morning) patients will use LASECON should be left to the discretion of the physician. Symptoms start to improve with LASECON within 24 hours of treatment. Once asthma control is achieved, the dose of LASECON is individualized according to the patient’s condition and the minimum maintenance dose at which the disease can be well controlled is preferred.

Patients with severe asthma are at risk of acute attacks and should have regular assessments of their asthma control including pulmonary function tests. Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control. If patients find that short-acting

relief bronchodilator treatment becomes less effective, or they need more inhalations than usual, medical attention must be sought.

In this situation, patients should be reassessed and consideration given to the need for increased anti-inflammatory treatment therapy (e.g. a higher dose of LASECON or a course of oral corticosteroids). Severe asthma exacerbations should be managed the usual way.

Method of administration:
LASECON is for inhalation use only.
The needs of patients who have difficulty adjusting their breathing function while simultaneously activating the inhaler device should not be ignored. In such cases, LASECON can be used with the help of a suitable air chamber (spacer).

Recommendations for use:
The patient needs to be instructed how to use the inhaler correctly.

If LASECON is to be taken out of its box and used for the first time or has not been used for more than 1 week, it should be sprayed into the air 3 times before administration. No shaking is necessary as this is a solution aerosol.

During inhalation, the patient should preferably sit or stand, and the inhaler should be held upright with the thumb on the base, below the mouthpiece.

The patient should be instructed to remove the mouthpiece cover, place the inhaler into their mouth, close their lips around the mouthpiece, and breathe in slowly and deeply. While breathing in through the mouth, the top of the inhaler should be pressed down once. Then, patients should remove the inhaler from their mouth, and hold their breath for about 10 seconds, or as long as is comfortable. The patient is not to breathe out into the inhaler. Finally, patients should breathe out slowly and replace the mouthpiece cover.

The mouthpiece should be cleaned with a dry tissue or cloth weekly. The inhaler should not be washed or put in water.

Additional information on special populations:
Renal/Hepatic impairment
No dose adjustment is required in patients with hepatic impairment.
However, there is no sufficient data on the dose of the drug in severe hepatic and renal failure.

Pediatric population
Ciclesonide is not recommended for children under 6 years of age, as there are insufficient data on the use of ciclesonide in the treatment of this age group.

Geriatric population
No dose adjustment is required in elderly patients.

4.3 Contraindications

LASECON is contraindicated in patients with hypersensitivity to ciclesonide or to any of the excipients.

4.4 Special warning and precautions for use

As with all other inhaled corticosteroids, LASECON should be used with caution in patients with active or asymptomatic pulmonary tuberculosis or fungal, viral or bacterial infections only if these patients are adequately treated.

As with all inhaled corticosteroids, LASECON is not indicated in the treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

As with all inhaled corticosteroids, LASECON is not designed to relieve acute asthma symptoms for which an inhaled short-acting bronchodilator is required. Patients should be advised to have such rescue medication available.

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 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 therefore important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

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.

Pediatric population
It is recommended that the height of children and adolescents 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.

Hepatic impairment
There is no data available in patients with severe hepatic impairment. An increased exposure in patients with severe hepatic impairment is expected and these patients should therefore be monitored for potential systemic effects.

Adrenal impairment
The benefits of inhaled ciclesonide should minimise the need for oral steroids. However, patients transferred from oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled ciclesonide. The possibility of respective symptoms may persist for some time. Before any intervention, these patients may need to be taken under the supervision of a specialist in terms of adrenal insufficiency. The possibility of residual impaired adrenal response should always be considered in a medical or surgical emergency and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

Switching to inhaled ciclesonide in patients being treated with oral corticosteroids:
The transfer of oral steroid-dependent patients to inhaled ciclesonide, and their subsequent management, needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time.

Patients who have been treated with systemic steroids for long periods of time, or at a high dose, may have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.

Gradual withdrawal of the systemic steroid is started by reducing the dose by 1 mg prednisolone per week, or equivalent amount of other derivatives. For maintenance doses of prednisolone in excess of 10 mg daily, it may be appropriate to cautiously use larger reductions in dose at weekly intervals.

Some patients feel unwell in a non-specific way during these gradual withdrawal phases, even though their respiratory functions do not change or even improve. They should be encouraged to persevere with inhaled ciclesonide and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency.

Patients transferred from oral steroids to inhaled ciclesonide whose adrenocortical function is still impaired should carry a steroid warning/information card indicating that they need supplementary systemic steroid during periods of stress (e.g. increased frequency of 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 systemic drug.

Paradoxical bronchospasm with an immediate increase of wheezing or other symptoms of bronchoconstriction after dosing should be treated with an inhaled short-acting bronchodilator, which usually results in quick relief. The patient should be assessed and therapy with LASECON should only be continued, if after careful consideration the expected benefit is greater than the possible risk. Correlation between severity of asthma and general susceptibility for acute bronchial reactions should be kept in mind (see section 4.8).

Patients inhaler technique should be checked regularly to make sure that inhaler actuation is synchronised with inhaling to ensure optimum delivery to the lungs.

Concomitant treatment with ketoconazole or other potent CYP3A4 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 side effects of corticosteroids (see section 4.5), in which case patients should be monitored for systemic corticosteroid side-effects.

Pneumonia in COPD patients
An increased incidence of pneumonia, including pneumonia requiring hospitalization, has been observed in COPD patients receiving inhaled medications containing corticosteroids. There is evidence of an increased risk of pneumonia with increasing steroid doses, but this has not been conclusively demonstrated across studies.

There is no definitive clinical evidence for an intraclass difference in the magnitude of the pneumonia risk of corticosteroid-containing inhaled medications. Physicians should be vigilant against the

potential development of pneumonia in COPD patients due to the potential for confounding between the clinical features of infections and exacerbations of COPD symptoms.

Risk factors for pneumonia in COPD patients include smoking, older age, low body mass index, and severe COPD.

This medicine contains 4.74 mg of ethanol in each spray. The amount in a dose of this medicine is equivalent to less than 1 ml beer or wine.
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

In vitro data indicate that CYP3A4 is the major enzyme involved in the metabolism of the active metabolite of ciclesonide M1. In a drug-drug interaction study at steady state with ciclesonide and ketoconazole as a potent CYP3A4 inhibitor, the exposure to the active metabolite M1 increased approximately 3.5-fold, whereas the exposure to ciclesonide was not affected. Therefore the concomitant administration of potent inhibitors of CYP 3A4 (e.g. ketoconazole, itraconazole cobicistat-containing products and ritonavir or nelfinavir) should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids, in which case patients should be monitored for systemic corticosteroid side-effects.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is “C”.

Women of child-bearing potential / Birth control (Contraception)
No data available.

Pregnancy
There are no adequate and well-controlled studies in pregnant women.

In animal studies glucocorticoids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended inhalation doses.

As with other glucocorticoids, ciclesonide should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus. The lowest effective dose of ciclesonide needed to maintain adequate asthma control should be used.

Infants born of mothers who received corticosteroids during pregnancy are to be observed carefully for hypoadrenalism.

Lactation
It is unknown whether inhaled ciclesonide is excreted in human breast milk. Administration of ciclesonide to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Reproductive ability / Fertility
Adequate clinical data are no available.

4.7 Effects on ability to drive and use machines

Ciclesonide inhalation has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Approximately 5% of patients experienced adverse reactions in clinical trials with ciclesonide given in the dose range 40 to 1280 micrograms per day. In the majority of cases, these were mild and did not require discontinuation of treatment with ciclesonide.

The frequency of undesirable effects, including ciclesonide and reactions reported in patients treated with ciclesonide, is listed below. The effects observed with ciclesonide are usually dose- or concentration-dependent.

Undesirable effects are listed by the following categories:
Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations
Common: Pneumonia (in patients with COPD)
Uncommon: Oral fungal infections*

Immune system disorders
Rare: Angioedema, hypersensitivity

Psychiatric disorders
Not known: Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavior changes (predominantly in children)

Nervous system disorders
Uncommon: Headache*

Eye Disorders
Uncommon:Blurred vision (see section 4.4)
Not known: Central serous chorioretinopathy

Cardiac disorders
Rare: Palpitations**

Vascular disorders
Rare: Hypertension

Respiratory, thoracic and mediastinal disorders
Uncommon: Paradoxical bronchospasm*, cough after inhalation*, dysphonia

Gastrointestinal disorders
Uncommon: Nausea, vomiting*, bad taste
Rare: Abdominal pain*, dyspepsia*

Skin and subcutaneous tissue disorders
Uncommon: Eczema, rash

General disorders and administration site conditions
Uncommon: Application site reactions, application site dryness

(*) Similar or lower incidence when compared with placebo
(**) Palpitations were observed in clinical trials in cases mostly confounded with concomitant medication with known cardiac effects (e.g. theophylline or salbutamol).

Paradoxical bronchospasm may occur immediately after dosing and is an unspecific acute reaction to all inhaled medicinal products, which may be related to the active substance, the excipient, or evaporation cooling in the case of metered dose inhalers. In severe cases, withdrawal of LASECON should be considered.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the national reporting system

4.9 Overdose

Acute: Inhalation by healthy volunteers of a single dose of 2880 micrograms of ciclesonide was well tolerated.
The potential for acute toxic effects following overdose of inhaled ciclesonide is low. No specific treatment is necessary after acute overdosage.

Chronic: After prolonged administration of 1280 micrograms of ciclesonide, no clinical signs of adrenal suppression were observed. However, if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression cannot be excluded. In this case, monitoring of adrenal reserve may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: R03BA08
Pharmacotherapeutic group: Other drugs for obstructive airway diseases (inhalants) / Glucocorticoids

Ciclesonide exhibits low binding affinity to the glucocorticoid-receptor. Once orally inhaled, ciclesonide is enzymatically converted in the lungs to the principal metabolite C21-des-methylpropionyl-ciclesonide (M1). C21-des-methylpropionyl-ciclesonide, the active metabolite of ciclesonide, has strong local anti-inflammatory activity.

Clinical efficacy and safety

In four clinical trials, ciclesonide has been shown to reduce airway hyperresponsiveness to adenosine monophosphate in hyperreactive patients with maximal effect observed at the dose of 640 micrograms. In another trial, pretreatment with ciclesonide for seven days significantly attenuated the early and late phase reactions following inhaled allergen challenge. Inhaled ciclesonide treatment was also shown to attenuate the increase in inflammatory cells (total eosinophils) and inflammatory mediators in induced sputum.

A controlled study compared 24-hour plasma cortisol AUC (area under the concentration-time curve) in 26 adult asthmatic patients following 7 days of treatment. Compared to placebo, treatment with ciclesonide 320, 640, and 1,280 micrograms/day did not statistically significantly lower the 24-hour time averages of plasma cortisol nor was a dose-dependent effect seen.

In a clinical trial involving 164 adult male and female asthmatic patients, ciclesonide was given at doses of 320 micrograms or 640 micrograms/day over 12 weeks. At the end of the 12th week, patients were administered 1 or 250 micrograms of cosyntropin, no significant changes in plasma cortisol levels were observed versus placebo.

Double-blind placebo-controlled trials of 12-weeks duration in adults and adolescents have shown that treatment with ciclesonide resulted in improved lung function as measured by FEV_1 and peak expiratory flow, improved asthma symptom control, and decreased need for inhaled beta-2 agonist.

In a 12-week study of 680 severe asthmatics, previously treated with 500-1000 micrograms fluticasone propionate per day or equivalent, 87.3% and 93.3% of patients remained exacerbation-free during treatment with 160 or 640 micrograms of ciclesonide, respectively. At the end of the 12 week study period, the results showed a statistically significant difference between the doses of 160 micrograms and 640 micrograms/day ciclesonide with regard to the occurrence of an exacerbation after the first day of the study: 43 patients/339 (12.7%) in the 160 micrograms/day group and 23 patients/341 (6.7%) in the 640 micrograms/day group (Hazard ratio=0.523 p=0.0134). Both ciclesonide doses resulted in comparable FEV1 values at 12 weeks.Treatment-related adverse events were seen in 3.8% and 5% of patients treated with 160 or 640 micrograms per day of ciclesonide respectively.

A further 52 week trial involving 367 patients with mild to moderate asthma, was unable to demonstrate a significant difference in the effect of higher doses of ciclesonide (320 or 640 mcg per day) as compared to a lower dose (160 mcg per day) on asthma control.

5.2 Pharmacokinetic properties

General properties
Ciclesonide is presented in HFA-134a propellant and ethanol as a solution aerosol, which demonstrates a linear relationship between different doses, puff strengths and systemic exposure.

Absorption
Studies with oral and intravenous dosing of radiolabeled ciclesonide have shown an incomplete extent of oral absorption (24.5%). The oral bioavailability of both ciclesonide and the active metabolite is negligible (<0.5% for ciclesonide, <1% for the metabolite). Based on a γ-scintigraphy experiment, lung deposition in healthy subjects is 52%. In line with this figure, the systemic bioavailability for the active metabolite is >50% by using the ciclesonide metered dose inhaler. As the oral bioavailability for the active metabolite is <1%, the swallowed portion of the inhaled ciclesonide does not contribute to systemic absorption.

Distribution
Following intravenous administration to healthy subjects, the initial distribution phase for ciclesonide was rapid and consistent with its high lipophilicity. The volume of distribution averaged 2.9 L/kg. The total serum clearance of ciclesonide is high (average 2 L/h/kg) indicating a high hepatic extraction. The percentage of ciclesonide bound to human plasma proteins averaged 99%, and that of the active metabolite 98-99%, indicating an almost complete binding of circulating ciclesonide/active metabolite to plasma proteins.

Biotransformation
Ciclesonide is primarily hydrolyzed to its biologically active metabolite by esterase enzymes in the lung. Investigation of the enzymology of further metabolism by human liver microsomes showed that this compound is mainly metabolized to hydroxylated inactive metabolites by CYP3A4 catalysis. Furthermore, reversible lipophilic fatty acid ester conjugates of the active metabolite were detected in the lung.

Elimination
Ciclesonide is predominantly excreted via the feces (67%), after oral and intravenous administration, indicating that excretion via the bile is the major route of elimination.

Linearity/Non-linearity
Its pharmacokinetics are linear. At recommended therapeutic doses, systemic exposure is dose-proportional.

Characteristics in patients
Hepatic impairment
Reduced liver function may affect the elimination of corticosteroids. In a study including patients suffering from liver cirrhosis, a higher systemic exposure to the active metabolite was observed.

Renal impairment
Studies have not been conducted in patients with renal insufficiency due to the inability of the active metabolite to be excreted by the kidneys.

Geriatric population
According to population pharmacokinetics, age has no impact on the systemic exposure of the active metabolite.

Others
Ciclesonide shows no pharmacokinetic changes in mild asthmatic patients compared to healthy subjects.

5.3 Preclinical safety data

Preclinical data with ciclesonide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential.

In animal studies on reproductive toxicity, glucocorticosteroids have been shown to induce malformations such as cleft palate, skeletal malformations. However, these animal results do not seem to be relevant for humans given recommended doses.

A treatment-related effect on the ovaries (namely atrophy) was observed at the top dose in two 12-month studies in dogs. This effect occurred at systemic exposures 5.27-8.34 times those noted at the 160 mcg daily dose. The relevance of this finding to humans is unknown.

Animal studies with other glucocorticoids indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the risk for intrauterine growth retardation, adult cardiovascular and/or metabolic disease and/or changes in glucocorticoid receptor density, neurotransmitter turnover and behavior. The relevance of these data to humans administered ciclesonide by inhalation is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous ethanol
Hydrofluoroalkane HFA 134a (Pharma Grade)

6.2 Incompatibilities

It does not have any known incompatibilities.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

An aluminum vial (tube) with a metering valve, containing 60 doses of aerosol inhalation solution, and a package leaflet are supplied in a cardboard box.

Each canister (tube and valve) is placed in a plastic sprayer (activator) with a orange-red body and an orange-red cap equipped with a dust cover to ensure the required spraying in accordance with the intended use of the inhaler.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. 34303 No.:1
Küçükçekmece / İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2017/245

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 13.04.2017
Date of last renewal :

10. DATE OF REVISION OF THE TEXT