SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ciclesonide ADVANZ PHARMA 80 mcg per metered dose pressurised inhalation, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ciclesonide ADVANZ PHARMA 80 mcg per metered dose pressurised inhalation, solution:

1 actuation (delivered dose from the mouthpiece) contains 80 micrograms of ciclesonide

The canisters are fitted into plastic actuators incorporating an atomising orifice and fitted with green dust cap.

Excipient with known effect:

1 actuation contains 4.7 mg of ethanol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, solution

Clear and colourless

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciclesonide Advanz Pharma is indicated in treatment to control persistent asthma in

adults and adolescents (12 years and older).

4.2 Posology and method of administration

The medicinal product is for inhalation use only.

Posology

Dosing recommendation for adults and adolescents:

The recommended dose of Ciclesonide Advanz Pharma is 160 micrograms once daily, which leads to asthma control in the majority of patients. In patients with severe asthma and while reducing or discontinuing oral corticosteroids a higher dose of up to 640 mcg/day may be used (see section 5.1). Patients should be given a dose of inhaled ciclesonide which is appropriate to the severity of their disease.

Symptoms start to improve with Ciclesonide Advanz Pharma within 24 hours of treatment. Once control is achieved, the dose of Ciclesonide Advanz Pharma should be individualised and titrated to the minimum dose needed to maintain good asthma control.

Dose reduction to 80 micrograms once daily may be an effective maintenance dose for some patients.

Ciclesonide Advanz Pharma should preferably be administered in the evening although morning dosing of Ciclesonide Advanz Pharma has also been shown to be effective. The final decision on evening or morning dosing should be left to the discretion of the physician.

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 Ciclesonide Advanz Pharma for a short period (see section 5.1) or a course of oral corticosteroids). Severe asthma exacerbations should be managed the usual way.

To address specific patient needs, such as finding it difficult to press the inhaler and breathe in at the same time, Ciclesonide Advanz Pharma can be used with the AeroChamber Plus Flow-Vu spacer device.

Special populations

Elderly and patients with renal or hepatic impairment

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

Paediatric population

The safety and efficacy of ciclesonide in children aged under 12 years have not yet been established. No sufficient data are available.

Method of administration

Precautions to be taken before handling or administering the medicinal product

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

If the inhaler is new or has not been used for one week or more, three puffs should be released into the air. 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.

Instruct the patient 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. 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.

For instructions on use of medicinal product before administration, see section 6.6.

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

As with all inhaled corticosteroids, Ciclesonide Advanz Pharma should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal, viral or bacterial infections, and only if these patients are adequately treated.

As with all inhaled corticosteroids, Ciclesonide Advanz Pharma 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, Ciclesonide Advanz Pharma 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.

Paediatric 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. These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in an emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

For the transfer of 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.

After approximately a week, gradual withdrawal of the systemic steroid is started by reducing the dose by 1 mg prednisolone per week, or its equivalent. 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 the withdrawal phase despite maintenance or even improvement of respiratory function. 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 whose adrenocortical function is still impaired should carry a steroid warning card indicating that they need supplementary systemic steroid during periods of stress, e.g. 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 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 Ciclesonide Advanz Pharma 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.

This medicine contains 4.7 mg of alcohol (ethanol) in each dose. 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 man. 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

Fertility and 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.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

Ciclesonide Advanz Pharma 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 Advanz Pharma 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 Advanz Pharma.

Frequency / **System Organ Class**	**Uncommon (>1/1 000, <1/100)**	**Rare (1/10 000 – 1/ 1 000)**	**Not known** (cannot be estimated from the available data)
Cardiac Disorders		Palpitations**	
Gastrointestinal Disorders	Nausea, vomiting* Bad taste	Abdominal pain* Dyspepsia*	
General disorders and administration site conditions	Application site reactions Application site dryness		
Immune System Disorders		Angioedema Hypersensitivity	
Infections and infestations	Oral fungal infections*		
Nervous System Disorders	Headache*		

Frequency / System Organ Class	**Uncommon (>1/1 000, <1/100)**	**Rare (1/10 000 – 1/ 1 000)**	**Not known** (cannot be estimated from the available data)
Eye disorders	Blurred vision (see also section 4.4)		Central Serous Chorioretinopathy
Psychiatric Disorders			Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough after inhalation* Paradoxical bronchospasm*		
Skin and subcutaneous tissue disorders	Eczema and rash		
Vascular disorders		Hypertension	

* 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 Ciclesonide Advanz Pharma 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 also section 4.4).

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 the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. After acute overdosage no specific treatment is necessary.

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. Monitoring of adrenal reserve may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, Inhalants, Glucocorticoids, ATC Code: R03B A08

Mechanism of action

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) which has a pronounced antiinflammatory activity and is thus considered as the active metabolite.

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 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 ($AUC_{(0-24)}$/24 hours) 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. After stimulation with 1 and 250 micrograms 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 500-1,000 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=0.526; p= 0.0134). Both ciclesonide doses resulted in comparable FEV_1 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

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 2.0 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 hydrolysed 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 faeces (67%), after oral and intravenous administration, indicating that excretion via the bile is the major route of elimination.

Pharmacokinetic/pharmacodynamics relationship(s):

Asthmatic patients

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

Elderly

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

Renal or hepatic impairment

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

Due to the lack of renal excretion of the active metabolite, studies on renal impaired patients have not been performed.

5.3 Preclinical safety data

Non-clinical 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 (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 160µg 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 permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour. The relevance of these data to humans administered ciclesonide by inhalation is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane
Ethanol, anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

The container contains a pressurised liquid. Do not expose to temperatures higher than 50°C.

The container should not be punctured, broken or burnt even when apparently empty.

6.5 Nature and contents of container

The inhaler comprises a pressurized container made from aluminium and is sealed with a metering valve, mouthpiece and cap both in polypropylene.

Ciclesonide Advanz Pharma 80 micrograms per actuation pressurised inhalation has a green dust cap.

Package size: 1 inhaler with 120 metered actuations

6.6 Special precautions for disposal

Patients should be carefully instructed in the proper use of their inhaler (see Patient Information Leaflet).

As with most inhaled medicinal products in pressurised containers, the therapeutic effect of this medicinal product may decrease when the container is cold. However, Ciclesonide Advanz Pharma delivers a consistent dose from –10°C to 40°C.

If the inhaler gets very cold, take the inhaler out of the plastic case and warm it in your hands for few minutes before use. Never use anything else to warm it up.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PLGB 56734/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/04/2024

10 DATE OF REVISION OF THE TEXT

25/04/2024