SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clipper 5 mg gastro-resistant prolonged release tablets ▼

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of beclometasone dipropionate
Excipient with known effect: lactose monohydrate
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant prolonged release tablets
Each ivory white, coated tablet is round and convex

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The tablets are indicated for the treatment of mild or moderate ulcerative colitis in active phase, as add-on therapy to 5-ASA containing drugs in patients who are non-responders to 5-ASA therapy in active phase.

4.2 Posology and method of administration

Posology

Dosage Recommendations
Adults
One Clipper 5 mg tablet a day to be taken in the morning before or after a light breakfast.

Therapy cycles of not more than four weeks are recommended.

Elderly
No special dose adjustment is recommended. However, experience with Clipper in the elderly is limited.

Paediatric Population
There is no experience with Clipper in the paediatric population. Clipper is not recommended for use in children.

Method of Administration

Tablets must be swallowed whole with a little liquid. The tablets should not be broken or chewed.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Tubercular, local mycotic and viral infections

4.4 Special warnings and precautions for use

As there are no data in patients with severe hepatic impairment, treatment with Clipper in these patients is not recommended.

There are no data in patients with hepatic or renal insufficiency, so these patients should only be treated with caution.

Use with caution in patients with tuberculosis, diabetes mellitus, gastro-duodenal ulcer, serious arterial hypertension, osteoporosis, hypoadrenalism, glaucoma and cataract.

In case of pre-existing intestinal infection, or where such infection arises during treatment, appropriate antibiotic therapy must be instituted immediately.

Clinical safety data on treatment duration of more than four weeks are not available, therefore, the use of the product for longer periods is not recommended.

After four weeks of treatment a reduction of the plasmatic levels of corticosteroids has been observed in up to 25% of patients treated with Clipper 5 mg per day. This percentage is much lower if compared to the percentage of patients treated with oral systemic corticosteroids, such as prednisolone at a dose of 40 mg per day, showing plasma cortisol levels below the normal range (76 % after eight weeks of treatment, published data). This is due to the low systemic availability of the active metabolite, beclometasone-17-monopropionate (B-17-MP), after administration of Clipper 5 mg per day, which is approximately 20% compared to the intravenous dose. The effect on HPA–axis could be considered as transient and a recovery of HPA function is expected to occur after withdrawal of the drug. However, due to the lack of follow up data after the usual treatment period, careful supervision of patients' clinical symptoms is recommended.

In case of prolonged treatment, possible adverse effects related to the suppression of HPA-axis may occur (see section 4.8). The suppression of the HPA-axis can reduce the stress response. Where patients are subject to surgery or other stresses, supplementary glucocorticoids treatment is recommended.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting the treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 pharmacokinetic interactions that can increase the risk of side effects), although dose levels do not allow prediction of the

onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.
Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depression or manic-depressive illness and previous steroid psychosis.

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.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed.

As beclometasone dipropionate undergoes a very rapid metabolism via esterases enzymes without involvement of cytochrome P450, it 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.

Clipper in clinical studies has been used in conjunction with oral or rectal treatment with mesalazine. Even if no specific pharmacodynamic interactions have been studied, clinical trials did not evidence any increase of adverse events severity due to the association of BDP with 5-ASA products. In addition, according to the different pharmacokinetic pathway of the two drugs, metabolic interactions are not expected to occur.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy
Data on a large number of exposed pregnancies indicate no adverse effects of 1 mg per day beclometasone dipropionate (after inhalation), on pregnancy or on the health of the newborn child. To date, no other relevant epidemiological data on oral administration of 5 mg beclometasone dipropionate are available. High doses of systemic corticosteroids for longer periods may cause intrauterine growth retardation.

Studies in animals have shown reproductive toxicity (see section 5.3). Clipper should not be used during pregnancy, unless strictly indicated after a careful risk / benefit evaluation. Foetal growth should be monitored.

Breast-feeding
It is not known whether beclometasone dipropionate is excreted in human milk. A risk to the newborns/infants cannot be excluded. Due to the lack of data, the administration of Clipper during lactation is not recommended unless strictly indicated after a careful risk / benefit evaluation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported with systemic corticosteroids. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated at 5-6%.
Psychological effects have been reported on withdrawal of corticosteroids; the frequency is not known.

The adverse reactions found during clinical studies in patients treated with 5 mg of Clipper were all classified as mild or moderate and were all uncommon (≤ 1/100 and > 1/1000):

SYSTEM ORGAN CLASS	UNDESIRABLE EFFECT
Psychiatric disorders	anxiety
Nervous system disorders	headache, somnolence
Gastrointestinal disorders	nausea, constipation, abdominal pain
Musculoskeletal and connective tissue disorders	muscle cramps
Reproductive system and breast disorders	menorrhagia
General disorders & administration site conditions	influenza like illness, pyrexia

During clinical trials carried out with Clipper 5 mg tablets a reduction of plasma cortisol levels at the end of four weeks treatment has been observed in up to 25 % of patients, however, clinical symptoms associated with adrenal suppression have not been reported.
Particularly at high doses of systemic corticosteroids taken for long periods, rare (≤ 1/1000 and > 1/10000) systemic adverse events may occur.

These may include:

SYSTEM ORGAN CLASS	UNDESIRABLE EFFECT
Infections and infestations	oropharyngeal candidiasis
Blood and the lymphatic system disorders	lymphopenia, monocytopenia, granulocytosis
Endocrine disorders	adrenal suppression, cushingoid

Metabolism and nutrition disorders	obesity
Nervous system disorders	headache, benign intracranial hypertension
Eye disorders	cataract and glaucoma
Skin and subcutaneous tissue disorders	lipohypertrophy, rosacea,
Musculoskeleta ,and connective tissue disorders	osteoporosis

Adverse events with frequency not known (cannot be estimated from the available data) have been identified as class risk effect of corticosteroids:

SYSTEM ORGAN CLASS	UNDESIRABLE EFFECT
Eye disorders	Vision blurred (see also section 4.4)
Respiratory, thoracic and mediastinal disorders	Hiccups

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

4.9 Overdose

No cases of overdose have so far been reported. However, in case of acute or chronic intake exceeding the therapeutic dose, the following measures should be taken :

Acute
Ingestion of the drug in doses in excess of those recommended may lead to temporary suppression of adrenal function. This does not require emergency action.

Chronic
Monitoring of adrenal reserve may be indicated. Treatment should be continued at a dose sufficient to control the ulcerative colitis and no more.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Corticosteroids for local use
ATC Code: A07E A07

Mechanism of action and pharmacodynamic effects

Clipper tablets contain beclometasone dipropionate (BDP), a pro-drug with weak glucocorticoid receptor binding affinity. BDP is hydrolysed via esterase enzymes to the active metabolite, beclometasone-17-monopropionate (B-17-MP), which has high topical anti-inflammatory activity (approximately thirty times the potency of BDP).

Scintigraphic study in healthy volunteers with Clipper demonstrated that tablets' integrity was maintained whilst the preparation resided within the stomach. Once in the small intestine, the tablets remained intact for a considerable period of time (57 to 118 minutes), before showing initial signs of disintegration. The prolonged release tablets core gradually eroded and a complete disintegration was achieved within 4 to 5 hours in the proximal colon and small intestine.

Clinical efficacy and safety

Effects on the pituitary-adrenal axis were evaluated in four clinical studies as well as in clinical pharmacology study conducted in ulcerative colitis patients. Even if serum morning cortisol level was influenced by the administration of Clipper Tablets, which lead to a suppression of the endogenous cortisol level at the end of treatment in a maximum of 25 % of patients, no corticosteroid-related adverse drug reaction was reported during the limited treatment period of the clinical trials.

As treatment with Clipper Tablets lasts for no more than four weeks, the effect on HPA–axis could be considered as transient and a recovery of HPA function is expected to occur after withdrawal of the drug.

5.2 Pharmacokinetic properties

Beclometasone dipropionate (BDP), is very rapidly hydrolysed to its active metabolite (B-17-MP), via esterase enzymes found mostly in liver and lung tissues. In human serum and intestinal juices, B-17-MP is probably formed by pancreatine. Minor inactive metabolites, beclometasone-21-monopropionate (B-21-MP), and beclometasone (BOH), are also formed. The hydrolysis of BDP in the intestinal fluids was confirmed during a study aimed to quantitate BDP and its metabolites in ileostomy effluents of patients who had a terminal ileostom. Following intravenous dosing, the disposition of BDP and B-17-MP are characterised by high plasma clearance (150 L per hour and 120 L per hour, respectively), with a small volume of distribution at steady state for BDP (20 L) and larger tissue distribution for B-17-MP (424 L). The terminal elimination half-lives are 0.5 hour and 2.7 hours for BDP and B-17-MP, respectively. Plasma protein binding is moderately high. The renal excretion of BDP and its metabolites is negligible. Faecal excretion is the major route of BDP elimination mainly as polar metabolites.

The pharmacokinetics of BDP and its active metabolite, B-17-MP after single and repeated oral administrations of Clipper was evaluated in ulcerative colitis disease patients. BDP levels were always under the limit of quantitation (< 20 µg per ml). The maximum plasma concentration of B-17-MP obtained after

two weeks treatment with Clipper 5 mg, once daily, appeared to be similar, ie., approximately 1 ng per ml, to the C_{max} observed with a 1 mg dose of BDP administered by inhalation. The systemic availability of B-17-MP evaluated in comparison with an intravenous dose was about 20 %.

5.3 Preclinical safety data

Chronic toxicity studies with beclometasone dipropionate resulted in dose dependent effects typical of glucocorticoids.

Beclometasone dipropionate is non-genotoxic and no evidence of carcinogenicity was observed in rats.

Reproduction toxicity studies in animals have revealed teratogenic and embryo-foetal effects in mice and rabbits and an increased abortion rate and retarded uterine growth in monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

In Tablet Core
Lactose monohydrate
Hypromellose (E. 464)
Microcrystalline cellulose
Maize starch
Magnesium stearate

In Tablet Coat
Macrogol 4000
Methacrylic acid-methyl methacrylate copolymer (1:1)
Titanium dioxide (E. 171)
Talc

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

6.5 Nature and contents of container

PVC / PVDC / Al / PVDC blister
Packs of 10 or 30 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Chiesi Limited
333 Styal Road
Manchester
M22 5LG
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 08829/0153

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7th January 2005

10 DATE OF REVISION OF THE TEXT

28/06/2019