This submission: Clinical Safety Update and PI/PIL reformat
Date of submission: 05 July 2021 – Approved 05 Sep 2021

Professional information for CETIRIZINE 10 BIOTECH

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

CETIRIZINE 10 BIOTECH 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg cetirizine dihydrochloride.

Excipients with known effect:

Contains sugar: Each tablet contains 66,4 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

CETIRIZINE 10 BIOTECH tablets are white to off white, round, film-coated tablets scored on the one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Allergic processes responding to a histamine H_1 receptor antagonist.

- Respiratory: Allergic rhinitis, hay fever.
- Cutaneous: Allergic skin conditions associated with pruritus e.g. urticaria.

4.2 Posology and method of administration

Adults and children 12 years of age or older: one 10 mg tablet daily.

Children aged 6 to 12 years: 10 mg (one tablet) once daily or 5 mg (half a tablet) twice daily.

At present there are no data to suggest that the dose needs to be reduced in elderly patients with normal renal function.

Dosage in renal impairment:

In patients with renal insufficiency (creatinine clearance less than 40 mL/min), the dosage should be reduced to half the usual recommended dose.

Dosage in hepatic impairment:

Half the recommended daily dose should be used in patients with moderate to severe hepatic impairment.

Paediatric population

Not suitable for children less than 6 years of age.

4.3 Contraindications

- Hypersensitivity to cetirizine, to any of the excipients (see section 6.1), to hydroxyzine or to any piperazine derivatives.
- Patients with severe renal impairment at less than 30 mL/min creatinine clearance.

4.4 Special warnings and precautions for use

Caution should be taken in patients with predisposition factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as CETIRIZINE 10 BIOTECH may increase the risk of urinary retention.

Porphyria: Use with caution

CETIRIZINE 10 BIOTECH tablets may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressants and therefore caution is recommended if alcohol is taken concomitantly with CETIRIZINE 10 BIOTECH.

Caution is recommended when CETIRIZINE 10 BIOTECH is used in epileptic patients and patients at risk of convulsions.

Response to allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

Pruritus and/or urticaria may occur when CETIRIZINE 10 BIOTECH is stopped, even if those symptoms were not present before treatment initiation. In some cases, the symptoms may be

intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

CETIRIZINE 10 BIOTECH contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take CETIRIZINE 10 BIOTECH.

Paediatric population

The use of CETIRIZINE 10 BIOTECH is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation.

4.5 Interaction with other medicines and other forms of interaction

Neither pharmacodynamic nor significant pharmacokinetic interaction was reported in interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased.

In sensitive patients, the concurrent use of alcohol or other central nervous system (CNS) depressants may cause additional reductions in alertness and impairment of performance, although cetirizine does not potentiate the effect of alcohol (0,5 g/L blood levels).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy and lactation has not been established.

Prospectively collected data on pregnancy outcomes do not suggest potential for maternal or foetal/embryonic toxicity above background rates.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. CETIRIZINE 10 BIOTECH should not be used during pregnancy.

Breastfeeding

Cetirizine is excreted in breast milk. Cetirizine is excreted in
human milk at concentrations representing 25 % to 90 % those measured in plasma, depending on sampling time after
administration. CETIRIZINE 10 BIOTECH should not be used when breastfeeding.

Fertility

Limited data is available on human fertility, but no safety concern has been identified. Animal data show no safety concern for human reproduction.

4.7 Effects on ability to drive and use machines

Patients should be warned that some individuals may experience sedation. It is therefore advisable to determine individual response before driving a vehicle or operating machinery. This effect may be compounded by the simultaneous intake of alcohol or other central nervous system depressants**.**

4.8 Undesirable effects

CETIRIZINE 10 BIOTECH at the recommended dosage has minor adverse effects on the CNS, including somnolence, fatigue, dizziness and headache. In some cases, paradoxical CNS stimulation has been reported.

CETIRIZINE 10 BIOTECH is a selective antagonist of peripheral H_1-receptors and is relatively free of anticholinergic activity. Nevertheless, cases of micturition difficulties, eye accommodation disorders and dry mouth have been reported following the use of CETIRIZINE 10 BIOTECH.

Instances of abnormal hepatic function with elevated hepatic enzymes accompanied by elevated bilirubin have been reported following the use of CETIRIZINE 10 BIOTECH. This may resolve upon discontinuation of the medicine.

Clinical trials

Double blind controlled clinical trials comparing cetirizine to placebo or other antihistamines at the recommended dosage (10 mg daily for cetirizine), of which quantified safety data are available, included more than 3 200 subjects exposed to cetirizine.

The following adverse reactions were reported:

Psychiatric disorders

Frequent: somnolence

Nervous system disorders

Frequent: dizziness, headache

Respiratory, thoracic and mediastinal disorders

Frequent: pharyngitis

Gastrointestinal disorders

Frequent: dry mouth, nausea

Less frequent: abdominal pain

General disorders and administration site conditions

Frequent: fatigue

Somnolence was mild to moderate in the majority of cases.

Objective tests as demonstrated by other studies have demonstrated that usual daily activities are unaffected at the recommended daily dose in healthy young volunteers.

Post-marketing experience

In addition to the adverse reactions reported during clinical studies and listed above, the following undesirable effects have been reported in post-marketing experience.

Blood and the lymphatic system disorders

Less frequent: thrombocytopenia

Immune system disorders

Less frequent: hypersensitivity, anaphylactic shock

Metabolism and nutrition disorders

Less frequent: increased appetite

Psychiatric disorders

Less frequent: agitation, aggression, confusion, depression, hallucination, insomnia, tics

Frequency unknown: suicidal ideation, nightmare

Nervous system disorders

Less frequent: paraesthesia, convulsions, dysgeusia, dyskinesia, dystonia, syncope, tremor, drowsiness, fatigue, dizziness, headache, anxiety, nervousness

Frequency unknown: amnesia, memory impairment

Eye disorders

Less frequent: accommodation disorder, blurred vision, oculogyration

Ear and labyrinth disorders

Frequency unknown: vertigo

Cardiac disorders

Less frequent: tachycardia

Gastrointestinal disorders

Less frequent: diarrhoea, nausea, gastrointestinal discomfort, dry mouth

Hepatobiliary disorders

Less frequent: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)

Frequency unknown: hepatitis

Skin and subcutaneous tissue disorders

Less frequent: pruritis, rash, urticaria, angioneurotic oedema, fixed drug eruption

Frequency unknown: acute generalized exanthematous pustulosis

Musculoskeletal and connective tissue disorders

Frequency unknown: arthralgia

Renal and urinary disorders

Less frequent: dysuria, enuresis

Frequency unknown: urinary retention

General disorders and administrative site conditions

Less frequent: asthenia, malaise, oedema

Investigations

Less frequent: weight increased

Description of selected adverse reactions

After discontinuation of CETIRIZINE 10 BIOTECH, pruritus (intense itching) and/or urticaria have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdose

Symptoms observed after an overdose of CETIRIZINE 10 BIOTECH are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect.

Adverse events reported are: confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritis, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.

Management

There is no known specific antidote to CETIRIZINE 10 BIOTECH.

Should overdose occur, symptomatic or supportive treatment is recommended.

CETIRIZINE 10 BIOTECH is not effectively removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.7.1 Medicines affecting autonomic function. Antihistaminics

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivatives,

ATC code: R06A E07.

Cetirizine is a metabolite of hydroxyzine. It is a non-sedating reversible, competitive inhibitor of histamine at the histamine-1 (H_1) receptor, devoid of any significant anticholinergic and antiserotonergic effects. The anti-allergic activity seems to be exerted primarily via effects on the release of mediators such as histamine. Cetirizine inhibits the late phase recruitment of eosinophils, in the skin and conjunctiva of atopic subjects submitted to allergen challenge.

5.2 Pharmacokinetic properties

Absorption

After oral administration, cetirizine is well absorbed from the gastrointestinal tract and peak plasma concentrations are reached within 1 hour. The steady state peak plasma concentrations is approximately 300 ng/mL. The distribution of pharmacokinetic parameters such as peak plasma

concentration (C_{max}) and area under curve (AUC), is unimodal. Food decreases the rate but not the extent of absorption.

Distribution

The apparent volume of distribution is 0,50 L/kg. Cetirizine is highly bound to plasma proteins, however does not modify the protein binding of warfarin.

Biotransformation

Cetirizine is only marginally affected by first pass metabolism in the liver.

Elimination

The terminal half-life is approximately 10 hours in adults. Cetirizine is excreted primarily (60 %) unchanged in the urine. No accumulation is observed for cetirizine following daily doses of 10 mg for 10 days

Linearity/Non-linearity

Pharmacokinetics are linear with plasma concentrations increasing proportionately with increasing doses.

Special populations

Renal impairment

The pharmacokinetics of cetirizine was similar in patients with mild impairment (creatinine clearance higher than 40 mL/min) and healthy volunteers. Patients with moderate renal impairment had a 3-fold increase in half-life and 70 % decrease in clearance compared to healthy volunteers. Patients on hemodialysis (creatinine clearance less than 7 mL/min) given a single oral 10 mg dose of cetirizine had a 3-fold increase in half-life and a 70 % decrease in clearance compared to normals. Cetirizine was poorly cleared by haemodialysis. Dosing adjustment is necessary in patients with renal impairment (see section 4.2)

Hepatic impairment

Patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20 mg of cetirizine as a single dose had a 50 % increase in half-life along with a 40 % decrease in clearance compared to healthy subjects.

Elderly

Following a single 10 mg oral dose, half-life increased by about 50 % and clearance decreased by 40 % in 16 elderly subjects compared to younger subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Paediatric population

The half-life of cetirizine was about 6 hours in children of 6 – 12 years and 5 hours in children 2 – 6 years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal anhydrous silica

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose.

Film-coating:

Opadry White Y-1-7000 (consisting of hypromellose (E646), titanium dioxide (E171) and polyethylene glycol 400 (E1521)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

CETIRIZINE 10 BIOTECH tablets are available in white plastic bottles, patient ready packs or in clear plastic/silver aluminium blister packs containing 10, 20, 28, 30, 120 or 500 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand 1685

South Africa

8. REGISTRATION NUMBER

37/5.7.1/0086

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 02 July 2007

10. DATE OF REVISION OF THE TEXT

Submitted – 05 July 2021

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