XYZAL ORAL SOLUTION AND TABLETS

SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE:

XYZAL

Levocetirizine dihydrochloride 5 mg film-coated tablets

XYZAL ORAL SOLUTION

Levocetirizine dihydrochloride 0,5 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains 5 mg levocetirizine dihydrochloride.

Excipient with known effect:

Contains sugar (63,50 mg lactose monohydrate per tablet).

Each 1 mL oral solution contains 0,5 mg levocetirizine dihydrochloride.

Excipients with known effect:

0,675 mg methyl parahydroxybenzoate per mL

0,075 mg propyl parahydroxybenzoate per mL

Contains sugar (0,4 g maltitol per mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

XYZAL: film-coated tablets.

White to off-white, oval film-coated tablet with a Y logo on one side.

XYZAL ORAL SOLUTION: oral solution.

Clear and colourless solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

XYZAL is indicated for the relief of symptoms associated with the following allergic conditions:

- seasonal allergic rhinitis
- perennial allergic rhinitis
- chronic idiopathic urticaria.

4.2 Posology and method of administration:

XYZAL film-coated tablet:

The film-coated tablet must be taken orally, swallowed with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

Adults and adolescents 12 years of age and older:

The daily recommended dose is one 5 mg tablet.

Elderly:

Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see “Patients with renal impairment below”).

Children:

For children aged 2 – 6 years no adjusted dosage is possible with the film-coated tablet formulation. **It is recommended to use XYZAL ORAL SOLUTION** (see section 4.4).

Children aged 6 – 12 years:

The daily recommended dose is one 5 mg tablet.

XYZAL ORAL SOLUTION:

An oral syringe is included in the package. The appropriate volume of oral solution should be measured with the oral syringe and poured in a spoon or in a glass of water. The oral solution must be taken immediately after dilution and may be taken with or without food.

Adults and adolescents 12 years of age and older:

The daily recommended dose is 5 mg (10 mL) once daily.

Elderly:

Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Patients with renal impairment below).

Children:

Children aged less than 2 years:

The administration of XYZAL to infants and toddlers aged less than 2 years is not recommended (see section 4.4).

Children aged 2 – 6 years:

The daily recommended dose 2,5 mg to be administered in 2 intakes of 1,25 mg (2,5 mL of solution twice daily).

Children aged 6-12 years:

The daily recommended dose is 5 mg (10 mL) once daily.

Tablets and oral solution:

Patients with renal impairment:

The dosing interval must be individualised according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min is needed.

The CL_{cr} (mL/min) may be estimated from serum creatinine (µmol/L) determination using the following formula:

$$CL_{cr} = \frac{[140 - age\ (years)]\ x\ weight\ (kg)}{72\ x\ serum\ creatinine\ (\mu mol/dL)} \quad (x\ 0{,}85\ for\ women)$$

Dosing adjustments for patients with impaired renal function:

Group	**Creatine clearance (mL/min)**	**Dosage and frequency**
Normal	≥ 80	5 mg once daily
Mild	50-79	5 mg once daily
Moderate	30-49	5 mg once every 2 days
Severe	< 30	5 mg once every 3 days
End-stage renal disease – patients undergoing dialysis	< 10	Contraindicated

In paediatric patients suffering from renal impairment:

The dose will have to be adjusted on an individual basis taking into account the renal clearance of the patient and his/her body weight. There are no specific data for children with renal impairment.

Patients with hepatic impairment:

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see "Patients with renal impairment above").

Duration of use:

Intermittent allergic rhinitis (symptoms < 4 days/week or for less than 4 weeks a year) has to be treated according to the disease and its history; it can be stopped once the symptoms have disappeared and can be restarted again when symptoms reappear. In case of persistent allergic rhinitis (symptoms > 4 days/week or for more than 4 weeks a year), continuous therapy can be proposed to the patient during the period of exposure to allergens. Clinical experience with XYZAL film-coated tablets is currently available for a 6-months treatment period.

4.3 Contraindications:

XYZAL is contraindicated:

- in hypersensitivity to levocetirizine, to cetirizine, to hydroxyzine, to any piperazine derivative or to any of the excipients of XYZAL excipients listed in section 6.1
- in patients with end stage renal disease, at less than 10 mL/min creatinine clearance.

4.4 Special warnings and precautions for use:

Alcohol:

Precaution is recommended with concurrent intake of alcohol (see section 4.5). XYZAL lacks significant sedative effects. Patients should, however, be warned that a small number of individuals may experience sedation. This effect may be compounded by the simultaneous intake of alcohol or other central nervous system depressants (see section 4.5).

Risk of urinary retention:

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

Risk of seizure aggravation:

Caution should be taken in patients with epilepsy and patients at risk of convulsion as XYZAL may cause seizure aggravation.

Allergy skin tests:

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

Withdrawal syndrome:

Pruritus may occur when XYZAL is stopped even if those symptoms were not present before treatment initiation (see section 4.8). The symptoms may resolve spontaneously. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

Infants and children under 2 years:

Data are not sufficient to support the administration of XYZAL to infants and toddlers aged less than 2 years. Therefore, administration of XYZAL to infants and toddlers aged less than 2 years is not recommended.

Children aged less than 6 years:

The use of the film-coated tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use XYZAL ORAL SOLUTION.

Excipient warnings:

XYZAL tablets contain lactose. Patients with the rare hereditary problems of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take XYZAL tablets.

XYZAL ORAL SOLUTION contains:

Maltitol: Patients with the rare hereditary problems of fructose intolerance should not take XYZAL ORAL SOLUTION.

Methyl parahydroxybenzoate, propyl parahydroxybenzoate:

The presence of methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicines and other forms of interaction:

No interaction studies have been performed with XYZAL (including no studies with CYP3A4 inducers). Studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions (with ketoconazole, erythromycin, azithromycin, cimetidine, antipyrine, pseudoephedrine, glipizide and diazepam).

Theophylline:

A decrease in the clearance of cetirizine (16 %) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.

Ritonavir:

In a multiple dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40 % while the disposition of ritonavir was decreased (-11 %).

Food:

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

Alcohol:

In sensitive patients the concurrent administration of XYZAL and alcohol or other central nervous system (CNS) depressants may cause additional reductions in alertness and impairment of performance.

4.6 Fertility, pregnancy and lactation:

XYZAL is not recommended in pregnancy, as safety has not been demonstrated.

XYZAL is not recommended in women who are breastfeeding their babies, since the active ingredient is excreted in breast milk.

Fertility:

No clinical data are available.

4.7 Effects on the ability to drive and use machines:

Some patients could experience somnolence, fatigue and asthenia during therapy with XYZAL. Patients experiencing these should avoid driving, engaging in potentially hazardous activities or use of machines.

4.8 Undesirable effects:

Clinical trial data:

Adults and adolescents above 12 years of age:

In therapeutic studies in women and men aged 12 to 71 years, 15,1 % of the patients in the XYZAL 5 mg group had at least one adverse reaction.

In therapeutic trials, the dropout rate due to adverse events was 1,0 % (9/935) with XYZAL 5 mg. Clinical therapeutic trials with XYZAL included 935 subjects exposed to the medicine at the recommended dose of 5 mg daily.

Adverse reactions are ranked under headings of frequency using the following convention:

Very common ≥ 1/10

Common ≥ 1/100 to < 1/10

Uncommon ≥ 1/1 000 to < 1/100

Rare ≥ 1/10 000 to < 1/1 000

Very rare < 1/10 000

Not known (cannot be estimated from the available data).

Immune system disorders:

Not known: angioedema

Nervous system disorders:

Common: headache, somnolence

Gastrointestinal disorders:

Common: dry mouth

Uncommon: nausea and gastro-intestinal discomfort. Abdominal pain

General disorders and administration site conditions:

Common: fatigue

Uncommon: asthenia, malaise

Skin and subcutaneous tissue disorders:

In some individuals, hypersensitivity reactions including skin reactions, urticaria and pruritus may develop.

Paediatric patients:

In paediatric patients less than 6 years, 159 subjects were exposed to XYZAL at the dose of 1,25 mg daily for 2 weeks or 1,25 mg twice daily. The following incidence of side effects were reported under XYZAL.

Psychiatric disorders:

Common: sleep disorders

Nervous system disorders:

Common: somnolence

Gastrointestinal disorders:

Common: diarrhoea, constipation

Uncommon: vomiting

In children aged 6 – 12 years double blind placebo-controlled studies were performed where 243 children were exposed to 5 mg XYZAL daily for variable periods ranging from less than 1 week to 13 weeks. The following incidence of side effects were reported:

Nervous system disorders:

Common: somnolence

Uncommon: headache.

Post-marketing data:

Immune system disorders:

Not known: hypersensitivity including anaphylaxis

Metabolism and nutrition disorders:

Not known: increased weight, increased appetite

Psychiatric disorders:

Not known: aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmares

Nervous system disorders:

Not known: convulsions, paraesthesia, dizziness, syncope, tremor, dysgeusia

Eye disorders:

Not known: visual disturbances, blurred vision, oculogyration

Ear and labyrinth disorders:

Not known: vertigo

Cardiac disorders:

Not known: palpitations, tachycardia

Respiratory, thoracic and mediastinal disorders:

Not known: dyspnoea

Gastrointestinal disorders:

Not known: nausea, vomiting, diarrhoea

Hepatobiliary disorders:

Not known: hepatitis, abnormal liver function test

Skin and subcutaneous tissue disorders:

Not known: angioedema, fixed drug eruption, pruritus, rash, uriticaria

Musculoskeletal and connective tissue disorders:

Not known: myalgia, arthralgia

Renal and urinary disorders:

Not known: dysuria, urinary retention

General disorders and administration site conditions:

Not known: oedema.

Skin reactions occuring after discontinuation of XYZAL:

After discontinuation of XYZAL, pruritus has been reported (see section 4.4).

Reporting of suspected adverse events:

Reporting suspected adverse reactions after authorisation of XYZAL is important. It allows continued monitoring of the benefit/risk balance of XYZAL. Healthcare providers are asked to report any suspected adverse reactions to: SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may occur, followed by drowsiness.

There is no known specific antidote to XYZAL. Should overdose occur, symptomatic or supportive treatment is recommended. Levocetirizine is not effectively removed by haemodialysis.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A 5.7.1 Antihistaminics.

Levocetirizine, the (R) enantiomer of cetirizine, is a histamine H_1 receptor antagonist.

5.2 Pharmacokinetic properties:

Levocetirizine is absorbed after oral administration with peak blood levels reached 0,9 hours after oral administration. Plasma levels are linearly related between 2,5 mg and 20 mg.

The extent of metabolism is less than 14 % of the dose.

The plasma half-life is approximately 8 hours in adults. The half-life is shorter in small children. The main route of excretion is via urine, accounting for approximately 85 % of the dose. Approximately 13 % is excreted in the faeces.

Levocetirizine is 90 % bound to human plasma proteins.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

XYZAL film-coated tablets:

Colloidal anhydrous silica

Magnesium stearate

Lactose monohydrate

Microcrystalline cellulose

Opadry® Y-1-7000 (consisting of hypromellose (E464), titanium dioxide (E171), and macrogol 400).

XYZAL ORAL SOLUTION:

Sodium acetate (for pH adjustment)

Acetic acid (for pH adjustment)

Glycerol 85 %

Saccharin sodium

Maltitol liquid (E965)

Parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Tutti Frutti flavour (501103A)

Purified water.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

XYZAL film-coated tablets: 60 months.

XYZAL ORAL SOLUTION: 36 months.

6.4 Special precautions for storage:

Store at or below 30 °C. Protect XYZAL film-coated tablets from moisture.

6.5 Nature and contents of container

XYZAL film-coated tablets are packaged in blisters (polyamide/ aluminium/PVC complex with a push through aluminium lidding foil or polyamide/aluminium/PVC complex with lidding material of paper backed aluminium foil) of 7 or 10 tablets. 1 strip (7 or 10 tablets) or 3 strips (30 tablets) are packed into cardboard boxes.

XYZAL ORAL SOLUTION is packed in amber glass bottles containing 75 mL or 150 mL of solution and closed by a white polypropylene childproof cap. It is packed in a cardboard box with a graduated syringe for oral dosing.

6.6 Special precautions for disposal and other handling:

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS:

XYZAL film-coated tablets: 36/5.7.1/0425

XYZAL ORAL SOLUTION: 41/5.7.1/0032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

XYZAL film-coated tablets: 28 May 2004

XYZAL ORAL SOLUTION: 27 January 2010

10. DATE OF REVISION OF TEXT: