# Epirizine
# Film-coated Tablets – Syrup

**1. Name of the medicinal product**
Epirizine Film-coated Tablets – Syrup.

**2. Qualitative and quantitative composition**
Each dosage unit
Each film coated Tablet contains:
Cetirizine dihydrochloride…….10mg

Each 5ml contains
Cetirizine dihydrochloride…….5mg

**3. Pharmaceutical form:**
Tablet: Oval, White, biconvex film coated tablets, scored from one side.
Syrup: Viscous yellow syrupy liquid having a characteristic aromatic odor.
**Clinical particulars:**
**3.1 Therapeutic indications:**
**Epirizine** is indicated in adults and children aged 2 years and above:
- for the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis.
- for the relief of symptoms of chronic idiopathic urticaria.

**3.2 Posology and method of administration**
**Dosage:**
10 mg once daily (10 ml oral solution (2 full spoons) or 1 tablet).
**Special population:**
**Elderly:**
Data do not suggest that the dose needs to be reduced in elderly subjects provided that the renal function is normal.
**Renal impairment:**
There are no data to document the efficacy/safety ratio in patients with renal impairment. Since cetirizine is mainly eliminated via renal route, in cases no alternative treatment can be used, the dosing intervals must be individualized 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 (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140 - age(years)] x weight(kg)}{72 x serum\ creatinine(mg/dl)} (x0.85\ for\ women)$$

**Dosing adjustments for adult patients with impaired renal function:**

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

**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 Renal impairment above).
**Pediatric population:**
The tablet formulation should not be used in children under 6 years of age as it does not allow the necessary dose adjustments.
**Children aged from 2 to 6 years:** 2.5 – 5 mg daily.
**Children aged from 6 to 12 years:** 5 – 10 mg daily.
**Adolescents over 12 years of age:** 10 mg once daily (10 ml oral solution (2 full spoons) (1 tablet)).
In pediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance, age and body weight of the patient.
**Administration:**
The solution can be swallowed as such.
The tablets need to be swallowed with a glass of liquid.

**3.3 Contraindications:**
Hypersensitivity to the active substance, to any of the excipients listed, to hydroxyzine or to any piperazine derivatives.
Patients with severe renal impairment with a creatinine clearance below 10 ml/min.

**3.4 Special warnings and precautions for use:**
At therapeutic doses, no clinically significant interactions have been demonstrated with alcohol (for a blood alcohol level of 0.5 g/l). Nevertheless, precaution is recommended if alcohol is taken concomitantly.
Caution should be taken in patients with predisposition factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as cetirizine may increase the risk of urinary retention.
Caution is recommended in epileptic patients and patients at risk of convulsions.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take **Epirizine**.
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 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.
**Pediatric population:**
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 a pediatric formulation of **Epirizine**.
The use of **Epirizine** is not recommended in children aged less than 2 years.

**3.5 Interaction with other medicinal products:**
Due to the pharmacokinetic, pharmacodynamic and tolerance profile of cetirizine, no interactions are expected with this antihistamine. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug 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 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).

**3.6 Pregnancy, Lactation and Fertility:**
**Pregnancy:**
For cetirizine 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. Caution should nevertheless be exercised when prescribing to pregnant women.
**Lactation:**
Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing **Epirizine**to lactating women.
**Fertility:**
Limited data is available on human fertility but no safety concern has been identified.Animal data show no safety concern for human reproduction.

**3.7 Effects on ability to drive and use machines:**
Objective measurements of driving ability, sleep latency and assembly line performance have not demonstrated any clinically relevant effects at the recommended dose of 10 mg. However, patients who experience somnolence should refrain from driving, engaging in potentially hazardous activities or operating machinery. They should not exceed the recommended dose and should take their response to the medicinal product into account.

**3.8 Undesirable effects:**
**Clinical studies:**
**- Overview:**
Clinical studies have shown that cetirizine at the recommended dosage has minor undesirable effects on the CNS, including somnolence, fatigue, dizziness and headache. In some cases, paradoxical CNS stimulation has been reported.

Although cetirizine is a selective antagonist of peripheral H1-receptors and is relatively free of anticholinergic activity, isolated cases of micturition difficulty, eye accommodation disorders and dry mouth have been reported.
Instances of abnormal hepatic function with elevated hepatic enzymes accompanied by elevated bilirubin have been reported. Mostly this resolves upon discontinuation of the treatment with cetirizine dihydrochloride.
- Listing of ADRs:
From this pooling, the following adverse reactions were reported for cetirizine 10 mg in the placebo-controlled trials at rates of 1.0 % or greater:
***General disorders and Administration site conditions:***Fatigue.
***Nervous system disorders:*** Dizziness, headache.
***Gastro-intestinal disorders:*** Abdominal pain, dry mouth, nausea.
***Psychiatric disorders:*** Somnolence.
***Respiratory, Thoracic and Mediastinal disorders:*** Pharyngitis.
Although statistically more common than under placebo, 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.
**Pediatric population:**
Adverse reactions at rates of 1 % or greater in children aged from 6 months to 12 years, included in placebo-controlled clinical trials are:
***Gastro-intestinal disorders:*** Diarrhea.
***Psychiatric disorders:*** Somnolence.
***Respiratory, Thoracic and Mediastinal disorders:*** Rhinitis.
***General disorders and Administration site conditions:*** Fatigue.
**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.
Undesirable effects are described according to MedDRA System Organ Class and by estimated frequency based on post-marketing experience.
Frequencies are defined as follows: 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).
***Blood and Lymphatic disorders:***
Very rare: thrombocytopenia.
***Immune system disorders:***
Rare: hypersensitivity.
Very rare: anaphylactic shock.
***Metabolism and Nutrition disorders:***
Not known: increased appetite.
***Psychiatric disorders:***
Uncommon: agitation.

Rare: aggression, confusion, depression, hallucination, insomnia.
Very rare: tics.
Not known: suicidal ideation, nightmare.
***Nervous system disorders:***
Uncommon: paraesthesia.
Rare: convulsions.
Very rare: dysgeusia, syncope, tremor, dystonia, dyskinesia.
Not known: amnesia, memory impairment.
***Eye disorders:***
Very rare: accommodation disorder, blurred vision, oculogyration.
***Ear and Labyrinth disorders:***
Not known: vertigo.
***Cardiac disorders:***
Rare: tachycardia.
***Gastro-intestinal disorders:***
Uncommon: diarrhea.
***Hepatobiliary disorders:***
Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin).
Not known: hepatitis.
***Skin and Subcutaneous tissue disorders:***
Uncommon: pruritus, rash.
Rare: urticaria.
Very rare: angioneurotic oedema, fixed drug eruption.
Not known: acute generalized exanthematous pustulosis.
***Musculoskeletal and Connective tissue disorders:***
Not known: arthralgia.
***Renal and Urinary disorders:***
Very rare: dysuria, enuresis.
Not known: urinary retention.
***General disorders and Administration site conditions:***
Uncommon: asthenia, malaise.
Rare: oedema.
**Investigations:**
Rare: weight increased.
**Description of selected adverse reactions:**

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

**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 to National Regulatory Authority

**3.9 Overdose:**

**Symptoms:** Symptoms observed after an overdose of cetirizine are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect.

Adverse events reported after an intake of at least 5 times the recommended daily dose are: confusion, diarrhea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.

**Management:**

There is no known specific antidote to cetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug.

Cetirizine is not effectively removed by hemodialysis.

**4. Pharmacological properties:**

**4.1 Pharmacodynamic properties:**

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivatives.

**Mechanism of action:**

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H1-receptors. In vitro receptor binding studies have shown no measurable affinity for other than H1-receptors.

**Pharmacodynamic effects:**

In addition to its anti-H1 effect, cetirizine was shown to display anti-allergic activities: at a dose of 10 mg once or twice daily, it inhibits the late phase recruitment of eosinophils, in the skin and conjunctiva of atopic subjects submitted to allergen challenge.

**4.2 Pharmacokinetic properties:**

**Absorption:**

The steady - state peak plasma concentrations is approximately 300 ng/ml and is achieved within 1.0 ± 0.5 h.. The distribution of pharmacokinetic parameters such as peak plasma concentration (Cmax) and area under curve (AUC) is unimodal.

The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased. The extent of bioavailability is similar when cetirizine is given as solutions or tablets.

**Distribution:**

The apparent volume of distribution is 0.50 l/kg. Plasma protein binding of cetirizine is 93 ± 0.3 %. Cetirizine does not modify the protein binding of warfarin.

**Biotransformation:**

Cetirizine does not undergo extensive first pass metabolism.

**Elimination:**

The terminal half-life is approximately 10 hours and no accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. About two third of the dose are excreted unchanged in urine.

**Linearity/Non-linearity:**
Cetirizine exhibits linear kinetics over the range of 5 to 60 mg.
**Renal impairment:** The pharmacokinetics of the drug 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 moderate or severe renal impairment.
**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.
Dosing adjustment is only necessary in patients with hepatic impairment if concomitant renal impairment is present.
**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 the normal subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.
**Pediatric population:** The half-life of cetirizine was about 6 hours in children of 6-12 years and 5 hours in children 2-6 years. In infants and toddlers aged 6 to 24 months, it is reduced to 3.1 hours.

## 6.1 List of excipients

**F.C. Tablets:** Maize starch, lactose anhydrous, avicel, povidone K25, poly plasdone XL, colloidal silicon dioxide, magnesium stearate, polyethylene glycol 6000, polyethylene glycol 35000, hydroxypropylmethyl cellulose, titanium dioxide.
**Syrup:** Sodium citrate anhydrous, citric acid anhydrous, methyl paraben, propyl paraben, sorbitol 70%, glycerin, sucrose, propylene glycol, saccharin sodium, quinoline yellow E104, pineapple powder flavour, purified water.

## 6.2 Incompatibilities:

None.

## 6.3 Shelf life:

**F.C. Tablets:** 3 years
**Syrup:** 3 years

## 6.4 Special precautions for storage:

Store in a dry place at a temperature not exceeding 30ºC.

**6.5 Nature and contents of container:**

**Epirizine F.C. Tablets:** Box of one strip (Al/transparent PVC) of 10 F.C. Tablets and insert leaflet.

**Epirizine Syrup:** Carton box containing amber glass (type III) bottle containing 60 ml syrup with white pilfer proof aluminum cap with LDPE liner and measuring cap and insert leaflet.

**6.6 Special precautions for disposal and other handling:**

No special requirements

**7. Marketing authorisation holder:**

EIPICO

**8. Date of revision of the text**

December 2015.

**9. Marketing authorisation number(s)**