CETZINE A

Cetirizine Hydrochloride and Ambroxol Hydrochloride Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Cetirizine Hydrochloride IP  5 mg
Ambroxol Hydrochloride IP  60 mg
Colours: Ferric Oxide USPNF & Titanium Dioxide IP

PHARMACEUTICAL FORM

Film Coated Tablets.

CLINICAL PARTICULARS

Therapeutic Indications

For the symptomatic relief of productive cough associated with allergic rhinitis, when both anti-histamine and mucolytic agents are desired.

Posology and Method of Administration

The secretolytic effect of ambroxol is supported by adequate fluid intake.

Route of Administration

For oral use.

Adults

One tablet twice daily.

Elderly

There are no relevant data available for the combination of cetirizine and ambroxol.

Children

CETZINE A is not recommended for use in children.

Renal impairment

Caution must be exercised and dosing interval must be extended depending on the renal function.

Since cetirizine is mainly excreted via renal route, in cases where no alternative treatment can be used, the dosing intervals 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 (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$\text{CL}_{\text{cr}} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85 \text{ for women}$$

Dosing adjustments for adult patients with impaired renal function.

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≥80</td>
<td>No adjustment required</td>
</tr>
<tr>
<td>Mild</td>
<td>50 – 79</td>
<td>No adjustment required</td>
</tr>
<tr>
<td>Moderate</td>
<td>30 – 49</td>
<td>One tablet once daily</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>One tablet once every 2 days</td>
</tr>
<tr>
<td>End-stage renal disease -</td>
<td>&lt; 10</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>Patients undergoing dialysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hepatic impairment**

In severe hepatic impairment caution should be exercised.

**Patients with Hepatic impairment and Renal impairment**

Dose adjustment is recommended (see Renal Impairment above).

**Contraindications**

*CETZINE A* is contraindicated in:

- patient with history of hypersensitivity to any of the ingredients of the formulation, to hydroxyzine or to any piperazine derivatives,
- patients with severe renal impairment at less than 10 ml/min creatinine clearance.

**Special Warnings and Special Precautions for Use**

**Alcohol**

At therapeutic doses, no clinically significant interactions of cetirizine have been demonstrated with alcohol (for a blood alcohol level of 0.5 g/L). Nevertheless, precaution is recommended if alcohol is taken concomitantly with *CETZINE A* (see Interaction with Other Medicaments and Other Forms of Interaction).

**Increased risk of urinary retention**

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 (see Undesirable Effects).

**Patients at risk of convulsions**

Caution in epileptic patients and patients at risk of convulsions is recommended.
**Skin reactions**

Pruritus and/or urticaria may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation (see Undesirable Effects). In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

**Allergy skin tests**

Allergy skin tests are inhibited by antihistamines and a wash-out period of 3 days is recommended before performing them.

**Food**

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

**General warning**

Patient should be reassessed, if the cough persists for more than 14 days.

**Renal impairment**

Careful assessment advised prior to prescribing CETZINE A in renal insufficiency. In severe renal impairment, accumulation of ambroxol metabolites formed in the liver must be expected. Therefore, caution should be exercised while using CETZINE A in renal impairment. The dose of CETZINE A must be adjusted as described in Posology and Method of Administration.

**Secretion impairment**

In patients with symptoms of chronic impairment of secretion production or secretion clearance, CETZINE A should be used with caution.

**Peptic ulcers**

The use of CETZINE A should be carefully considered in patients predisposed to peptic ulcers.

**Ciliary dyskinesia**

In patients with ciliary dyskinesia the benefit of liquefaction of secretions should be carefully weighed against the risk of congestion of secretions.

**Antitussives**

Concomitant administration of antitussives should be avoided due to the risk of congestion of secretions (see Interaction with Other Medicaments and Other Forms of Interaction).

**Skin damage** (see Undesirable Effects)
There have been reports of severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) associated with the administration of ambroxol. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, CETZINE A treatment should be discontinued immediately and medical advice should be sought.

Interaction with Other Medicaments and Other Forms of Interaction

Cetirizine hydrochloride

Due to the pharmacokinetic, pharmacodynamic and tolerance profile of cetirizine, no interactions are expected with this antihistamine. Neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

Alcohol and other CNS depressants

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) (see Special Warnings and Special Precautions for Use).

Ambroxol hydrochloride

Antitussives

Concomitant administration of antitussives may impair the expectoration of liquefied bronchial mucus due to inhibition of the cough reflex and cause congestion of secretions (see Special Warnings and Special Precautions for Use).

Antibiotics

After using ambroxol the concentrations of the antibiotics amoxicillin, cefuroxime and erythromycin in bronchial secretions and sputum are increased.

Pregnancy and Lactation

Fertility

Limited data is available on human fertility but no safety concern has been identified.

Animal data show no safety concern for human reproduction.

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/foetal development, parturition or postnatal development.
Ambroxol use during the first trimester of pregnancy is not recommended. Ambroxol crosses the placenta. Animal studies do not show either a direct or indirect harmful effect on pregnancy, embryofoetal development, parturition or postnatal development. Comprehensive controlled studies of ambroxol in pregnant women after the 28th week have not shown any harmful effects on the foetus.

Caution should be exercised when prescribing CETZINE A to pregnant women and use during the first trimester of pregnancy is not recommended.

**Lactation**

Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration.

Ambroxol is excreted in breast milk and should not be taken during lactation. However, no adverse effects on the breastfed infant are expected.

*CETZINE A* is not recommended for use by nursing mothers.

**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 a dose of 10 mg cetirizine.

However, patients who experience somnolence should refrain from driving, engaging in potentially hazardous activities or operating machinery.

No studies on the effects of ambroxol on the ability to drive and use machines have been performed. An effect on the ability to drive and operate machines is unknown.

Patients intending to drive, engaging in potentially hazardous activities or operating machinery should not exceed the recommended dose and should take their response to *CETZINE A* into account.

**Undesirable Effects**

In absence of availability of adverse event data on the fixed dose combination of cetirizine and ambroxol, adverse event data of the individual ingredient is presented below.

**Cetirizine hydrochloride**

*Clinical Trial Data*

Clinical studies have shown that cetirizine 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.

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.

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 3200 subjects exposed to cetirizine.

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:

<table>
<thead>
<tr>
<th>Adverse reactions (WHO-ART)</th>
<th>Cetirizine 10 mg (n= 3260)</th>
<th>Placebo (n = 3061)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.63 %</td>
<td>0.95 %</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.10 %</td>
<td>0.98 %</td>
</tr>
<tr>
<td>Headache</td>
<td>7.42 %</td>
<td>8.07 %</td>
</tr>
<tr>
<td>Gastro-intestinal system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.98 %</td>
<td>1.08 %</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.09 %</td>
<td>0.82 %</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.07 %</td>
<td>1.14 %</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>9.63 %</td>
<td>5.00 %</td>
</tr>
<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1.29 %</td>
<td>1.34 %</td>
</tr>
</tbody>
</table>

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.

Post Marketing Data

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).

Blood and lymphatic system 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, dyskinesia, dystonia, syncope, tremor.
*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.

**Gastrointestinal disorders**

*Uncommon*: diarrhoea.

**Hepatobiliary disorders**

*Rare*: hepatic function abnormal, (transaminases increased, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased).
*Not known*: hepatitis

**Skin and subcutaneous tissue disorders**

*Uncommon*: pruritus, rash.
*Rare*: urticaria.
*Very rare*: angioedema, fixed drug eruption.
**Not known:** acute generalized exanthematous pustulosis (AGEP),

**Musculoskeletal and connective tissue disorders**

**Not known:** arthralgia

**Renal and urinary disorders**

**Very rare:** dysuria, enuresis.
**Not known:** urinary retention (see Special Warnings and Special Precautions for Use).

**General disorders and administration site conditions**

**Uncommon:** asthenia, malaise.
**Rare:** oedema.

**Investigations**

**Rare:** weight increased.

**Skin reactions occurring after discontinuation of cetirizine**

After discontinuation of cetirizine, pruritus (intense itching) and/or urticaria have been reported (see Special Warnings and Special Precautions for Use).

**Ambroxol hydrochloride**

**Clinical Trial Data and Post Marketing Data**

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

- **Very common**: ≥1/10
- **Common**: ≥1/100 to <1/10
- **Uncommon**: ≥1/1000 to <1/100
- **Rare**: ≥1/10000 to <1/1000
- **Very rare**: <1/10000
- **Not known** (cannot be estimated from the available data)

**Immune system disorders** (see also **Skin and subcutaneous tissue disorder**)

**Rare:** hypersensitivity reactions
**Not known:** anaphylactic reactions including anaphylactic shock), angioedema and pruritus.

**Gastrointestinal disorders**

**Common:** nausea.
**Uncommon:** diarrhoea, vomiting, dyspepsia, abdominal pain.

**Skin and subcutaneous tissue disorders**

**Rare:** rash, urticaria.
Not known: severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis).

Overdose

Symptoms and signs

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 of cetirizine are: confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.

In reports of unintentional overdosing and/or medication errors with ambroxol, the symptoms have largely corresponded with the known adverse effects.

Treatment

There is no known specific antidote to cetirizine. Cetirizine is not effectively removed by haemodialysis. Should overdose occur with CETZINE A, symptomatic or supportive treatment is recommended.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Cetirizine hydrochloride

Pharmacotherapeutic group: Antihistamines for systematic use, piperazine derivatives; ATC Code R06AE07.

Mechanism of Action and Pharmacodynamic Effects

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 receptors other than H₁-receptors.

*Ex vivo* experiments in mice have shown that systemically administered cetirizine does not significantly occupy the cerebral H₁-receptors.

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 inflammatory cells, notably eosinophils, in the skin and conjunctiva of atopic subjects submitted to antigen challenge, and the dose of 30 mg/day inhibits the influx of eosinophils in the bronchoalveolar lavage fluid during a late-phase bronchial constriction induced by allergen inhalation in asthmatic subjects. Moreover, cetirizine inhibits the late-phase inflammatory reaction induced
in chronic urticaria patients by intradermal administration of kallikrein. It also down-regulates the expression of adhesion molecules, such as ICAM-1 and VCAM-1, which are markers of allergic inflammation.

Studies in healthy volunteers show that cetirizine, at doses of 5 and 10 mg strongly inhibits the wheal and flare reactions induced by very high concentrations of histamine into the skin, but the correlation with efficacy is not established. The onset of activity after a single 10 mg dose occurs within 20 minutes in 50 % of the subjects and within one hour in 95 %. This activity persists for at least 24 hours after a single administration.

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and concomitant mild to moderate asthma, cetirizine 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine to allergic patients with mild to moderate asthma. In a placebo-controlled study, cetirizine given at the high daily dose of 60 mg for seven days did not cause statistically significant prolongation of QT interval. At the recommended dosage, cetirizine has demonstrated that it improves the quality of life of patients with perennial and seasonal allergic rhinitis.

When a treatment with cetirizine is stopped after repeated administration, the skin recovers its normal reactivity to histamine within 3 days.

**Ambroxol hydrochloride**

Pharmacotherapeutic group: Expectorants, excluding combinations with cough suppressants, mucolytics; ATC Code R05CB06.

**Mechanism of action and Pharmacodynamic Effects**

Ambroxol is the active metabolite of bromhexine. Ambroxol causes an increase in secretion in the respiratory tract. It promotes surfactant production and stimulates ciliary activity. These effects assist the flow of mucus and its removal (mucociliary clearance). An improvement in mucociliary clearance was demonstrated in clinical pharmacological studies. The increase in secretion and mucociliary clearance facilitate expectoration and reduce the cough.

In *in vitro* studies ambroxol showed a significant reduction in cytokine release, both in the blood and in mononuclear and polynuclear cells. The clinical relevance of these findings is unclear.

**Pharmacokinetic Properties**

**Cetirizine hydrochloride**

**Absorption**

The steady-state peak plasma concentration is approximately 300 ng/ml and is achieved within 1.0 ± 0.5 h.

The distribution of pharmacokinetic parameters such as peak plasma concentration (C\text{max}) 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.

**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.

**Metabolism and Elimination**

Cetirizine does not undergo extensive first pass metabolism. About two-thirds of the dose is excreted unchanged in urine. The terminal half-life is approximately 10 hours and no accumulation is observed for cetirizine following daily doses of 10 mg for 10 days.

Cetirizine exhibits linear kinetics over the range 5 to 60 mg.

**Special Patient Populations**

**Elderly**

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

**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 haemodialysis (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 normal. 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 hepatically impaired patients if concomitant renal impairment is present.

**Ambroxol hydrochloride**

**Absorption**
Ambroxol is absorbed swiftly and almost completely after oral administration. Plasma concentrations are in a linear relationship to the dose. Peak plasma levels are attained after 0.5 to 2.5 hours.

**Distribution**

Bioavailability of ambroxol hydrochloride is not affected by food. Plasma protein binding is around 90% in the therapeutic range. After oral, intravenous and intramuscular administration ambroxol is distributed swiftly and extensively from the blood into the tissues. The highest active ingredient concentrations are measured in the lung. The distribution volume is estimated to be 552 l after oral administration.

**Metabolism**

Ambroxol hydrochloride is metabolised in the liver through glucuronidation (mainly) and phase-I-reaction to dibromo anthranilic acid (around 10% of the dose), apart from some other insignificant metabolites. Studies in human liver microsomes showed that CYP3A4 is responsible for the breakdown of ambroxol hydrochloride into dibromo anthranilic acid. Within 3 days of oral intake, around 6% was found in the urine in free form and around 26% in conjugated form.

**Elimination**

Around 30% of an oral dose is eliminated via the first-pass effect. The terminal half-life is about 10 hours. Total clearance is in the region of 660 ml/min, and renal clearance is 8% of total clearance.

**Special Patient Populations**

**Elderly, Gender**

Age and gender do not affect the pharmacokinetics of ambroxol to any clinically relevant extent; therefore, adjustment of the dose is unnecessary.

**Renal impairment**

An accumulation of metabolites (predominantly conjugates of the parent substance) cannot be ruled out in severe renal impairment.

**Preclinical Safety Data**

**Cetirizine hydrochloride**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

**Ambroxol hydrochloride**

No mutagenic, carcinogenic, teratogenic or embryotoxic effects were observed in the usual tests for genotoxicity, carcinogenicity and reproductive toxicity.
PHARMACEUTICAL PARTICULARS

List of Excipients

Micro Crystalline Cellulose, Aerosil (Colloidal silicon dioxide), Sodium starch Glycolate, Polyvinylpyrrolidone K-30, Magnesium Stearate, Opadry 06F56858 Brown.

Opadry 06F56858 Brown contains Hypromellose, Polyethylene Glycol (Macrogol), Talc, Titanium Dioxide, Ferric Oxide (red) and Ferric Oxide (yellow).

Incompatibilities

There are no relevant data available.

Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Store at a temperature not exceeding 30°C, protected from direct sunlight.

Keep out of reach of children.

Nature and Specification of Container

Blister strips in a carton.

Instructions for Use / Handling

There are no special requirements for use or handling of this product.

For further information, please contact:
GlaxoSmithKline Pharmaceuticals Limited
Registered Office
Dr Annie Besant Road, Worli,
Mumbai 400030, India.

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