

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

ANTHIX 10 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

12.8 mg rupatadine fumarate, equivalent to 10 mg rupatadine

Excipients:

Bovine lactose..... 49.975 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet

Biconvex, round, light salmon-colored tablets.

4. CLINICAL CHARACTERISTICS

4.1. Therapeutic indications

With a single dose a day in patients of 12 years of age and over, is indicated symptomatic treatment of

- Allergic rhinitis (seasonal or perennial / intermittent or persistent)
- Urticaria.

4.2. Posology and method of administration

Posology/frequency and duration of administration:

Unless recommended otherwise by the doctor, 1 tablet (10 mg) per day must be used in adults and adolescents (12 years of age and over) with or without food.

Method of administration:

Only for oral administration.

May be taken before or after meals.

Additional information for special populations:

Kidney/Liver failure: Due to lack of clinical experience, it is not recommended to use ANTHIX in patients with renal or hepatic failure.

Pediatric population: The safety and efficacy of rupatadine has not been shown in children below 12 years of age.

Geriatric population: Due to possible increase in sensitivity, it must be used with caution in elderly patients (65 years of age and over).

4.3. Contraindications

- Contraindicated for persons with hypersensitivity to the active agent or any of the excipients.
- Must not be used in children under 12 years of age.

4.4. Special warnings and special precautions for use

In patients with prolonged QT interval, in patients with uncontrollable hypokalemia, in patients with clinically significant bradycardia, in cases of acute myocardial ischemia, the use of pharmaceutical must be avoided.

Due to possible increase in sensitivity, it must be used with caution in elderly patients (65 years of age and over).

Since it contains lactose, the patients with rare galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption problem must not use this pharmaceutical.

In patients with impaired liver or hepatic function (see, section 4.2).

4.5. Interactions with other medicinal products and other forms of interaction

ANTHIX 10 mg Tablet must not be used in combination with ketoconazole, erythromycin and grapefruit juice or other substances, which are potential inhibitors of CYP3A4 isoenzyme among P450 enzymes. The drugs and substances in question increase plasma concentrations of rupatadine.

In clinical studies with rupatadine, asymptomatic CPK (creatine phosphokinase) elevations have been rarely reported. Since some statins are metabolized with P450 CYP3A4 isoenzyme, the risk of interaction with statins is unknown. Therefore it must be used with caution with statins.

Just like in other antihistamines, interaction with central nervous system depressants must not be ignored.

Following administration of alcohol, although 10 mg rupatadine has caused marginal effects on psychomotor performance, these effects were not significantly different than the effects, formed following administration of alcohol alone. 20 mg rupatadine has increased disturbance, related to alcohol intake.

4.6. Pregnancy and lactation

General recommendation

Pregnancy Category C.

Women with childbearing potential/ Contraception

Adequate data concerning the use of ANTHIX in pregnant women is not available.

Animal studies are insufficient with respect to harmful effects with respect to pregnancy and/or embryonic/fetal development and/or parturition and/or postnatal development (see, Section 5.3). The potential risk for humans is unknown.

Pregnancy

ANTHIX must not be used during pregnancy unless necessary and must only be used after an assessment of risks and benefits on fetus by the physician.

Lactation

Since the excretion of rupatadine to breastmilk is not known, it must not be used during lactation unless absolutely necessary according to rupatadine risk/benefit assessment.

Fertility

Has no effects on fertility.

4.7. Effects on ability to drive and operate machinery

The patient must exercise caution when driving or operating machinery until the determination of individual response to rupatadine.

4.8. Undesired effects

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10.000$ to $< 1/1000$); very rare ($< 1/10.000$); unknown (unpredictable with the available data)

Metabolism and Nutrition disorders

Uncommon: Increased appetite

Psychiatric disorders

Uncommon: Irritability

Nervous system disorders

Common: Somnolence, headache, dizziness

Uncommon: Disturbance in attention

Respiratory, thoracic, and mediastinal disorders

Uncommon: Epistaxis, dry nose, pharyngitis, cough, dry throat, pharyngolaryngeal pain, rhinitis

Gastrointestinal disorder

Common: Dry mouth

Uncommon: Nausea, upper and lower abdominal pain, diarrhea, dyspepsia, vomiting, constipation

Skin and subcutaneous tissue disorders

Uncommon: Redness on skin

Musculoskeletal, connective tissue and bone disorders

Uncommon: Back pain, arthralgia, myalgia

General disorders and administration site conditions

Common: Fatigue, asthenia

Uncommon: Feeling of thirst, feeling of malaise, high fever

Investigations

Uncommon: Elevation in blood creatin phosphokinase, alanine aminotransferase, aspartate aminotransferase levels, liver function test anomalies, weight gain

Reporting of side effects

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also reporting suspected adverse reactions after authorization 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 national reporting system

4.9. Overdose and Treatment

No overdose cases have been reported with rupatadine. In cases of accidental overdose of pharmaceutical, symptomatic treatment with supportive measures must be applied.

5. PHARMACOLOGICAL PROPERTIES**5.1. Pharmacodynamic Properties**

Pharmacotherapeutic group: Other Systemic Anti-histamines

ATC code: R06AX28

Rupatadine is a long-acting histamine antagonist, which does not cause sedation and which blocks peripheral H₁-receptor selectively. When used at the recommended dose of 10 mg the antihistamine activity occurs within 30 minutes and lasts 24 hours.

Rupatadine has anti-allergic properties, such as inhibition of mast cell degranulation, induced by immunological and non-immunological stimulants, and in particular inhibition of cytokine

release, in particular, $\text{TNF}\alpha$, produced by human mast cells and monocytes. In addition, as shown in in vitro and in vivo studies, it also blocks thrombocyte activating factor (PAF) receptors. The clinical significance of this action on patients, is not yet clear.

In clinical studies, conducted on volunteers with allergic rhinitis and chronic idiopathic urticaria (n=375) and in patients (n=2650) rupatadine has caused no significant effects on electrocardiogram at doses between 2 to 100 mg.

Independent from etiology, since the underlying pathophysiology is similar or since it is easier to recruit prospective chronic patients, chronic idiopathic urticaria has been chosen as a clinical model for urticarial conditions. Since the factor, causing all urticarial conditions is the release of histamine, as stated in treatment guidelines, it is expected that Rupatadine is effective in the removal of other urticarial conditions, along with chronic idiopathic urticaria.

5.2. Pharmacokinetic properties

General characteristics

Absorption: Following oral use, rupatadine is rapidly absorbed, t_{max} is approximately 45 minutes. Mean C_{max} , following single oral dose of 10 mg is 2.6 ng/ml and following 20 mg dose is 4.6 ng/ml.

Distribution: The pharmacokinetics of rupatadine absorption is linear. It is bound to plasma proteins at a high rate (98.5 to 99 %).

Biotransformation: Rupatadine is mainly metabolized by P450 (CYP3A4) enzyme system. Some metabolites (desloratadine and hydroxylated metabolites) are active.

Elimination: Most of the rupatadine are excreted in feces and the remainder in urine. Mean plasma elimination half-life is ($t_{1/2}$) 5.9 hours.

Characteristics in patients

Geriatric population:

In elderly rupatadine AUC and C_{max} values are higher compared to young people. Possible reason of this is the decrease in first pass hepatic metabolism in elderly. These differences were not seen in analyzed metabolites. Rupatadine elimination half-life is 8.7 hours and 5.9 hours respectively in elderly and in young individuals. Since these results for rupatadine and its metabolites are not clinically significant, it was concluded that in the elderly, there was no need to make a dosage adjustment for 10 mg dose.

5.3. Pre-clinical safety data

It has not caused any prolongation in QTc or QRS intervals at doses, more than 100 times of the clinically recommended doses (10 mg), and in addition, has not caused arrhythmia in various animal species. In a series of tests, rupatadine has not shown any genotoxic or carcinogenic potential. It has not shown any effects on reproduction at 25 mg/kg dose and at

120 mg/kg doses, it has caused a significant decrease in female and male fertility.

6. PHARMACEUTICAL CHARACTERISTICS

6.1. List of excipients

Bovine lactose
Microcrystalline cellulose
Red iron oxide
Yellow iron oxide
Pregelatinized Starch
Magnesium Stearate

6.2. Incompatibilities

It has no determined incompatibilities, determined until today.

6.3. Shelf-life

24 months.

6.4. Special warnings for storage

Keep at room temperature below 30°C in original package.

6.5. Nature and content of the package

Packaged in transparent PVC/PE/PVDC/Al foil blister package, comprising 20 and 30 tablets, in a cardboard box, together with package leaflet.

6.6. The disposal of remnants of human medicinal product and other special precautions

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

<Date of latest renewal: {DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<{DD/MM/YYYY}>

<{DD month YYYY}>

[To be completed nationally]