SUMMARY PRODUCT CHARACTERISTIC

La-Son
25 mg Film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT - La-Son 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains:
Active ingredient: Hydroxyzine hydrochloride – 25 mg;
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
White biconvex oval scored film-coated tablets.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
La-Son is indicated to assist in the management of anxiety in adults.
La-Son is indicated for the management of pruritus associated with acute and chronic urticaria, including cholinergic and physical types, and atopic and contact dermatitis in adults and children.

4.2. Posology and method of administration
Posology
La-Son should be used at the lowest effective dose and for the shortest possible duration.
In adults and children over 40 kg in weight, the maximum daily dose is 100 mg per day.
Anxiety
Adults 50-100mg daily in divided doses
Pruritus
Adults Starting dose of 25mg at night increasing as necessary to 25mg three or four times daily.
Elderly
In the elderly, the maximum daily dose is 50 mg per day (see section 4.4). A reduced dose is advised. This is due to a possible increase in the volume of distribution, prolonged action and the possible effect of age-related changes on pharmacologic functions; including hepatic metabolism and renal excretion (see Section 5.2 'Pharmacokinetic properties')
Paediatric Population
For treating itching in children
This product is not recommended for children under 6 years of age. In children up to 40 kg in weight, other appropriate strengths and dosage forms containing hydroxyzine should be administered.
For children over 6 years, starting at 15-25mg and increasing to 50-100mg daily in divided doses adjusted according to the child's weight.
As with all medications, the dosage should be adjusted according to the patient's response to therapy.
Hepatic impairment
The total daily dose should be reduced by 33%. Use in patients with severe liver disease should be avoided (see Section 4.4 'Special Warnings and Precautions for Use')
Renal impairment
For patients with moderate or severe renal impairment, it is recommended that the total daily dosage should be reduced by 50% (see Section 4.4 'Special Warnings and Precautions for Use').
Method of administration: oral.

4.3. Contraindications

La-Son is contra-indicated in the following:

• patients who have shown previous hypersensitivity to hydroxyzine hydrochloride, cetirizine, other piperazine derivatives, aminophylline or ethylenediamine, or any of the excipients of La-Son (for a full list of excipients see section 6.1 'List of excipients')

• Patients with a known acquired or congenital QT interval prolongation.

• Patients with a known risk factor to QT interval prolongation including a known cardiovascular disease, significant electrolytes imbalance (hypokalaemia, hypomagnesaemia), family history of sudden cardiac death, significant bradycardia, concomitant use with drugs known to prolong the QT interval and/or induce Torsade de Pointes (see sections 4.4 and 4.5).

• asthmatics who have previously experienced a serious anti-histamine-induced adverse bronchopulmonary effect

• porphyria

• pregnancy and breast-feeding (see section 4.6 'Fertility, pregnancy and lactation')

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4. Special warnings and precautions for use

Cardiovascular effects

Hydroxyzine has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been cases of QT interval prolongation and torsade de pointes in patients taking hydroxyzine. Most of these patients had other risk factors; electrolyte abnormalities and concomitant treatment that may have been contributory (see section 4.8).

Hydroxyzine should be used at the lowest effective dose and for the shortest possible duration.

Treatment with hydroxyzine should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should seek immediate medical attention.

Patients should be advised to promptly report any cardiac symptoms.

Patients with hepatic impairment

Due to its sedative properties, use of hydroxyzine should be avoided in severe liver disease due to an increased risk of coma, and in patients with hepatic failure due to possibility of hepatic encephalopathy. Hydroxyzine elimination is impaired in patients with hepatic dysfunction secondary to primary biliary cirrhosis. Dosage should be modified for patients with hepatic impairment (see Section 4.2 'Posology and Method of Administration')

Patients with renal impairment

La-Son should be used with caution in patients with impaired renal function (see Section 4.2 'Posology and Method of Administration'). It is uncertain whether the drug may accumulate or have other adverse effects in such patients. La-Son is completely metabolised and one of the metabolites is the active metabolite cetirizine. Cetirizine is renally excreted and clearance is reduced in patients with moderate renal impairment and on dialysis compared to normal volunteers.

Elderly patients

Hydroxyzine is not recommended in elderly patients because of a decrease of hydroxyzine elimination in this population as compared to adults and the greater risk of adverse reactions (e.g. anticholinergic effects) (see sections 4.2 and 4.8). In elderly patients, it is recommended to reduce the dose of hydroxyzine due to a possible increase in the volume of distribution, prolonged action, and the possible effect of age-related changes on pharmacologic functions, including hepatic metabolism and renal excretion (see Section 4.2 'Posology and Method of Administration' and Section 5.2 'Pharmacokinetic properties')

Because of its potential antimuscarinic actions, LA-Son should be used with caution in patients suffering from angle-closure glaucoma, urinary retention, prostatic hyperplasia, or pyroduodenal obstruction.
Caution is required in patients suffering the following conditions:
• seizure disorders including epilepsy
• myasthenia gravis
• dementia
• decreased GI motility
• bladder outflow obstruction
• stenosing peptic ulcer
• patients with breathing problems (e.g. emphysema, chronic bronchitis)
• increased intraocular pressure
• hyperthyroidism
• cardiovascular disease
• hypertension
Dosage adjustments may be required if La-Son is used simultaneously with other CNS depressants or with drugs having, antimuscarinic properties (see section 4.5 'Interaction with other medicinal products and other forms of interaction').
The concomitant use of alcohol and hydroxyzine should be avoided (see section 4.5 'Interaction with other medicinal products and other forms of interaction').
Treatment should be stopped for one week before skin testing for allergy is undertaken, and for 96 hours prior to a methocholine test.
Children and the elderly are more susceptible to side effects.
Patients should be warned of impaired judgement and dexterity.

4.5. Interaction with other medicinal products and other forms of interaction
Associations contraindicated
Co-administration of hydroxyzine with drugs known to prolong the QT interval and/or induce Torsade de Pointes e.g. class IA (e.g. quinidine, disopyramide) and III antiarrhythmics (e.g. amiodarone, sotalol), some antihistamines, some antipsychotics (e.g. haloperidol), some antidepressants (e.g. citalopram, escitalopram), some antimalarial drugs (e.g. mefloquine), some antibiotics (e.g. erythromycin, levofloxacin, moxifloxacin), some antifungal agents (e.g. pentamidine), some gastro-intestinal medicines (e.g. prucalopride), some medicines used in cancer (e.g., toremifene, vandetanib), methadone, increase the risk of cardiac arrhythmia. Therefore, the combination is contra-indicated (see section 4.3).
Associations requiring precaution of use
Caution with bradycardia and hypokalaemia-inducing drugs.
Hydroxyzine is metabolized by alcohol dehydrogenase and CYP3A4/5 and an increase in hydroxyzine blood concentrations may be expected when hydroxyzine is co-administered with drugs known to be potent inhibitors of these enzymes.
La-Son may also have the following interactions:

Methocholine test	Treatment should be stopped for 96 hours prior to a methocholine test, to avoid effects on the test results (see section 4.4 'Special warnings and precautions for use')
Skin testing for allergy	Treatment should be stopped at least one week before skin testing for allergy to avoid effects on the test results (see section 4.4 'Special warnings and precautions for use')
CNS depressants	Patients should be warned that La-Son may enhance their response to

	alcohol, barbiturates, benzodiazepines, hypnotics, opioids, anxiolytics, antipsychotics, antidepressents, antiemetics, antiepileptics, other antihistamines, skeletal muscle relaxants, sedatives, anaesthetics and other CNS depressants (see section 4.4 'Special warnings and precautions for use')
Antimuscarinics	Antimuscarinic side effects (both peripheral and central) may be increased if La-Son is given with antimuscarinics such as atropine and some antidepressants (both tricyclics and MAOIs) (see section 4.4 'Special warnings and precautions for use')
Adrenaline	Hydroxyzine has been shown to inhibit and reverse the vasopressor effect of adrenaline (see Section 4.9 'Overdose')
Anticholinergic agents	Additive anticholinergic effects may occur if hydroxyzine is administered concomitantly with other anticholinergic agents
Anticholinesterase drugs	Hydroxyzine may antagonise the effects of anticholinesterase drugs
Betahistine	Hydroxyzine may antagonise the effects of betahistine
Cimetidine	Cimetidine, 600mg twice a day, has been shown to increase the serum concentrations of hydroxyzine and to decrease peak concentrations of the metabolite cetirizine
CYP2D6 & cytochrome P450	Hydroxyzine is an inhibitor of CYP2D6 and may cause drug-drug interactions with CYP2D6 substrates. Cetirizine does not interact with other drug substances via cytochrome P450
Drugs which have effects on the brain	Drugs which have effects on the brain will interact with antihistamines
Drugs that affect the hepatic microsomal enzyme system	Metabolism may be reduced in patients concomitantly receiving drugs that affect the hepatic microsomal enzyme system. Decreased metabolism may result in accumulation of potentially toxic concentrations of unchanged antihistamine
Ototoxic drugs	It has been suggested that some sedating antihistamines could mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibiotics
Porter-Silber reaction or the Glenn-Nelson method	Hydroxyzine has been reported to cause falsely elevated urinary concentrations of 17-hydroxycorticosteroids when the Porter-Silber reaction or the Glenn-Nelson method is used

4.6. Fertility, pregnancy and lactation

Pregnancy

La-Son should not be used during pregnancy (see section 4.3 'Contraindications').

Clinical data in humans are inadequate to establish safety in early pregnancy.

The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

Animal studies have shown reproductive toxicity. Foetal abnormalities have been reported when hydroxyzine was administered, at doses substantially above the human therapeutic dose, to the pregnant mouse, rat and rabbit.

Hydroxyzine crosses the placental barrier which may lead to higher foetal than maternal concentrations.

The following events were observed in a neonate whose mother received high dose (600mg per day) hydroxyzine during pregnancy; hypotonia, movement disorders including extrapyramidal disorders, clonic movements, tachypnea and poor feeding.

Lactation

It is expected that La-Son may be excreted into breast milk. The effects on the nursing infant are unknown. La-Son should not be given to nursing mothers (see section 4.3 'Contraindications').

4.7. Effects on ability to drive and use machines

Patients should be warned that La-Son may impair their ability to perform activities requiring mental alertness or physical co-ordination such as operating machinery or driving a vehicle. Concomitant use of hydroxyzine with alcohol or other CNS depressants should be avoided as this may aggravate these effects (see section 4.5 'Interaction with other medicinal products and other forms of interaction).

4.8. Undesirable effects

The most common adverse effect of the sedating antihistamines is CNS depression. Effects vary from slight drowsiness to deep sleep, and include lassitude, dizziness, and incoordination. Paradoxical stimulation may occasionally occur, especially at high doses and in children and the elderly. If sedative effects occur, they may diminish after a few days of treatment. Other common adverse effects include headache, psychomotor impairment and antimuscarinic effects.

Undesirable effects are listed by MedDRA System Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings:

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

System Organ Class	**Undesirable Effect**	**Frequency**
Blood and lymphatic system disorders	blood disorders, including agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia	Not known
Immune system disorders	hypersensitivity reactions, anaphylaxis, angioedema	Not known
Metabolic and nutritional disorders	porphyria, anorexia	Not known
Psychiatric disorders	agitation, confusion, disorientation, hallucinations, sleep disturbances, depression, increased anxiety, nightmares	Not known
Nervous system disorders	dyskinesia[4], insomnia, sedation, drowsiness, dizziness, weakness, headache, tremor[1] convulsions[2], psychomotor impairment, paraesthesias, extrapyramidal effects, seizure, coma, somnolence, disturbance in attention,	Not known

	involuntary motor activity[3], ataxia, slurred speech, bitter taste in mouth, faintness	
Eye disorders	accommodation disorder, blurred vision	Not known
Ear and labyrinth disorders	tinnitus, labrynthitis, vertigo	Not known
Cardiac disorders	ventricular arrhythmias (e.g. Torsade de Pointes), QT interval prolongation (see section 4.4), tachycardia, palpitation	Not known
Vascular disorders	hypotension, flushing	Not known
Respiratory, thoracic and mediastinal disorders	bronchospasm, thickened respiratory tract secretions, wheezing, nasal stuffiness, dryness of throat	Not known
Gastrointestinal disorders	constipation, dryness of the mouth, nausea, vomiting, increased gastric reflux, diarrhoea, epigastric pain, increased GI peristalsis	Not known
Hepatobiliary disorders	liver dysfunction	Not known
Skin and subcutaneous tissue disorders	dermatitis, fixed drug eruption, pruritis, erythema, papular rash, sweating increased, urticaria, hair loss, eczema, acute generalised exanthematous pustulosis (AGEP), toxic epidermal necrolysis Stevens-Johnson syndrome, erythema multiforme	Not known Very rare
Muscoskeletal and connective tissue disorders	myalgia	Not known
Renal and urinary disorders	urinary retention, dysuria	Not known
Reproductive system and breast disorders	priapism, impotence, early menses	Not known
General disorders and administration site conditions	fatigue, malaise, lassitude, pyrexia, dryness of respiratory mucosae, asthenia, tightness of chest, irritability, chills	Not known
Investigations	liver function tests abnormal	Not known

Footnotes

[1,2, 3] reported usually with doses considerably higher than those recommended. Continuous therapy with over 1g/day has been employed in some patients without these effects having been encountered

[4] dyskinesia may follow termination of prolonged antihistamine therapy.

Children and the elderly are more susceptible to side effects.

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 via Arpimed "LLC" by going to www.arpimed.com and fill out the appropriate form ″Report an adverse reaction or inefficiency of drug″. Hotline number: (+374 55) 05 79 86. And by using Scientific Centre of Drug and Medical Technology Expertise after academician E. Gabrielyan ″CJSC ″, going to the site: www.pharm.am in ″Report about adverse effect of medicine″ section and fill out the ″Report of adverse reaction or manufacturing problem of medicinal product″.

Hotline numbers: +37410200505; +37496220505.

4.9. Overdose

Overdosage with sedating antihistamines is associated with antimuscarinic, extrapyramidal, and CNS effects. If CNS stimulation predominates over CNS depression, ataxia, excitement, seizures, tremors, psychoses, hallucinations, convulsions and hyperpyrexia can occur. Coma and cardiorespiratory collapse may follow. CNS stimulation is more likely in children and elderly. In adults, CNS depression is more common with drowsiness, postictal depression, coma, and convulsions, progressing to respiratory failure and cardiovascular collapse. In children and adults, cerebral oedema and upper nephron nephrosis, a deepening coma, tachycardia, QRS widening, heart block, cardiorespiratory collapse/arrest, cardiogenic shock, and death may occur.

Common features include excessive sedation, nausea, vomiting, flushing, dilated pupils, dry mouth and tongue, hot dry skin, fever, sinus tachycardia, hypertension, ataxia, nystagmus, delirium, agitation, psychosis and visual hallucinations. Uncommon systemic features include myoclonic jerking, muscle rigidity, coma, convulsions, cardiac conduction abnormalities, QT prolongation and arrhythmias, cardiovascular collapse, paralytic ileus, urinary retention, hyperkalaemia, metabolic acidosis and rhabdomyolysis.

Peak concentrations occur approximately two hours post ingestion, and elimination half-life has been reported approximately 14 hours and 20 hours post ingestion (see section 5.2 'Pharmacokinetic properties').

There is no specific antidote. It is doubtful whether haemodialysis or peritoneal dialysis has any value in the treatment of overdosage with La-Son. However, if other agents such as barbiturates have been ingested concomitantly, dialysis may be indicated.

Consider activated charcoal only if the patient presents within 1 hour of ingestion of a potentially toxic amount. Gastric lavage is rarely required; for substances that cannot be removed effectively by other means, it should be considered only if a life-threatening amount has been ingested within the previous hour. It should be carried out only if the airway can be protected adequately. Induction of emesis is not recommended.

General supportive care, including frequent monitoring of the vital signs and close observation of the patient is indicated. Clear airways should be maintained, and there should be adequate ventilation. Assisted ventilation is indicated if hypercapnia is present. Observation for 6 hours after ingestion, without any other specific treatment, will be sufficient for the majority of patients. Monitor BP, pulse and body temperature. In symptomatic patients measure U&Es and creatine kinase. Perform a 12-lead ECG and monitor cardiac rhythm. Patients who have been u nconscious may be hypothermic.

Hypotension, though unlikely, may be controlled with intravenous fluids. In adults, if severe hypotension persists, determine the cause and consider treatment with the following; if hypotension is mainly due to decreased systemic vascular resistance, drugs such as noradrenaline or high dose dopamine may be beneficial, if hypotension is due to reduced cardiac output dobutamine, or in severe cases, adrenaline may be beneficial. However, it should be noted that hydroxyzine has been shown to inhibit and reverse the vasopressor effect of adrenaline.

Analeptic agents should not be used since they may cause seizures.
As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics
ATC code: N05B B01
La-Son is unrelated chemically to benzodiazepines, phenothiazines, reserpine and meprobamate.

Mechanism of action

Hydroxyzine is a first generation antihistamine, a piperazine derivative, with antimuscarinic and sedative properties.
Antihistamines act as competitive antagonists of histamine at H_1 histamine receptors, thus inhibiting H_1 receptor-mediated reactions, such as vasodilation, flare and itch reactions and sneezing.
First-generation H_1 antagonists easily cross the blood-brain barrier, consequently producing well-documented sedative and anticholinergic effects.
First-generation antihistamines also have affinity for 5-HT receptors, alpha-adrenoreceptors, and muscarinic receptors. They also reduce cyclic GMP concentrations, increase atrioventricular nodal conduction, and inhibit activation of airway vagal afferent nerves.

Pharmacodynamic effects

Hydroxyzine has CNS depressant, anticholinergic, antispasmodic, and local anaesthetic activity, in addition to antihistaminic effects. The drug also has sedative, antiemetic and primary skeletal muscle relaxant activity.
An onset of sedative action of hydroxyzine is usually noted within 15 to 30 minutes after oral administration. Sedative effects persist for 4-6 hours following administration of a single dose.
Hydroxyzine suppresses the inflammatory response (wheal and flare reaction) and pruritus for up to 4 days after intradermal skin tests with allergens and histamine.
The therapeutic range for plasma hydroxyzine concentrations and the relationship of plasma concentration to clinical response or toxicity have not been established.
Hydroxyzine does not appear to increase gastric secretions or acidity, and usually has mild antisecretory effects.
It induces a calming effect in anxious tense adults. It is not a cortical depressant, but its action may be due to a suppression of activity in certain key regions of the subcortical area of the central nervous system.

Clinical efficacy and safety

La-Son has been shown clinically to be a rapid-acting anxiolytic with a wide margin of safety.
Antihistamine effects have been demonstrated experimentally and confirmed clinically; it is highly effective in alleviating pruritus.

Paediatric population

The pharmacokinetics and antipruritic effects of hydroxyzine were studied in 12 children (mean age 6.1 +/- 4.6 years) with severe atopic dermatitis, each given a single 0.7 mg/kg oral dose. Pruritis was significantly suppressed from 1 to 24 hours after the administration of the dose, with greater than 85% suppression from 2 to 12 hours. The potent antipruritic effect persists even when serum concentrations of the drug are low (only 10% of the maximum levels achieved). In children, the biologic effects of hydroxyzine appear to be much more prolonged than would be predicted from the half life values.

5.2. Pharmacokinetic properties

Absorption

Hydroxyzine is rapidly absorbed from the gastrointestinal tract.

After a single oral dose of hydroxyzine, 0.7 mg/kg (mean dose 39.0 +/- 5.4 mg) a mean maximum serum hydroxyzine concentration of 72.5 +/- 11.1 ng/ml has been shown to occur at a mean time of 2.1 +/- 0.4 hours.

Distribution

Distribution of hydroxyzine into human body tissues and fluids has not been fully characterised. Following administration of hydroxyzine to animals, the drug is widely distributed into most body tissues and fluids with highest concentrations in the liver, lungs, spleen, kidneys, and adipose tissue. The drug is also distributed into bile in animals.

Hydroxyzine crosses the placental barrier which may lead to higher foetal than maternal concentrations.

Serum hydroxyzine concentrations do not necessarily reflect hydroxyzine tissue binding or distribution to skin receptor sites. Suppression of wheals, flares, and associated pruritis has been shown to persist even when serum hydroxyzine concentrations are low.

First-generation H_1 antagonists easily cross the blood-brain barrier.

In a study group of healthy adults, the mean apparent volume of distribution has been found to be 16.0 +/- 3.0 L/kg.

Biotransformation

Hydroxyzine is metabolised in the liver. Metabolites include cetirizine, which has antihistaminic activity. Cetirizine is formed from hydroxyzine via an oxidative biotransformation step.

Elimination

An elimination half life of 20.0 +/- 4.1 hours and of 14.0 hours has been reported for hydroxyzine.

Total body clearance in adults is generally in the range of 5 to 12 ml/min/kg.

Hydroxyzine is eliminated by hepatic metabolism in humans. Cetirizine is mainly renally excreted.

Special populations

Elderly patients

The pharmacokinetics of hydroxyzine were studied in nine healthy elderly (mean age 69.5 +/- 3.7 years) subjects who ingested a single dose of hydroxyzine, 0.7 mg/kg (mean dose 49.0 +/- 6.7 mg). The mean serum elimination half life value of hydroxyzine in this elderly group was 29.3 +/-10.1 hours (range 20.2 to 53.3 hours), which was significantly longer than that reported in younger subjects. The mean apparent volume of distribution of hydroxyzine in this elderly group was 22.5 +/- 6.3 L/kg (range 13.4 to 30.7L/kg), which was significantly larger than that reported to be found in young adults. Hydroxyzine has a long mean serum elimination half life value, a large volume of distribution and a prolonged pharmacodynamics effect (suppressive effect on wheal and flare response to histamine) in the elderly.

In the elderly, a number of age-related biological and physiological changes may have an effect on the pharmacology of hydroxyzine and its metabolite, cetirizine. These changes may impact upon the pharmacologic functions of absorption, distribution, metabolism, excretion, and receptor sensitivity.

Dosage reduction may be appropriate in elderly patients (see section 4.2 'Posology and Method of Administration')

Paediatric patients

The pharmacokinetics and antipruritic effects of hydroxyzine hydrochloride was studied in 12 children aged 1 to 14 years (mean age 6.1 +/- 4.6 years) with severe atopic dermatitis. The children were given a single orally administered dose of 0.7 mg/kg hydroxyzine. The mean peak serum concentration of 47.4 +/- 17.3 ng/ml occurred at a mean time of 2.0 +/- 0.9 hours. Terminal elimination half life was shorter in children than in adults, at a mean of 7.1+/- 2.3 hours. This resulted from a larger clearance rate in children of 32.08 +/- 11.05 ml/min/kg. The elimination half-life values increased with increasing age. Half life values were approximately 4 hours in the 1 year old patients and 11 hours in the 14 year old patient.

Dosage should be adjusted in the paediatric population (see section 4.2 'Posology and Method of Administration')

Hepatic impairment

The pharmacokinetics and pharmacodynamics of hydroxyzine were studied in eight patients (mean age 53.4 +/- SD11.2 years) with primary biliary cirrhosis, given a single dose of 0.7 mg/kg (mean dose 43.9 +/- 6.6mg) hydroxyzine. All patients had abnormal liver biochemistry tests, all had biopsies compatible with primary biliary cirrhosis, and seven of eight had positive tests for antimitochondrial antibodies.

Hydroxyzine elimination was found to be impaired in patients with primary biliary cirrhosis. Mean peak hydroxyzine levels occurring at 2.3 +/- 0.7 hours were found to be 116.5 +/- 60.6 ng/ml, which was significantly higher than in other patient groups studied previously. Mean serum elimination half-life of hydroxyzine was 36.6 +/- 13.1 hours, which was significantly longer than in patients with normal hepatic function studied previously.

Dosage should be adjusted in patients with hepatic impairment (see section 4.2 'Posology and Method of Administration')

Renal impairment

The pharmacokinetics of hydroxyzine and of its active metabolite cetirizine were studied in patients with reduced kidney function. Eight healthy volunteers and eight patients with renal insufficiency received a single peroral dose of 50 mg hydroxyzine.

With regards to hydroxyzine, results showed moderate elevation of the average terminal half-life in the patients group ($t_{1/2}$14 vs. 23 h). The areas under the concentration-time curves (AUC) were 996 $ng \cdot h \cdot ml^{-1}$ in the healthy volunteers group and 1621 $ng \cdot h \cdot ml^{-1}$ in the patients group. For cetirizine, AUC measured 6036 $ng \cdot h \cdot ml^{-1}$ in the healthy volunteers group and 31635 $ng \cdot h \cdot ml^{-1}$ in the patients group. The study concluded that the reduced renal clearance of cetirizine may be of clinical importance in patients with renal failure.

Dosage should be adjusted in patients with renal impairment (see section 4.2 'Posology and Method of Administration')

5.3. Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:

Microcrystalline cellulose,
lactose monohydrate,
calcium hydrogen phosphate,
sodium starch glycolate,
povidone K30,
magnesium stearate,
aerosil.

Tablet coating:

Hypromellose,
titanium dioxide,
propylene glycol,
talc.

6.2. Incompatibilities
Hydroxyzine hydrochloride has been reported to be incompatible with aminophylline, benzylpenicillin salts, chloramphenicol sodium succinate, dimenhydrinate, doxorubicin hydrochloride (in a liposomal formulation), thioridazine, and some soluble barbiturates.

6.3. Shelf life
3 years. Do not use after expiry date.

6.4. Special precautions for storage
Store at a temperature below 25°C, protect from light and moisture and out of the reach of children.

6.5. Nature and contents of container
10 tablets in blister PVC-Aluminum. 2 blisters (20 tablets) and leaflet inserted in the cardboard box.

6.6. Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORIZATION HOLDER
"ARPIMED" LLC
Kotayk Marz, Abovyan, 2nd Micro-District, 19 Building, Republic of Armenia
Tel.: (374) 222 21703 Fax: (374) 222 21924

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23.07.2013 (Date of first authorisation).

10. DATE OF REVISION OF THE TEXT