OLEDRO PEDIATRIC SYRUP

Summary of Product Characteristics (SPC)

1 NAME OF THE MEDICINAL PRODUCT

OLEDRO Pediatric Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Each 5 mL syrup consists 1mg chlorpheniramine maleate,5 mg phenylephrine HCI and 160 mg paracetamol

Excipients: Each 5ml;

Ethanol	520 mg
Propylene glycol	650 mg
Sugar (sucrose)	1750 mg
Sodium methyl hidroxybenzoate	70 mg
Sodium propyl hidroxybenzoate	30 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup

Colorness, raspberry flavor, clear viscous syrup

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of common cold, headache, high temperature which accompaniment to cold.

4.2 Posology and method of administration

Unless otherwise prescribed by the physician;

If not advised otherwise by the doctor, it is used at the following doses:

Children over 12 years old and adults (≥ 44 kg):

Each 6 hour 20 ml

Children 6-12 years (23kg - 43 kg)

6 years and over: Per four hours daily 1 Scale (5 mL)

Each 6 hour 10 ml

It should not be used more than 4 doses within 24 hours.

Method of application

Taken by orally

Additional information about special population:

Renal/Liver failure:

OLEDRO pediatric syrup should be used with caution when used in patients with liver or renal failure. OLEDRO is contraindicated in patients with severe liver or renal failure.

Paediatric population:

OLEDRO should not be used in patients under 6 years of age.

Use between 6-12 years is not recommended.

Geriatric population:

The use of OLEDRO pediatric syrup in the elderly has not been investigated.

Other:

People who take alcohol should not exceed 2 g of daily paracetamol dose (see sec. 4.4)

4.3 Contraindications

The medicinal product is contra-indicated in the following situations:

- hypersensitivity to active substances, other adrenergic drugs or excipients in combination
- Severe liver (Child-Pugh category> 9) or kidney disease
- Diseases accompanied by Severe hypertension and tachycardia
- Coronary artery disease
- In patients treated with monoamine oxidase inhibitors is contraindicated. (OLEDRO is contraindicated in patients receiving and / or continuing to receive MAOI (including an antibacterial furazolidone) / RIMA within 14 days of using pediatric syrup) Pseudoephedrine and the use of such a drug at the same time may cause blood pressure to rise.
- After the micturition, some urine remained in the abdomen, prostate adenoma

- Bladder neck obstruction
- Piloroduodenal obstruction
- Stenosis-causing peptic ulcer
- Diabetes Mellitus
- Hyperthyroidism
- Lung diseases (including asthma)
- Epilepsy
- Narrow-angle glaucoma
- In patient with phaeochromocytoma
- Use under 6 years is contraindicated.

4.4 Special warnings and special precautions for use

OLEDRO Pediatric Syrup,

- In patients over 60 years of age
- Arrhythmias, cardiovascular diseases, ischemic heart disease
- Hypertension
- Prostate hypertrophy
- Kidney failure
- Use in thyroid function disorders should be avoided.
- Diet
- Psycosis
- In case of dyspnea
- Patients with anemia should be used carefully under the supervision of a physician in patients with pulmonary disease, liver and renal dysfunction.
- Patients with pre-existing hepatic disease may need to perform liver function tests at periodic intervals during high-dose or long-term treatment.
- In the event of renal failure (creatinine clearance <10 ml / min), the physician must carefully evaluate the benefit / risk ratio of paracetamol use. Dosage adjustment should be done and the patient should be monitored continuously.
- Hepatic necrosis in a patient receiving daily doses of therapeutic paracetamol for one year and liver damage in a patient using an overdose for a shorter period have been reported. Within 12-48 hours, liver enzymes may rise and prothrombin time may prolong. However, clinical symptoms may not appear until 1-6 days after dosing

- Because of the risk of hepatotoxicity, paracetamol should not be taken at higher doses or longer than recommended. Patients with mild to moderate hepatic insufficiency (Child-Pugh category <9) should use paracetamol carefully.
- During paracetamol administration at therapeutic doses, the serum alanine aminotransferase (ALT) level may increase. Concurrent use of paracetamol and other drugs that increase hepatic oxidative stress and reduce hepatic glutathione reserve in therapeutic doses, alcoholism, sepsis or diabetes mellitus can lead to an increased risk of hepatic toxicity.
- Use in diagnosed or suspected congenital prolonged QT syndrome or Torsades de Pointes patients should be avoided.
- OLEDRO pediatric syrup should not be used during the use of monoamine oxidase inhibitors or for 2 weeks following use.
- In the event of surgery, it is recommended that treatment be stopped several days in advance. The use of halogenated anesthetics increases the risk of hypertensive crisis.
- In susceptible patients with tachycardia or palpitations, treatment should be discontinued.
- If you use paracetamol in the first or previous use, the rash or other solution will occur in the first dose or repeated doses of the use. In this case, contact with the doctor is required to stop the use of the medicine and an alternative treatment is required.
- People who have skin reacted with paracetamol should not use this medicine or any other medicine containing paracetamol. This situation can lead to skin reactions including severe and fatal Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematosus pustulosis (AGEP).
- When high doses are achieved following prolonged use of paracetamol containing drugs, the possibility of developing analgesic nephropathy with irreversible renal insufficiency can not be ruled out.
- The use of paracetamol in patients with Gilbert's syndrome can cause clinical symptoms such as jaundice and more pronounced hyperbilirubinemia. For this reason, these patients should use paracetamol carefully.
- In the case of hematopoietic dysfunction, measures such as dose reduction and / or prolongation of the dose between doses should be taken
- Caution should be exercised in patients with asthma, chronic rhinitis, and chronic urticaria, especially those who are hypersensitive to anti-inflammatory drugs. Asthma

attacks and anaphylactic shock have been reported rarely with drugs containing propifenazone and paracetamol in susceptible individuals.

- Glucose 6-phosphate should be used with caution in those with dehydrogenase deficiency. Rare cases of hemolysis can be seen.
- Taking concurrent paracetamol with moderate alcohol can lead to an increased risk of liver toxicity. It should be used carelessly in alcoholic patients with liver disease.
- People who drink alcohol should not exceed 2 g daily paracetamol dose because of the risk of hepatotoxicity.
- Paracetamol, chlorpheniramine maleate, and other drugs containing phenylephrine HCl should be avoided simultaneously OLEDRO pediatric syrup.
- Patients are advised to discontinue use of paracetamol and consult a physician if new symptoms develop within 3-5 days, or if pain and / or fever do not decrease.
- Paracetamol causes acute high dose of severe liver toxicity. It can cause liver damage in chronic daily doses in adults.
- Sympathomimetic drugs, rarely including phenylephrine, have been reported reversible posterior encephalopathy (PRES), reversible cerebral vasoconstriction syndrome (SCVS). Symptoms reported include sudden onset of severe headache, nausea, vomiting, and impaired vision. Most of the cases have improved in a few days with proper treatment. If symptoms of CVS develop, phenylephrine should be discontinued immediately.
- Cerebral atherosclerosis
- Idiopathic orthostatic hypotension
- Children under the age of 6 should not be used without compulsory medical reasons.
- The recommended dose should not be exceeded or should not be used longer than 5 days afterwards.

High doses of paracetamol and, in the meantime, a high total dose used over a long period of time; Irreversible liver failure may cause analgesic-induced nephropathy. Patients should be advised not to use any other products containing paracetamol when using this medicine.

This medicine contains 10.4% alcohol (w/v) by volume. Each 5 ml dose contains 520 mg ethanol. In other words, it contains ethanol which equals to 12.8 ml beer or 5.34 ml vine. It may be harmful for people with alcohol addiction. It should be used cautiously with pregnant

and breastfeeding woman, children or patients who has high risk diseases such as liver disease or epilepsy.

Due to presence of propylene glycol, it may cause alcohol like symptoms.

Due to presence of Methyl and propyl hydroxybenzoates, it may cause allergic reactions (probably delayed)

This medicinal product contains less than 1 mmol (23 mg) Sodium for each 5 ml i.e. essentially 'sodium- free'.

Because of its sugar content, patients with a rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency problem should not use this drug

4.5 Interaction with other medicinal products and other forms of interaction

- Drugs that slow down gastric emptying, such as propantheline, may cause slow absorption of paracetamol and therefore the later onset of paracetamol effect.
- Medicines that accelerate gastric emptying, such as metoclopramide, may cause paracetamol to be absorbed more rapidly, and therefore the effect of paracetamol may be initiated more quickly.
- Concomitant use of certain hypnotics and antiepileptic drugs (glutetimid, fenobarbital, fenitoin, karbamazepin, etc.) or drugs that cause hepatic microsomal enzyme induction in the liver, such as rifampicin, with harmless paracetamol doses that can be used alone may lead to liver damage. Taking paracetamol, even at therapeutic doses, in the case of excessive alcohol consumption can also cause liver damage.
- The use of paracetamol in combination with chloramphenicol may prolong the half-life of chloramphenicol and therefore increase the toxicity of this drug.
- Parasetamol (veya metabolitleri), K vitaminine bağımlı koagülasyon faktörü sentezinde rol oynayan enzimler ile etkileşir. Interactions between paracetamol and warfarin or coumarin derivatives may result in an increase in the "International Normalized Ratio" (INR) value and an increased risk of bleeding. For this reason, patients using oral anticoagulants should not use long-term paracetamol without medical supervision and control.
- Tropisetron and granisetron, 5-hydroxytryptamine (serotonin) type 3 receptor antagonists, can completely suppress the analgesic effect of paracetamol with pharmacodynamic interaction.

- Concurrent use of paracetamol and azidotimidine (AZT-zidovudine) increases neutropenic tendency. Therefore, paracetamol should not be taken with AZT unless medical advice is given.
- Avoidance of combination therapy with more than one pain reliever is recommended. There is little evidence that this provides an extra benefit to the patient and generally leads to an increase in adverse effects.
- The rate of absorption of paracetamol may be increased with metoclopramide or domperidone and decreased with cholestyramine.
- St. John's Wort (Hypericum perforatum - tipton's weed) may reduce blood levels of paracetamol.
- Paracetamol overdose is at risk for liver damage and paracetamol toxicity; When used in conjunction with other medicinal products that may produce toxic effects in the liver, may increase in patients with chronic alcoholism or starvation.
- The absorption rate of paracetamol may decrease when taken with food.
- OLEDRO pediatric syrup should not be used in MAOI / RIMA areas.
- Use with monoamine oxidase inhibitors (including furazolidone), which affect catabolism of tricyclic antidepressants, appetite suppressants, sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) and sympathomimetic amines, can sometimes cause blood pressure to rise.(seesec. 4.3) Co-administration with moclobemide and oxytocin may cause elevated blood pressure.
- Chlorpheniramine may increase the effects of drugs acting on the central nervous system (sympathomimetics, antidepressants).
- The central nervous system such as alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytics and antipsychotics may increase the effects of depressants. Atropine may increase antimuscarinic effects of tricyclic antidepressants and MAO inhibitors.
- Chlorpheniramine inhibits phenytoin metabolism, which may cause phenytoin toxicity.
- Antihistamines should be discontinued a few days before allergy tests are performed, as they may suppress the histamine response in the periphery.

4.6 Pregnancy and lactation

General Advise

Pregnancy Category: C

Women with childbearing potential / Contraception

There is no study of OLEDRO pediatric syrup on women with potential childbirth / contraceptive effects.

Pregnancy

Studies on animals are insufficient in terms of effects on pregnancy / and - or / embryonal / fetal development / and - or / birth / and / or postnatal development.(see sec 5.3) The potential risk for humans is unknown.

Lactation

OLEDRO pediatric syrup should not be used during pregnancy unless it is necessary.

Fertility

There is no clinical study of the effect of OLEDRO pediatric syrup on fertility.

Chronic toxicity studies in animals have reported that paracetamol was caused by testicular atrophy and inhibited spermatogenesis

4.7 Effects on ability to drive and use machines

Because OLEDRO pediatric syrup can sedation, when the vehicle or machine is in use you need to be careful.

4.8 Undesirable effects

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1.000, <1/100); rare (≥1/10.000, <1/1.000); very rare (<1/10.000); Not known (cannot be estimated from the available data)

Paracetamol

Blood and lymphatic system diseases

Rare: When taken in too much anemia, methemoglobinemia, long-term use hemolytic anemia related thrombocytopenia, thrombocytopenic purpura, leukopenia, neutropenia, pancytopenia. These side effects are not causal with paracetamol.

Very rare: Agranulocytosis

Immune system diseases

Rare: Allergic reactions, anaphylaxis

Very Rare: Lyell syndrome

Not known: Bronchospasm, positive allergy test, immun thrombocytopenia

Nervous system diseases

Common: Headache, dizziness, somnolence, paresthesia

Not known: Central nervous system stimulation, encephalopathy, insomnia, tremor

Respiratory, thoracic and mediastinal diseases

Common: Upper respiratory tract infection indication

Rare: Asthma and bronchospasm, including analgesic asthma syndrome

Gastrointestinal diseases

Common: Nausea, vomiting, dyspepsia, flatulence, abdominal pain, constipation

Uncommon: Gastrointestinal bleeding

Rare: diarrhea

Hepatobiliary diseases

Rare: Hepatic impairment when taken in large quantities

Skin and subcutaneous tissue diseases

Rare: Urticaria and other skin rash, pruritus, allergic edema and angioedema, acute generalized exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (including fatal results)

This symptom disappears when the medicine is stopped.

Kidney and urinary tract diseases

Uncommon:Following therapeutic doses of paracetamol, nephrotoxic effects are not common. Papillary necrosis has been reported for a long time.

Patients who can not tolerate acetylsalicylic acid (eg, asthmatic patients) may react commonly to paracetamol (5-10%).

Chlorpheniramine maleate

Blood and lymphatic system diseases

Rare: Anemia, hemolytic anemia, methemoglobinemia, thrombocytopenia, thrombocytopenic purpura, leukopenia, neutropenia, pancytopenia, agranulocytosis

Metabolism and nutritional diseases

Rare: Anorexia

Psychiatric diseases

Rare: Depression, nightmare

Nervous system diseases

Rare: Dizziness, irritability, unable to concentrate

Not known: Headache, sedation, paradoxical excitation in children, confusional psychosis in the elderly

Eye diseases:

Rare: Blurred vision

Ear and inner ear diseases

Rare: Tinnitus

Cardiac diseases

Rare: Tachycardia, palpitations, arrhythmia, hypotension

Respiratory system diseases

Rare: Thickening in bronchial secretion

Gastrointestinal diseases

Rare: Nausea, vomiting, dyspepsia, abdominal pain, diarrhea

Not known: Xerostomia

Hepato-biliary diseases

Rare: Hepatitis including jaundice

Skin and subcutaneous tissue diseases

Not known: Urticaria, allergic reactions including exfoliative dermatitis, photosensitivity, skin reactions

Musculoskeletal disorders, connective tissue and bone diseases

Not known: Fasciculation and incoordination

Kidney and urinary tract diseases

Not known: Urinary retention

General disorders and diseases related to the application zone

Rare: Asthenia and chest tightness

Phenylephrine hydrochloride

The most common adverse events observed in clinical studies with phenylephrine are listed below.

Endocrine diseases

Not known: Effects of metabolic function on endocrine and other regulators

Psychiatric diseases

Not known: Irritability, restlessness and excitement

Nervous system diseases

Not known: İnsomnia

Cardiac diseases

Not known: Elevation of blood pressure (especially in hypertensive diseases), reflex bradycardia

Gastrointestinal diseases

Not known: Nausea, vomiting

Kidney and urinary tract diseases

Not known: It was reported to strain at the onset of the micturition and to make drops and painful urination.

The adverse events identified after marketing are described below. The frequency of these adverse events is unknown.

Eye disease

Not known: Midriasis, acute angle glaucoma (it is more likely to be seen in those with closed-angle glaucoma).

Skin and subcutaneous tissue diseases

Not known: Allergic reactions (eg rash, urticaria, allergic dermatitis) are hypersensitivity reactions that involve cross sensitivities that can occur with other sympathomimetics.

Kidney and urinary tract diseases

Not known: Dysuria, urinary retention, this is mainly due to bladder outlet obstruction, may lead to a slight increase in the phenylephrine heart rate, such as prostatic hypertrophy Rarely, dizziness, headache, hypertension and restlessness have been reported.

4.9 Overdose and treatment

Paracetamol

Adults with a paracetamol greater than 10 g are likely to have toxicity. Additionally, overdose damage is greater in people with non-cirrhotic alcoholic liver disease. Liver dysfunction following childhood overdose is relatively rare. With paracetamol overdose with liver cell damage, paracetamol half-life, which is around 2 hours in normal adults, usually lasts for 4 hours or more. After ^{14}C- aminopyrine, decreasing excretion of $^{14}CO_2$ is reported. This, plasma paracetamol concentration or half-life or better correlation between hepatocellular damage and paracetamol overdose compared to measurements of conventional liver function tests may result in renal failure due to acute tubular necrosis following fulminant hepatic failure due to paracetamol. However, this group is not frequent in patients when compared with patients with fulminant hepatic failure due to other reasons for their incidence. Rarely, renal tubular necrosis can occur with minimal hepatic toxicity only 2-10 days after taking the drug. It has been reported that chronic alcohol intake in a patient who received an overdose of paracetamol contributed to the development of acute pancreatitis. In addition to acute exacerbations, liver damage and nephrotoxic effects have been reported following daily extreme doses of paracetamol.

Symptoms: Sedation and ataxia are the most common symptoms of overdose. Nausea, blurred vision, vomiting, tachycardia are other symptoms.

Wanness, anorexia, nausea and vomiting are common early symptoms of paracetamol overdose.

Hepatic necrosis is a dose related complication of paracetamol overdose.

Hepatic enzymes can rise and prothrombin time lasts from 12 to 48 hours, but clinical symptoms of 15/22 may not appear for 1 to 6 days following ingestion of the drug.

Treatment: In acute overdose, paracetamol may have hepatotoxic effects, even causing liver necrosis. The paracetamol overdose should be treated immediately to protect the patient against delayed hepatotoxicity. For this, it is necessary to reduce absorption (gastric lavage or activated charcoal) followed by intravenous N-acetylcysteine or oral methionine. Methionine should not be used if the patient is vomiting or conjugated with active charcoal. Peak plasma concentrations may be delayed by up to 4 hours following excessive dosing. For this reason, plasma paracetamol levels should be measured at least 4 hours after drug ingestion to determine the risk of hepatotoxicity. Additional treatment (supplemental oral methionine or intravenous N-acetylcysteine) should be assessed under the light of blood paracetamol content

and time since drug ingestion. In patients taking hepatic enzyme-inducing drugs, it is recommended that 30% to 50% reduction of the therapeutic dose with N-acetyl cysteine be achieved in patients with long-lasting alcohol dependence, or in those with chronic nutritional deficiencies, because these patients may be more susceptible to the toxic effects of paracetamol. Fulminant hepatic failure treatment that may develop following paracetamol overdose may require specialization.

Phenylephrine hydrochloride

Symptoms: Phenylephrine overdose is similar to the effects listed under adverse reactions.
Additional symptoms may include hypertension and possible reflex bradycardia. Confusion, hallucinations, seizures, and arrhythmias may occur in severe cases.
However, the amount required to produce severe phenylephrine toxicity will be greater than those causing paracetamol-related toxicity.

Treatment: The treatment should be clinically appropriate. Serious hypertension requires treatment with alpha-blockers such as phenolamine.

Chlorpheniramine maleate

Symptoms: Sedation, CNS paradoxical stimulation, toxic psychosis, attack, apnea, convulsions, anticholinergic effects, cardiovascular collapse including dystonic reactions and arrhythmia.

Treatment: Gastric lavage or silk syrup should be started by emesis. Then the active carbon and the cathartics are applied to reduce the absorption. Other symptomatic and 16/22 supportive measures should be applied with special care to the heart, respiration, kidney and liver functions and fluid-electrolyte balance.
Hypotension and arrhythmias should be treated. CNS convulsions can be treated with IV diazepam. Hemoperfusion can be used in severe cases.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cold preparations
ATC code: R05X

Chlorpheniramine maleate is an antihistamine effective on H1-receptors; eliminates common allergic symptoms in respiratory tract diseases. Reduces permeability in capillaries and resolves such symptoms as nasal discharge, sneezing, watering in the eye and itching.
Paracetamol is an analgesic and antipyretic agent. It is believed that the therapeutic effects of paracetamol are due to the inhibition of the inhibitory effect of cyclooxygenase enzyme on the synthesis of the resulting prostaglandin. There is evidence that paracetamol is a more effective inhibitor on central cyclooxygenase than peripheral cyclooxygenase. Paracetamol has analgesic and antipyretic properties but shows only weak anti-inflammatory properties.
This situation; inflammatory tissues contain cellular peroxides at higher levels than other tissues and can be explained by the inhibition of cyclooxygenase inhibition of these cellular peroxides. It does not inhibit platelet aggregation, it does not affect prothrombin response.

Phenylephrine hydrochloride is a sympathomimetic substance that has a direct effect on the major adrenergic receptors. As a nasal decongestant, it relieves swelling in the upper respiratory tract mucosa, alleviating the nasal and sinus obstructions by the effect of vasoconstrictor.

5.2 Pharmacokinetic properties

General properties

Chlorpheniramine maleate

Absorbation: Chlorpheniramine is absorbed relatively slowly through the gastro-intestinal tract.
The highest plasma concentrations after oral administration are achieved within 2.5-6 hours. Bioavailability is 25-50%.
Dispersion: 70% of chlorpheniramine in circulation is bound to proteins. Chlorpheniramine is distributed throughout the body, including the central nervous system.
Chlorpheniramine is absorbed relatively slowly through the gastro-intestinal tract.
Biotransformation: Significantly first-pass metabolism in the liver. High doses of Chlorpheniramine is metabolised. Desmethyl and didesmethyl Chlorpheniramine are metabolites.
Elimination: There are distinct individual differences on chlorpheniramine pharmacokinetics; it is reported the half life is between 2-43 hours. Chlorpheniramine maleate in body gets high incidence biotransformation and metabolites are discarded via urinary tract.
Linearity and non-linear situation: There is no available data.

Phenylephrine Hydrochloride

Absorbation: It is randomly absorbed from the gastrointestinal system because of monoaminooxidases

Dispersion: When it is taken by orally, it preserves its activity as congestant, drug dispersion is dispersed to the vascular layer of nasal mucosa by systemic circulation. Dispersion volume (V_d) starting: 26-61; stable situation dispersion volume (V_{dss}) 184-543 L (average:340 L)

Biotransformation: Phenylephrine is firstly metabolized by monoaminoaxidase on bowel and liver. It has limited oral bioavailability because of the first transition effect.

Elimination: Phenylephrine is primarily eliminated via urinary tract as inactive metabolites. Elimination half-life alpha phase is about 5 min and terminal phase is 2-3 hours.

Linearity and non-linear situation: There is no available data.

Paracetamol

Absorbation: Paracetamol is absorbed from gastrointestinal tract with pasive diffusion quickly and completely; depending on the formulation the highest concentrations in plasma is generally obtained between 30-90 min after the oral treatment depending on the formulation. Gastric discharge is a rate-limiting step for oral treated paracetamol absorption. Paracetamol do not do systemic circulation implicitly after the oral treatment because of variable rate of the first transition metabolism.

The oral bioavailability in adults seems to depend on the amount of paracetamol administered. When oral bioavaibility is %63 after the dose of 500 mg, it rises to %90 after 1 or 2 g (tablet form) dose.

Dispersion: Paracetamol disperses to many body fluid equally; estimated dispersion volume is 0.95 1/kg. In pursuit of the therapeutic doses, paracetamol plasma do not connect to proteins considerably.

Dispersion kinetics on children (Vd/F) is similar to adults.

Biotransformation: Paracetamol metabolizes in liver and defines a lot of metabolites in human. Major metabolites that are eliminated via urine are glucuronide and sulfate conjugate.

Up to 10% of paracetamol is converted to acetamidoquinone, a metabolite reactive with cytochrome P-450 mixed-function oxidase system (mainly CYP2E1 and CYP3A4) in a minor way. This metabolite conjugated with rapidly reduced glutathione and eliminated as cysteine and mercapturic acid.

When the large amounts of parasetamol are taken, hepatic glutathione may be reduce and it causes hepatocyte acetamido kinon which is nonpolarly bonded to vital hepatocellular macromolecules accumulates excessively. This leads to hepatic necrosis, which can be seen in the case of overdose.

Elimination: Elimination half-life is 1-3 hours on therapeutic doses. 90-100% of the dose is excreted through the kidneys as glucuronide (60%), sulphate (35%) or cysteine (3%) conjugation products within 24 hours.

Following single dose (1000 mg i.v.), paracetamol has a total body clearance of about 5 ml / min / kg. Renal clearance of the parasetamol is depend on the urine flow rate, but it does not depend on the pH.

Less than % 4 of the treated drug is excreted as unchanged paracetamol. In healthy individuals, about 85-95% of the therapeutic dose is excreted in the urine within 24 hours.

Linearity and non-linear situation: Bonding reactive paracetamol metabolite to cell proteins causes hepatocellular damage. At terapeutic doses, these metabolites is connected by glutathione and form nontoxic conjugates. However, in the case of massive over-dose, SH donors storage of the liver (make glutathione formation easier and stimulate) run out of;

toxic metabolites of the drug accumulate in the liver and liver cell necrosis develops, which in turn impairs liver function and progresses to the hepatic coma.

When it is used appropriate for the posology, pharmacokinetics are linear.

Characteristics of patients

Renal impairment

The patients who normal average plasma half-life between the hours 2-8 and renal impairment is the same, but elimination rate in renal impairment between the hours 8-24 reduces. In chronic renal impairment, there are explicit accumulation in glucronide and sulfate conjugates.

Some extra elimination may occur in paracetamol conjugates that accumulate in patients with chronic renal failure due to limited regeneration of the parent compound. Extending the paracetamol dosage range is recommended in chronic renal impairment. İn hemodialyses, because of paracetamol plasma levels can be decrease, in order to preserve therapeutics blood levels, additional paracetamol doses can be necessary.

Liver failure

The average plasma half-life in patients with mild liver disease is similar to that of normal individuals; but in serious liver failure, it will extend significantly (about %75). In addition to

this, the prolongation of the half-life is not clear to the clinic; because in patients with liver disease there is no evidence of drug accumulation and hepatotoxicity, and glutathione conjugation is not reduced.

Administration of paracetamol 4 days / day for 13 days to 20 patients with chronic stable liver disease did not cause deterioration of liver function. When taken at the recommended doses in mild liver disease, paracetamol has not been proven to be harmful. In addition this, in severe liver disease, half-life of the plasma paracetamol half-life is prolonged considerably.

In elderly patients

Differences in pharmacokinetic parameters between young and elderly healthy subjects are not considered clinically important. However, the serum paracetamol half-life has increased significantly (about %84) and there are evidences that paracetamol clearance is reduced (about 47%) in weak, sedentary and elderly patients relative to healthy younger subjects.

In children

Studies have shown that paracetamol major metabolite is paracetamol sulphate in newborns between 0-2 days and in children 3-10 years of age.

The data in adults and in children aged 12 years and over show that the major metabolite is glucuronide conjugation. In addition this, there are no significant age-related differences in the overall elimination rate of paracetamol or in the total amount of medication being administered.

5.3 Preclinical safety data

There are no animal studies with OLEDRO pediatric syrup.

Chlorpheniramine maleate

Chlorpheniramine is used by humans for a long time and shows that pharmacovigilance data are very well tolerated, teratogenic or non-carcinogenic and do not irreversibly produce any toxicity even at severe overdoses.

Paracetamol

Acute Toxicity: Paracetamol has been found to be slightly toxic after oral administration to adult rats and guinea pigs. The more toxic in mice and neonatal rats is probably due to a different metabolism of the substance in the rats and the immature hepatic enzyme system in neonatal rats.

It caused puking when given at higher doses to dogs and cats. For this reason, oral LD_{50} values were not detected in these animal species.

Chronic Toxicity: Following the administration of toxic doses, effects such as slow weight gain, diuresis, aciduria and dehydration and increased susceptibility to infections were observed in experimental animals. During the autopsy, blood flow increase in abdominal organs, intestinal mucosa irritation was observed.

Mutagenic and Tumorigenic Potential: In rats, a potential genotoxicity was observed at the hepatotoxic dose level and this finding was not directly attributed to DNA damage but as an indirect consequence of hepatotoxicity / myelotoxicity. Therefore, a threshold dose can be assumed.

No evidence of carcinogenic activity of paracetamol has been reported in a 2-year study in male rats up to 6,000 ppm in diet. Because of the increased incidence of mononuclear cell leukemia, there are some carcinogenic activity findings in female rats. In a 2-year study of mice with a diet of up to 6,000 ppm, no evidence of carcinogenic activity of paracetamol was detected.

Reproductive Toxicity: There has been no increase in embryo toxic or teratogenic risk after extensive use in humans. Paracetamol is also frequently taken during pregnancy and there is no adverse effect on the unborn child, even if the pregnancy progresses.

Chronic toxicity studies in animals have reported that paracetamol was caused by testicular atrophy and inhibited spermatogenesis.

Phenylephrine hydrochloride

There is not enough preclinical experience.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol

Propylene glycol

Raspberry essence

Sugar

Glycerin

Sodium methyl hidroxybenzoate

Sodium propyl hidroxybenzoate

Citric acid

Deionized water

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Store in the original package under 25ºC temperature.

6.5 Nature and contents of container

Type II colored glass bottle closed with polyethylene cap, with spoon scale

Outer Packing: Carton box

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORIZATION HOLDER

Drogsan İlaçları San. Tic. A.Ş.

Oğuzlar Mah. 56. Sok. 7/3

Balgat/ANKARA

Turkey

Tel: 0 312 287 74 10
Faks: 0 312 287 61 15

8 MARKETING AUTHORIZATION NUMBER

199/76

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

First Registration Date: 02.04.2002

Registration renewal date: 17.07.2014

10 DATE OF REVISION OF THE TEXT