SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1 NAME OF THE MEDICINAL PRODUCT

Oledro Hot Effervescent Granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active pharmaceutical ingredient:

Each Effervescent Granules contains;

Paracetamol……500mg

Phenylephrine HCl…….10 mg

Chlorpheniramine maleat……2 mg

Oxolamine citrate……100 mg

Excipients:

Sodium bicarbonate…….350,00 mg

Sodium carbonate……30,00 mg

Sugar (sucrose)……7.918,80 mg

For excipients, See Section 6.1.

3 PHARMACEUTICAL FORM

Single Dosage Effervescent Granules Containing Sachet

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

It is used in the symptomatic treatment of pain, fever and cold that are related to flu and cold.

4.2 Posology and method of administration

Posology/ Administration frequency and duration:

In children over 12 years and adults:

Effervescent Granules are used by orally as follows:

Each Effervescent Granules should be dissolved in 2/3 of a glass hot water and should be drunk hot. It can be taken in per 6 hours. It should not be used more than 4 doses in a day.

It should not be used for more than 5 days.

People who take alcohol should not exceed 2000 mg daily paracetamol dose (4 Effervescent Granules sachets) because of the risk of hepatotoxicity.

Method of Application:

It is used orally.

Additional information on special populations

Kidney / Liver failure:

OLEDRO HOT should be used with caution when used in patients with liver or renal insufficiency.

OLEDRO HOT is contraindicated in patients with severe liver or renal insufficiency.

Pediatric Population:

OLEDRO HOT should not be used in children under 12 years of age.

Geriatric population:

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

Other:

People who take alcohol should not exceed 2000 mg daily paracetamol dose (4 Effervescent Granules sachets).

4.3 Contraindications

OLEDRO HOT is contra-indicated in the following situations:

- Hypersensitivity to active substances or to other adrenergic drugs or to any of its ingredients
- Severe cardiovascular, liver (Child-Pugh category> 9) or kidney disease
- Severe hypertension and diseases accompanied by tachycardia
- Coronary artery disease
- Some urine remaining in the post-micturition cavity, prostate adenoma
- Bladder neck obstruction
- Piloroduodenal obstruction
- Stenotic peptic ulcer
- Lung diseases (including asthma)
- Narrow angle glaucoma

- G-6PD (glucose-6-phosphate dehydrogenase) deficiency
- Epilepsy
- Pregnancy and lactation (See 4.6 Pregnancy and lactation)
- Children under 12 years old

4.4 Special warnings and special precautions for use

It should be used carefully under doctor's control in patients with anemia, lung disease, liver and kidney dysfunction. For patients with pre-existing hepatic disease, during high-dose or long-term treatment it may be necessary to perform liver function tests at periodic intervals. In the case of renal insufficiency (creatinine clearance <10 ml / min) the physician must carefully evaluate the benefit / risk ratio of paracetamol use. Dosage adjustment should be performed and the patient should be monitored continuously.

- The recommended dose should not be exceeded or should not be used longer than 5 consecutive days. **High doses of paracetamol and a high total dose over a long period of time; may cause to develop analgesic-induced nephropathy with irreversible liver failure. When patients use this drug, they should be warned not to use other products containing paracetamol.**
- **Paracetamol may cause liver damage at chronic daily doses in adults.**
- As use of paracetamol with alcohol may cause liver damage, alcoholic beverages should not be consumed while this product is in use.
- It should be used with caution in alcoholic liver patients. People who take alcohol should not exceed 2000 mg daily paracetamol dose due to the risk of hepatotoxicity.
- Paracetamol causen acute high doses liver toxicity.
- First time users of paracetamol or those with a history of use before, at the first dose or repeated doses of use, rash, skin eruption or a skin reaction may occur. In this case, contact with the doctor to discontinue the use of the drug and an alternative treatment is required. People with skin reaction with paracetamol should not use this drug or another drug containing paracetamol. This can lead to skin reactions, including severe and fatal Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).

- In a patient receiving daily doses of therapeutic paracetamol for one year a patient with hepatic necrosis and a shorter duration of overdose liver damage has been reported.
- Liver enzymes may rise in 12-48 hours and prothrombin time may be prolonged. 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 impairment (Child-Pugh category <9) should use paracetamol carefully.
- During paracetamol administration at therapeutic doses, the serum alanine aminotransferase (ALT) level may increase.
- Simultaneous use of drugs that increase hepatic oxidative stress with paracetamol at therapeutic doses and reduce hepatic glutathione reserve, various conditions such as alcoholism, sepsis or diabetes mellitus may increase the risk of hepatic toxicity.
- Long-term use of paracetamol in high doses may cause kidney damage.
- It should be used with caution in glucose-6-phosphate dehydrogenase deficient patients. Rare cases of hemolysis can be seen.
- The use of paracetamol by patients with Gilbert syndrome may cause clinical symptoms such as jaundice and more pronounced hyperbilirubinemia. For this reason, these patients should use paracetamol carefully.
- Where anesthetics used that increase myocardial susceptibility to sympathomimetic drugs, preparations containing phenylephrine should not be used.
- Because of the possible vasoconstrictive effect of phenylephrine, it is necessary to be careful in patients over 70 years of age with cardiovascular disease.
- Use in diagnosed or suspected congenital prolonged QT syndrome or Torsades de Pointes patients should be avoided.
- Diseases of cardiovascular system
- Bronchial asthma
- Cerebral atherosclerosis

- Diabetes Mellitus
- Hypertension
- Idiopathic orthostatic hypotension
- Fechromocytoma
- Prostate hypertrophy
- Use in thyroid function disorders should be avoided.
- OLEDRO HOT should not be used in children under 12 years of age.
- It should not be used for more than 5 days. Apart from acute exacerbations, ıt should not be used in the treatment of phenylephrine chronic rhinitis.

Sodium stimulus

Each sachet contains 350 mg of sodium bicarbonate and 30 mg of sodium carbonate. This should be considered for patients on a controlled sodium diet.

Sugar (sucrose) stimulus

As OLEDRO HOT contains sugar, Patients with rare hereditary fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency problems should not use this drug.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol

Drug-drug interactions with paracetamol are usually minor and only become important if the therapeutic index of the other drug is low (eg, warfarin and kumarin) or is an anticonvulsant drug.

Co-administration of paracetamol with non-steroidal anti-inflammatory drugs (NSAIDs) may increase the adverse effects of NSAIDs on the kidneys.

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 unwanted effects.

Pharmacodynamic interactions have been found between paracetamol and other analgesics such as caffeine and opiates.

Probenecid prevents paracetamol metabolism.

Current data support that paracetamol hepatotoxicity does not increase when used with antiepileptic drugs such as phenobarbital, phenytoin or carbamazepine.

Rifampicin and isoniazid, used in the treatment of tuberculosis, increase the toxic effect of paracetamol on the liver.

Paracetamol and zidovudine, especially when used together during chronic treatment, may lead to an increase in the incidence of neutropenia. Therefore, paracetamol should not be taken with zidovudine unless medical advice is given.

Paracetamol (or its metabolites) interacts with enzymes involved in vitamin K-dependent coagulation factor synthesis. Interactions between paracetamol and warfarin or coumarin derivatives may lead to an increase in the "International Normalized Ratio" (INR) value and an increase in the risk of bleeding. For this reason, patients using oral anticoagulants should not use long-term paracetamol without medical supervision and control.

Simultaneous use of some hypnotics and antiepileptic drugs (glutethimide, phenobarbital, phenytoin, carbamazepine, etc.) or drugs that cause hepatic microsomal enzyme induction in the liver such as rifampicin with paracetamol doses that are harmless when used alone may lead to liver damage. Taking paracetamol even at therapeutic doses, in case of excessive alcohol consumption, can also cause liver damage.

The use of paracetamol in combination with chloramphenicol can prolong the half-life of coloramplanicol and therefore the toxicity of this drug may increase the risk.

Tropisetron and granisetron, 5-hydroxytryptamine (serotonin) type 3 receptor antagonists with pharmacodynamic interaction can completely suppress the analgesic effect of paracetamol.

Drugs that slow down gastric emptying, such as propantheline may cause slow absorption of paracetamol and so that the effect of paracetamol may occur later.

Drugs that accelerate gastric emptying, such as metoclopramide may cause paracetamol faster absorption and therefore may cause the paracetamol effect to start faster.

The rate of absorption of paracetamol may increase with metoclopramide or domperion and may decrease with cholestyramine.

St. John's Wort (Hypericum perforatum - yellow wort) may reduce blood levels of paracetamol.

When taken with food, the absorption rate of paracetamol may decrease.

Phenylephrine hydrochloride

Phenylephrine; monoamine oxidase (MAO) inhibitors (including macrobemide), alpha-and beta-blockers and antihypertensives (debrisoquine, guanethidine, reserpine), phenothiazine-type antihistamines (for example promethazine), bronchodilator sympathomimetics, tricyclic antidepressants (e.g., imipramine, amitriptyline), guanethidine or atropine, digitalis, Rauwolfia alkaloids, indometazine, methyldopa, other central nervous system stimulants and possibly theophylline have potency to interact.

The effect of phenylephrine pressor, which is used together with oxytocic drugs, is increased and phenylephrine used with some general anesthetics rarely reported as a risk of arrhythmia. In patients using intravenous ergot alkaloids (ergotamine and methylserjit), the blood pressure is likely to rise excessively. Digoxin and cardiac glycosides increase irregular heartbeat and heart attack risk.

Chlorpheniramine maleate

Chlorpheniramine may increase the effects of centrally acting drugs (sympathomimetics, antidepressants).

It may increase the effects of the central nervous system depressants such as alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytics and antipsychotics. 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 testing, as they may suppress the immediate histamine response.

Oxolamine citrate

Those treated with anticoagulant medication should consult a physician before using OLEDRO HOT.

4.6 Pregnancy and lactation (Category C)

General advice

Pregnancy Category: C

Women with childbearing potential / Contraception (Contraception)

There are no studies on the effects of OLEDRO HOT on women with potential for childbearing / contraception.

Pregnancy period:

There is not enough data on the use of OLEDRO HOT in pregnant women. Studies on animals are insufficient in terms of pregnancy, embryonal / fetal development, birth or postnatal developmental effects.

The potential risk for humans is unknown.

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

Lactation period:

OLEDRO HOT should not be used during breastfeeding unless it is necessary.

Reproduction ability / Fertility

There is no clinical study of the effect of OLEDRO HOT on reproductive ability.

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

OLEDRO HOT may cause drowsiness.

For this reason, patients should be warned to be cautious when driving a vehicle or machine. Sleepiness can be increased by the use of sedatives, tranquilizers and alcoholic beverages.

4.8 Undesirable effects

Drowsiness, dizziness, mouth or throat instability, headache, insomnia, irritability and nervousness, tachycardia and palpitations are the most frequently reported side effects. Sometimes uneasiness and sleep disturbances can occur, especially in children. Gastrointestinal disorders including constipation, diarrhea or bloating may occur; nausea and vomiting have been reported.

The following terms and frequency ratings were used:

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), unknown (can not be estimated from the given data)

<u>Paracetamol</u>

The undesirable effects of paracetamol are usually slight. If taken over 10 g, toxicity is likely to be seen.

Blood and lymph system diseases

Rare: When taken in large quantities, anemia, methemoglobinemia, thrombocytopenia due to haemolytic anemia for prolonged use, thrombocytopenic purpura, leukopenia, neutropenia and pancytopenia like blood count changes.

These side effects are not within the cause-effect relationship with paracetamol.

Very rare: Agranulocytosis

Immune system diseases

Rare: Allergic reactions, anaphylaxis

Very rare: Lyell syndrome

Unknown: 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

Hepatobilier diseases

Rare: hepatic impairment when taken in large quantities

Skin and subcutaneous tissue diseases

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

This symptom disappears when the medicine is stopped.

Kidney and urinary tract diseases

Uncommon: Nephrotoxic effects following the therapeutic doses of paracetamol are not common. Papillary necrosis has been reported in long-term administration. Patients who cannot tolerate acetylsalicylic acid (eg, asthmatic patients) may commonly react to paracetamol (5-10%)

Phenylephrine hydrochloride

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

Endocrine diseases

Unknown: The effects of metabolic function on endocrine and other regulators.

Psychiatric diseases

Unknown: Nervousness, irritability, restlessness and excitability.

Nervous system diseases

Unknown: Insomnia

Cardiac diseases

Unknown: elevation of blood pressure (especially in hypertensive patients), reflex bradycardia

Gastrointestinal diseases

Unknown: Nausea, vomiting

Kidney and urinary tract diseases

Unknown: Strain at the beginning of the mucosa and drop, painful urination has been reported.

The adverse events identified after marketing are described below. The frequency of these adverse events is not known but is likely to be infrequent.

Eye diseases

Unknown: Midriya, acute angle glaucoma (more likely to occur in those with closed angle glaucoma).

Skin and subcutaneous tissue diseases

It is not known: Allergic reactions (eg rash, urticaria, allergic dermatitis) are hypersensitivity reactions that involve cross-sensitization with other sympathomimetics.

Kidney and urinary tract diseases

Unknown: such as dysuria, urinal retention, this is mainly due to bladder outlet obstruction, prostatic hypertrophy

Phenylephrine may cause a slight increase in heart rate. Rarely, dizziness, headache, hypertension and restlessness have been reported.

Chlorpheniramine maleate

Blood and lymph 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

Unknown: Headache, sedation, paradoxical excitation in children, confused psychosis in the elderly

Rare: dizziness, irritability, unable to concentrate

Eye diseases

Rare: Blurred vision

Ear and inner ear diseases

Rare: Tinnitus

Cardiac diseases

Rare: Tachycardia, palpitations, arrhythmia, hypotension

Respiratory system diseases

Rare: thickening of the bronchial secretion

Gastrointestinal diseases

Unknown: Mouth dryness

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

Hepato-biliary diseases

Rare: Hepatitis, including Jaundice

Skin and subcutaneous tissue disorders

Unknown: allergic reactions including urticaria, exfoliative dermatitis, photosensitivity, skin reactions

Musculoskeletal disorders, connective tissue and bone diseases

Unknown: Muscle staging and incoordination

Kidney and urinary tract diseases

Unknown: Urinary retention

General disorders and application zone diseases

Rare: weakness, chest compression

Oxolamine citrate

Eye diseases

Rare: cases of optical illusion in children

Gastrointestinal diseases

Rare: Nausea, vomiting, burning of the stomach, increased intestinal motility, reduced transient mucus sensation

Skin and subcutaneous tissue diseases

Very rare: Urticaria

4.9 Overdose

Paracetamol

There is a possibility of toxicity in adults who take more than 10 g of paracetamol. Moreover, overdose damage is greater in people with non-cirrhotic alcoholic liver disease. Liver dysfunction following childhood overdose is relatively rare. The paracetamol half-life, which is around 2 hours in normal adults with paracetamol overdose with liver cell damage, usually lasts for 4 hours or more. Decrease in $^{14}CO_2$ elimination after ^{14}C -aminopyridine has been reported. It; compared to plasma paracetamol concentration or half-life, or conventional liver function test, establishes better relationship between paracetamol overdose and liver cell damage, renal failure may occur due to acute tubular necrosis following fulminant hepatic failure due to paracetamol.

However, this group is less common 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 overdosage, liver damage and nephrotoxic effects have been reported following ingestion of paracetamol daily excessive amounts.

Symptoms: Wilt, 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 the prothrombin time lasts from 12 to 48 hours, but clinical symptoms may not appear for 1 to 6 days after ingestion of the drug. Especially in children, visual disturbances, nausea, vomiting, headache, circulatory disorders, coma, convulsions, behavioral changes, hypertension and bradycardia are the symptoms that can be seen due to the mutual strengthening of the sympathomimetic effect of phenylephrine with the parasympatholytic effect of antihistamines.

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 up to 4 hours following overdose. For this reason, plasma paracetamol levels should be measured at least 4 hours after drug ingestion to determine the risk of hepatotoxicity. Additional treatment (additional oral methionine or intravenous N-acetylcysteine) should be evaluated under blood paracetamol content and time since drug ingestion. In patients receiving hepatic enzyme-inducing drugs, in long-term alcohol addicts or chronic nutritional deficiencies, It is suggested to reduce the treatment threshold by 30-50% with N-acetyl cysteine, because these patients may be more susceptible to the toxic effects of paracetamol. Following paracetamol overdose, fulminant hepatic failure treatment 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 during severe cases. However, the amount required to produce severe phenylephrine toxicity will be greater than the amounts that cause paracetamol-associated toxicity.

Treatment: The treatment should be clinically appropriate. Treatment with alpha-blocker drugs such as serious hypertension, phenolamine is required.

Chlorpheniramine maleate

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

Treatment: The treatment should be started by Ggastric lavage or silk syrup. Then the active carbon and the cathartics are applied to reduce the absorption. Other symptomatic and supportive precautions should be applied with special care according to heart, respiration, kidney and liver functions and liquid-electrolyte balance.

Hypotension and arrhythmia should be treated. CNS convulsions can be treated with IV diazepam. Hemoperfusion can be used in severe cases.

Oxolamine citrate

It has been reported treatment-free treatment of dizziness and color fadiness in a 3.5-year-old child receiving 600 mg in the literature; untreated recovery of dizziness, vomiting and agitation with sedative and analeptic administration in a 16-month-old child receiving 1300 mg. No antidote.

If earlier, the stomach is emptied, symptomatic and elimination of the symptoms are performed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other cold preparations

ATC code: R05X

Paracetamol is an effective pain reliever and fever reducer. It is though that the therapeutic effects of paracetamol is based on the inhibition of prostaglandin synthesis due to the inhibition of the cyclooxygenase enzymes. There is evidence that paracetamol is a more effective inhibitor of central cyclooxygenase than peripheral cyclooxygenase. Paracetamol has analgesic and antipyretic properties but it shows only weak anti-inflammatory properties. This situation can be explained by inflammatory tissues contain cellular peroxides at higher levels than other tissues and preventation of inhibition of cyclooxygenase by paracetamol of 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 blockages in the nose and sinuses with vasoconstrictor effect.

Chlorpheniramine maleate; It is an antihistaminic (antiallergic) substance that reduces the permeability in the capillaries and resolves such symptoms as nasal discharge, sneezing, watering in the eye and itching.

Oxolamine citrate

Oxolamine is an anti-inflammatory agent. Cough is usually a manifestation of inflammation and irritation of the airways mucosa. Coughing and symptomatic cuts are not the main treatment.

Oxolamine abolishes the inflammation of the respiratory tract mucosa along with its associated fever, pain and spastic irritation; dilutes secretions with mucolytic effect; As a result, it treats cough with reason. Due to its peripheral effect, oxolamine does not cause side effects (constipation, respiratory depression, dizziness, dizziness, habit) specific to the central cough cutter; does not inhibit siliceous movements.

5.2 Pharmacokinetic properties

Paracetamol

Absorption of paracetamol is mainly from the small intestines.

Absorption: Paracetamol is rapidly and completely absorbed through the gastro-intestinal tract by passive diffusion; the highest concentrations in the plasma are generally obtained between 30 and 90 minutes after oral administration, depending on the formulation. Gastric emptying is a rate-limiting step for oral paracetamol absorption. Paracetamol is not fully found in the systemic circulation after oral administration because it undergoes first pass metabolism in a variable manner. The oral bioavailability in adults seems to depend on the amount of paracetamol administered. Oral bioavailability increases from 63% after 500 mg dose to about 90% after 1 or 2 g (tablet form) dose.

Distribution: Paracetamol is distributed in equal amounts to most body fluids; the estimated distribution volume is 0.95 l / kg. Following therapeutic doses, paracetamol does not bind significantly to plasma proteins.

The distribution kinetics (Vd / F) in children is similar to that of adults.

Biotransformation: Paracetamol metabolizes in the liver and many metabolites are identified in the human body. The major metabolite is urinary glucuronide and sulphate 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 is rapidly conjugated with reduced glutathione and is released as cysteine and mercapturic acid conjugates. When large quantities of paracetamol are ingested, hepatic glutathione may be reduced and hepatocyte binding as a chase to vital hepatocellular macromolecules leads to excessive accumulation of acetaminophen. This leads to hepatic necrosis, which can be seen in the case of overdose.

Elimination: Following single dose (1000 mg i.v.), total body clearance of paracetamol is about 5 ml / min / kg. The renal clearance of paracetamol is dependent on the urine

flow rate, but not on pH. Less than 4% of the administered drug is discarded as unchanged paracetamol. In healthy individuals, about 85-95% of the therapeutic dose is excreted in the urine within 24 hours.

Linearity and non-linearity: Attachment of reactive paracetamol metabolites to liver cell proteins results in hepatocellular injury. At therapeutic doses, these metabolites are linked by glutathione and form nontoxic conjugates. However, in the event of a massive overdose, the SH-donors of the liver (which facilitate and stimulate glutathione formation) drain; However, in the event of a massive overdose, the SH-donors (which facilitate and stimulate glutathione formation) drain out of the liver; 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.

Pharmacokinetics are linear when used properly.

Phenylephrine hydrochloride

Absorption: Irregular absorption from the gastrointestinal tract due to monoaminoxidases.

Distribution: When taken orally, it maintains its efficacy as a nasal congestion and drug distribution is distributed to the vascular layer of the nasal mucosa via systemic circulation. Distribution volume (Vd) beginning: 26-61; steady-state distribution volume (Vdss) 184-543 L (mean: 340 L)

Biotransformation: Phenylephrine is first metabolised by monoaminoxidase in the intestine and liver. It has limited oral bioavailability due to first pass effect.

Elimination: Phenylephrine is excreted mainly in the form of inactive metabolites. The elimination half-life is about 5 min for the alpha phase and 2-3 hours for the terminal phase.

Linearity and non-linearity: Data is not available.

Chlorpheniramine maleate

Absorption: 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%.

Distribution: 70% of chlorpheniramine in circulation is bound to proteins. Chlorpheniramine in the body, including the central nervous system, are distributed widely.

Biotransformation: First-pass metabolism is apparent in the liver. Chlorpheniramine is highly metabolized. Metabolites are desmethyl and didesmethyl chlorpheniramine.

Elimination: There are distinct individual differences in the pharmacokinetics of chlorpheniramine; half-life is reported as 2-43 hours. Unchanged drugs and their metabolites are mainly excreted in the urine.

Linearity and non-linearity: Data is not available.

Oxolamine Citrate

Absorbation:

When you give by mouth,after absorption the antitussive effect is shown within 1 hour and this effect takes 3-4 hours.

Distribution:

When given orally, it is absorbed and then distributed to body tissues. Anesthesia occurs especially at the tips of the afferent nerve by penetrating into the bronchial mucosa and reduces impulse transmission.

Biotransformation:

With hydrolitic separation, it metabolizes to diethylamine and a neutral derivative. Some of the medicine is thrown out of the body as an unchanged molecule.

Elimination:

10% of the drug taken from urine is in unchanged form, 0.6% is in the form of neutral derivatives and diethylamine formed by hydrolysis.

Linearity / nonlinearity:

No data available.

5.3 Preclinical safety data

Paracetamol

Acute Toxicity

Paracetamol was found to be slightly toxic after oral administration to adult rats and guinea pigs. The reason being significantly more toxic in rats and newborn rats is

probably due to the different metabolism of the substance in mice and the hepatic enzyme system in newborn rats is immature.

It caused puking when given at higher doses to dogs and cats. For this reason, oral LD50 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 the 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 explained not as direct 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 embryotoxic 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

Chlorpheniramine maleate

There is not enough preclinical experience.

Oxolamine citrate

Toxicological studies on various animal species have shown that oxolamine is well tolerated; not forming teratogenic or mutagenic effects.

In various animal species tested oral LD50 values are between 650 and 2500 mg / kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid

Citric acid

Sodium bicarbonate

Sodium carbonate

Quinoline yellow

Lemon flavour

Collidone K-30

Saccharin sodium

Sugar (sucrose)

6.2 Incompatibilities

There is no known incompatibility.

6.3 Shelf Life

24 months.

6.4 Special precautions for storage

Keep in original package, do not store above 25°C and a dry place.

6.5 Nature and contents of container

On packages containing 6 and 12 Sachets

Primer packing: PET / AL / PE Sachet

Sekonder packing: Carton box

6.6 Removal of remaining substances from medical medicinal products and other special precautions

It must be disposed of in accordance with the "Regulation on Control of Medical Wastes" and "Control of Wastes on Packaging and Packaging".

7 MARKETING AUTHORISATION HOLDER

Drogsan İlaçları San. ve Tic. A.Ş.

Oğuzlar Mah. 1370. Sok. 7/3

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TURKEY

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