SUMMARY OF PRODUCT CHARACTERISTICS

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(S P C)

APOTEL PLUS®

Solution for injection (600+20) mg/4ml AMP.

1. **PRODUCT NAME**

APOTEL PLUS®

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION (in active substance)**

Each 4 ml ampoule contains 600mg Paracetamol and 20mg Lidocaine hydrochloride.

3. **PHARMACEUTICAL FORM**

Solution for injection for intramuscular use.

4. **CLINICAL DATA**

4.1. Therapeutical Indications

✓ **APOTEL PLUS®** is indicated for the management of pain in surgery, particularly postoperatively and also for the management of neoplasm-related pain.

✓ **APOTEL PLUS®•** is also indicated for the symptomatic treatment of infection-related fever or neoplastic fever.

4.2. Dosage and Administration

Adults: 1 ampoule (0.5 g – 1 g) 3 - 4 times daily.

An interval of 4 hours between administrations is recommended.

The maximum daily dose should not exceed the 5 ampoules.

In cases of acute renal failure (creatinine clearance <10ml/min), an interval of 8 hours between 2 administrations is recommended.

Children over 12 years old: 1 ampoule (0.5 g – 1 g) 3 - 4 times daily.

Children 6-12 years old: ½ -1 ampoule (250 mg – 500 mg) 3 - 4 times daily.

Children 1-6 years old: ¼ - 1/3 ampoule (125 mg – 250 mg or 10 mg/kg) 3 - 4 times daily.

4.3. Contraindications

APOTEL PLUS• is contraindicated to patients with:

- Hypersensitivity to paracetamol or lidocaine, or to any of the products excipients.
- During pregnancy since the excipient Glycerol Formal of the product has been associated with teratogenesis in laboratory animals. Cases of venosinal, sinoventricular and intraventicular block.
- History of spasms.
- Severe hepatic or renal insufficiency.

4.4. Warnings and Precautions during Administration

Attention: The product is administered intramuscularly. The intravenous administration is prohibited. The product should not be administered to patients that take anti-arrhythmic medications.

APOTEL PLUS• should be administered with caution in the following cases:

- To patients with hepatic or renal dysfunction,
- To patients with heart failure,
- To alcoholics,
- In chronic malnutrition (low hepatic glutathione reserves),
- Caution is required when it is administered during lactation given the fact that there are no studies on the effects of the excipient Glycerol Formal in this period,
- In porphyria,
- In anti-coagulant treatment in progress (risk of hematoma as with all drugs administered intramuscularly),
- To children since they are more sensitive to medicine overdose,
- In chronic administration or in administration of large doses of the medicine the liver function should be monitored.

4.5. Drug Interactions

Paracetamol:

- Cholestyramine reduces the absorption of paracetamol while metoclopramide and domperidone increase the absorption of paracetamol.

  Concurrent administration of drugs that are hepatic enzyme inducers (such as phenobarbital), or medicines that can act hepatotoxically (such as Non-Steroidal Anti-inflammatory Drugs, interferons) can increase the risk of hepatic injury.
- Patients taking barbiturates, tricyclic antidepressants and alcohol may show a reduced metabolic activity of large doses of paracetamol and increase paracetamol's half-life in plasma.
- Probenecid may reduce the renal absorption and increase paracetamol's plasma levels.

- Concurrent administration with oral anti-coagulants may increase the risk of hemorrhage.
- Paracetamol decreases the bioavailability of lamotrigine, however, the clinical significance of that is not clear.
- Following overdosage, alcohol may possibly increase the hepatotoxicity of paracetamol.
- Chronic oral administration of anti-epileptic drugs or steroidal contraceptives affect the hepatic enzymes and may interfere with the attainment of therapeutic levels in plasma by increasing either first order metabolism or elimination.

Lidocaine:

Combined therapy of cimetidine or propranolol could increase lidocaine's serum levels. Cimetidine and propranolol reduce the clearance of lidocaine.

Laboratory tests:

Paracetamol:

Paracetamol could give false blood uric acid results by the phosphotungstic acid method and false glucose results with the oxidase-hyperoxidase method.

Lidocaine:

The intramuscular administration of lidocaine could increase creatine-kinases serum concentrations, such as creatine-phosphokinase, so the determination of isoenzymes is required for the diagnosis of a possible acute myocardial infarction.

4.6. Pregnancy and Lactation

Pregnancy:

To date, no evidence has been generated that paracetamol has adverse effects on the fetus. However, the usual precautions concerning the use of medicines during pregnancy, especially during the first trimester, should be taken.

The safety of lidocaine during pregnancy has not been clarified, therefore it should be administered with caution.

The teratogenic effect of the excipient Glycerol Formal in humans cannot be ruled out. *(see section 5.3. Pre-clinical data relative to safety).* For this reason, the medicine should not be used during pregnancy and when pregnancy is likely to occur.

Lactation:

- Paracetamol is excreted in breast milk and has been detected at 1: 1 concentrations in plasma but does not appear to have adverse effects in the infant when administered according to the dosage regimen**.**
- Lidocaine is excreted into breast milk, therefore the necessary precautions should be taken.

There are no studies on the effects of the excipient Glycerol Formal during lactation and therefore caution is required when the product is administered during this period.

4.7. Effect on the ability to drive or use machinery

The administration of this medication does not affect the ability to drive of handle machinery.

4.8. Undesirable effects

***Paracetamol*:**

In the recommended doses, almost no adverse reactions have been reported.

Administration of large doses or long-term treatment may cause mild gastric disorders, hemolytic anemia, granulocytopenia, methemoglobinemia, skin reactions, pruritus, fever, hypoglycemia, excitation of the Central Nervous System or drowsiness and thrombocytopenic purpura.

Extended administration of high doses may cause nephropathy and rarely pancreatitis.

Cases of hypersensitivity, characterized by pruritus, dyspnoea and hypotension have been described rarely and discontinuation of the medication is required.

Lidocaine:

At therapeutic doses, dizziness, confusion, illusions, spasms and dyspnoea have been reported.

4.9. Overdose

Paracetamol:

Overdosage could be the result of an accidental or deliberate administration of large amounts of paracetamol or the result of a long term administration of high doses of paracetamol. The consequences can be extremely serious. Ingestion of 10 to 15 g of paracetamol by adults may cause severe hepatocellular necrosis and less often renal tubular necrosis.

The symptoms of an overdosage settle within 24 hours and become more severe. They include nausea, vomiting, sweating, lethargy, and abdominal pain. Liver damage is apparent even 4 to 6 days post-ingestion while the severity of the liver damage attains its maximum point within 3 to 4 days post-ingestion. Liver damage following an overdose may result in hepatic failure with encephalopathy, coma and even death. Acidosis, cerebraloedema, haemorrhage, hypoglycaemia, hypotension, infection and renal failure may be presented.

The laboratory findings include hypertransanaemia, hyperbilirubinemia and increased prothrombin time which is a reliable indicator of liver function and should be monitored regularly.
Acute renal failure and acute renal tubular necrosis may be caused even in the absence of hepatic failure.
Other symptoms of paracetamol overdosage may include myocardial abnormalities and pancreatitis.
The possibility of paracetamol's toxic effect increases in chronic alcoholism, in patients taking drugs that induce the hepatic enzymic systems or patients that suffer from malnutrition.
The toxicity of paracetamol is attributed to the production of one of it's metabolites, N-acetyl-p-benzoquinoneimine (NABQI), which is completely detoxified by conjugation with glutathione and excreted as mercaptopurine and cysteine conjugates. However, following paracetamol overdosage, tissue stores of glutathione become depleted allowing the free NABQI to accumulate and bind to sulfhydryl groups within hepatocytes, leading to their destruction.
Substances such as acetylcysteine and methionine which are capable of replenishing depleted stores of glutathione, are used as antidotes in paracetamol overdosage.
Prompt treatment of overdosage is essential and the patients should be admitted to the hospital.
Gastric lavage is of benefit when is done within 2 hours of ingestion because it removes from the stomach any drug residues. Activated charcoal may be given to reduce gastrointestinal absorption. Supportive measurements are necessary.
Administration of the antidote starts promptly, as long as the ingested dose is more than 125 mg/kg body-weight for adults, and more than 200 mg/kg body-weight for children and depending upon the levels of paracetamol in the plasma the antidote treatment is either continued or suspended.

Plasma paracetamol concentrations should be determined 4 hours post ingestion and the maximum time up to which the concentrations should be recorded is 16 hours post ingestion.

The patient's plasma-paracetamol concentration is compared against a standard Rumac Matthew nomogram reference line on a plot of plasma-paracetamol concentration against hours after ingestion. Administration of the antidote is necessary is the patient's levels are above the critical line. Generally it is considered that ingestion of more than 10g of paracetamol can clinically cause hepatocellular damage. Lethal damage is usually caused after ingestion of more than 25 g. Plasma-paracetamol concentrations are associated with the severity of the hepatic damage. Concentration levels above the 300μg/cubic cm 4 hours post ingestion are indicators of severe damage.

However, concentration levels below the 150μg/cubic cm suggest that hepatic damage is unlikely to develop.

Acetylcysteine is administered either orally or intravenously. Eventhough acetylcysteine is more effective when administered within 8 hours post ingestion, it is mandatory that it should be administered even if 24 hours have elapsed since the ingestion.

The initial intravenous dose is 150 mg/kg body-weight diluted in 200 cubic cm of glucose 5% given by infusion over 15-20 minutes, followed by an intravenous infusion of 50mg/kg body-weight in 500 cubic cm of glucose 5% over the next 4 hours and then 100 mg/kg body-weight in 1000 cubic cm of glucose 5% over the next 16 hours.

The total time of administration is 20 hours. If an anaphylactic reaction develops, it is managed with antihistamine drugs and the administration of acetylcysteine is possible to continue at a slower rate.

Acetylcysteine is given orally at an initial dose of 140 mg/kg followed by 70mg/kg every 4 hours, for 17 times.

Methionine should be administered at the latest 10 hours post ingestion, otherwise is effectiveness is reduced. 2.5 g are administered orally every 4 hours and for 4 times.
However, if the measured levels of paracetamol are below the critical point, the administration of the antidote is stopped.

If antidote treatment fails that indicates that liver transplantation has to be considered.

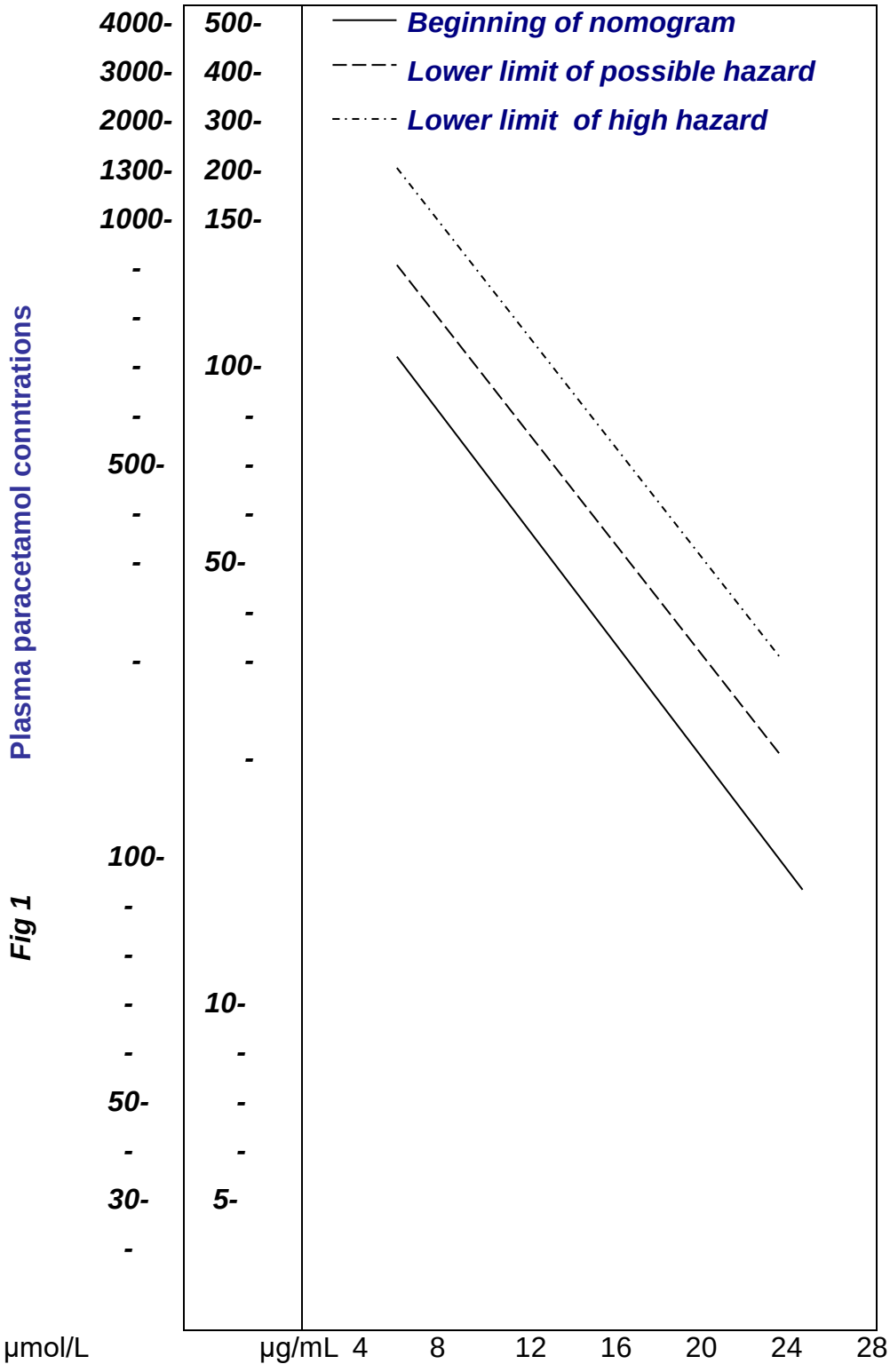

Fig 1

RUMACK MATTHEW nomogram of the determination of danger/hazzard of hepatocellular damage according to plasma paracetamol concentrations. It applies

only for once a day dose of paracetamol. For people in the high hazard area, the danger/hazard starts from the continuous line.

Lidocaine:

The high lidocaine plasma concentrations (>9μg/ml) may provoke severe reactions, in particular convulsions. Also, they may cause muscle tremor, loss of consciousness, coma, cardiovascular repression and respiratory failure. The high lidocaine plasma concentrations in patients presented with myocardial conduction disorders, could cause low blood pressure, arrhythmia, heart block and bradycardia that may result in cardiac arrest.

In patients under anesthesia, general phenomena of toxicity of central etiology or convulsions are not observed. However, cardiovascular depression is the first toxic manifestation in these patients.

- The appearance of severe reactions requires the suspension of treatment and urgent medical care. It is absolutely necessary to maintain sufficient ventilation and keep the air passages clear.
- The convulsions should be treated with low intravenous dosages of diazepam or barbituates with a very short onset (thiopental, thiamylal) or even pentobarbital or secobarbital. If the patient under anesthesia, it is recommended that succinylcholine should be administered intravenously.
- In case of circulatory depression, the intravenous administration of liquids and vasopressive substances such as ephedrine or metaraminol may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

ATC Code: N02BE51

Paracetamol:

Paracetamol is the major active metabolite of phenacetin but lacks its side effects. Paracetamol has an analgesic and antipyretic effect similar to acetysalicylic acid and mild antinflammatory action. Paracetamol is an inhibitor of the prostaglandine biosynthesis even though that if there is evidence that is more effective against the Central Nervous System enzymes comparing to those of the periphery.

Its antipyretic effect is due to a direct effect on hypothalamic thermoregulatory centers. The mechanism of its analgesic action is not known.

Single or repeated dose does not affect the cardiovascular or respiratory system. It does not cause gastric irritation like the salicylates do and it has a weak effect on platelets.

Lidocaine:

The effect of Lidocaine is due to the reduction of the permeability of the cellular membrane concerning sodium ions resulting in the retardation of the potential inversion to a degree where no action potential is created.

These changes cause a reversible blockage of the nerve impulse resulting in a temporary and local elimination of the sensitivity to pain.

Lidocaine chemically belongs to the amino-amide group and is considered as a medium duration topical anesthetic. Its effect is manifested immediately and its duration lasts from 90-200min.

The other pharmacological properties of Lidocaine (in cases of systemic infusion) are due to its extensive presence in the neural membranes at the stimulation phase and vary depending up on its concentration.

5.2. Pharmacokinetic Properties

PARACETAMOL:

Absorption

Paracetamol is absorbed rapidly when administered orally. Peak plasma concentrations are reached 30-60 min post ingestion.

Distribution

Paracetamol is rapidly distributed across all tissues. Concentrations are comparable in blood, plasma and saliva. Standard analgesic plasma concentrations are 5-20 mcg / ml. It has been found that there is a good relationship between its plasma concentration and its analgesic effect.

Its plasma protein binding ranges between 20% and 50% at toxic concentrations.

It penetrates the placenta and is excreted in the milk. Plasma protein binding is low.

Metabolism

Paracetamol is metabolized predominantly in the liver.

Paracetamol is mainly metabolised in the liver. Approximately 4% is metabolised by liver cytochromes P-450 and oxidized to a toxic metabolite which detoxifies by selective binding to hepatic glutathione and is excreted in the urine associated with cysteine and mercapturic acid.

The two most important routes of metabolism are the conjugation resulting in the formation of glucuronide as well as sulfate

compounds. It is excreted in the urine mainly in the form of glucuronide and of sulfate conjugates.

This second way is quickly saturated if doses larger than the therapeutic ones are administered.

A small quantity is metabolized through multiple – function of liver and kidney oxidases towards the hydroxylated metabolite N-acetyl-p-benzoquinoneimine (NABQI), which is toxic to the cells, but under the recommended doses, is inactivated by glutathione and is excreted conjugated with mercaptopurine and cysteine.

The mean half-life during excretion is 1-4 hours.

Excretion

Excretion occurs mainly with urine in the form of inactive glucuronide (60-80%) and sulphate metabolites (20-30%) and 5% is removed unchanged.

90% of the ingested oral dose is excreted by the kidneys in 24 hours as glucuronic acid conjugates (60-80%) or sulfate conjugate (20-30%).

Less than 5% is excreted as non-metabolized paracetamol.

The elimination half-life is about 2 hours.

Renal insufficiency

The elimination of paracetamol and its metabolites is retarded when the creatinine clearance is < 10ml/min.

Hepatic insufficiency

According to the latest studies the metabolism of paracetamol does not seem to be influenced by hepatic insufficiency.

Elderly

The ability of binding is not changed.

Neonates, infants and children

The pharmacokinetic parameters of paracetamol observed in infants and children are similar to those observed in adults, except for the plasma half-life, which is a little shorter (about 2 hours) than that of adults. In neonates, the half-life is longer than that of infants (about 3.5 hours).

Neonates, infants and children up to 10 years of age significantly excrete less glucuronides and more conjugated sulphates than adults. Total excretion of paracetamol and its metabolites is the same for all ages.

LIDOCAINE HYDROCHLORIDE:

Absorption

During its intramuscular administration, lidocaine exhibits gradually an increasing and extended increase of its concentration in blood plasma. The administration of 6mg/kg of lidocaine 10% into the deltoid muscle yields therapeutic concentrations greater than 1.5μg/ml for 120 min. The absorption differs depending upon the muscle in which the injection is performed. In the gluteus muscle the absorption is significantly lower in comparison to the deltoid muscle.

Distribution

Lidocaine is distributed mainly in the spleen, the lungs and the kidneys. It shows greater chemical affinity to plasma than to erythrocytes, which results in a lower concentration in blood than in plasma. The distribution volume is 1.32 l/kg. The percentage of plasma binding is approximately 65%.

Metabolism

95-97% of lidocaine is metabolized in the liver. During the first stage of metabolism two successive diethylations are observed from which

two active metabolites are produced, the monoethylglycine xylidate and then glycine xylidate.

Excretion

The amide bond of the substance is hydrolyzed and forms xylidine, which is hydroxylated to para(p-) position and excreted through the urine. The rate of clearance is approximately 10mg/min/kg. Due to the intense metabolism in the liver, its removal can be delayed in pathological or non-pathological cases (b-inhibitors of epinephrine, cimetidine) where there is reduction of the hepatic circulation or in the case of hepatic insufficiency.

5.3. Pre-clinical data relative to safety

Paracetamol:

The effects of paracetamol on the diet of rats and mice at 0, 600, 3000 and 6000 ppm for 2 years have been evaluated. There was no evidence of carcinogenic activity of paracetamol in male rats as well as in male and female mice. Ambiguous evidence of carcinogenicity was noted in female rats due to an increased incidence of mononuclear cell leukemia.

The comparative review of the genotoxic and carcinogenicity of paracetamol has shown that the genotoxic effects of paracetamol occur only at doses above the recommended range, resulting in severe toxic effects, including severe hepatocellular and bone marrow toxicity. The therapeutic doses of paracetamol do not exceed the limit for causing genotoxicity. Animal studies did not indicate carcinogenic potential at non-hepatotoxic levels. Oncogenic effects of paracetamol have been observed in older studies only after very high cytotoxic doses.

Lidocaine:

Not Applicable.

Excipient Glycerol Formal:

The excipient Glycerol Formal shows teratogenic effects in laboratory animals.

No teratogenic effects have been observed in humans.

6. PHARMACEUTICAL DATA

6.1. Excipients List

- Edetate disodium
- Sodium metabisulfite
- Disodium phosphate dodecahydrate
- Ethanol
- Glycerol formal
- Water for injection

6.2. Incompatibilities

None known.

6.3. Shelf Life

36 months, given that the product is kept in its original package according to the storage directions.

The medication should not be used after the date printed on the package has expired.

6.4. **Storage**

The product **APOTEL PLUS®** should be stored in the original closed package at temperature ≤ 30 °C.

6.5. **Packaging**

Carton box which contains 3 amber glass ampoules of 4ml solution for injection, packaged in Polyethylene pack, along with a Patient Information Leaflet.

6.6. **Administration Directions**

Not applicable.

7. **MARKETING AUTHORIZATION HOLDER**

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8. **MARKETING AUTHORIZATION NUMBER**

61314/14/30.03.2015.

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26.11.2002.

10. DATE OF REVISION OF THE TEXT

30.03.2015.