SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF PHARMACEUTICAL PRODUCT

APOTEL 500 mg tablets

APOTEL 125, 250 & 500 mg suppositories

APOTEL 500 & 1000 mg effervescent tablets

APOTEL 100 mg/ml oral drops, solution

APOTEL 120 mg/5 ml elixir

APOTEL 500 mg coated tablets

APOTEL 120 mg/5 ml syrup

APOTEL 80, 160, 500 & 1000 mg effervescent granules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

✓ ***APOTEL 500 mg tablets***

Each APOTEL tablet contains 500 mg paracetamol.

✓ ***APOTEL 125, 250 & 500 mg suppositories***

Each APOTEL suppository contains 125, 250 and 500 mg paracetamol respectively.

✓ ***APOTEL 500 & 1000 mg effervescent tablets***

Each APOTEL effervescent tablet contains 500 and 1000 mg paracetamol respectively.

Excipients with known effect:

Each APOTEL 500 mg effervescent tablet contains 330 mg sorbitol and 292.7 mg sodium.

Each APOTEL 1000 mg effervescent tablet contains 299.8 mg sorbitol and 381.2 mg sodium.

✓ ***APOTEL 100 mg/ml oral drops, solution***

Each product ml contains 100 mg paracetamol.

1 ml = 40 drops (in inclination).

Excipients with known effect:

Each product ml contains 60 mg polypropylene glycol, 2.4 mg sodium and 1 mg sodium metabisulphite.

✓ ***APOTEL 120 mg/5 ml elixir***

Each product ml contains 24 mg paracetamol.

Excipients with known effect:

Each product ml contains 70 mg sorbitol, 0.43 mg sodium and 0.05 mg sucrose.

✓ ***APOTEL 500 mg coated tablets***

Each APOTEL coated tablet contains 500 mg paracetamol.

✓ ***APOTEL 120 mg/5 ml syrup***

Every 5 ml of product contain 120 mg paracetamol.

✓ ***APOTEL 80, 160, 500 & 1000 mg effervescent granules***

Each sachet of APOTEL effervescent granules contains 80, 160, 500 and 1000 mg paracetamol, respectively.

Excipients with known effect:

APOTEL 80 mg effervescent granules contain 80 mg sorbitol and 35.67 mg sodium.

APOTEL 160 mg effervescent granules contain 160 mg sorbitol and 71.35 mg sodium.

APOTEL 500 mg effervescent granules contain 2,330 mg sorbitol, 49.78 mg sodium and 500 mg sucrose.

APOTEL 1000 mg effervescent granules contain 1,044.8 mg sorbitol, 99.55 mg sodium and 1000 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- ✓ Tablets.
- ✓ Suppositories.
- ✓ Effervescent tablets.
- ✓ Oral drops, solution.
- ✓ Elixir.
- ✓ Coated tablets.
- ✓ Syrup.
- ✓ Effervescent granules.

4. CLINICAL INFORMATION

4.1. Therapeutic indications

Treatment for mild to moderate intensity pain, dysmenorrhea and as antipyretic.

4.2. Posology and method of administration

In children and adults, the dosage should be determined according to the patient's body weight. To avoid the risk of overdose, confirm that concomitant medications (including prescription and over-the-counter) do not contain paracetamol (see 4.4 Special warnings and precautions for use). Accidental overdose may lead to serious hepatic damage and death (see 4.9 Overdose).

APOTEL tablets

For adults and adolescents older than 14 years old, APOTEL tablets should be administered in dosages of 10-15 mg/kg every 4 to 6 hours up to a maximum total daily dosage of 75 mg/kg/day. The maximum daily dose should not exceed 4 grams.

Table 1: Dosage of Apotel tablets for adults with body weight equal with or higher than 50 kg and adolescents over 14 years old.

APOTEL product	Paracetamol dose (mg)	Maximum Number of Tablets per Dose	Minimum Interval between doses[1] (hours)	Maximum Daily Dose (tablets)
500 mg tablets (simple, effervescent, coated)	500 mg	2	4 to 6 hours	8 (4,000 mg)
1,000 mg tablets (effervescent)	1,000 mg	1	4 to 6 hours	4 (4,000 mg)

The approximate age ranges in relation to body weight are provided for guidance only. The ages should be used based on the local standard growth curves.

Do not use these tablets in the dosage stated in table 1 in adults or children with body weight less than 50 kg. This will lead to the intake of a higher dose than the recommended one (overdose) and may cause damage to the liver.

For children over 10 years old, follow the dosage in table 2 for effervescent tablets.

Table 2: Dosage of APOTEL 500 mg effervescent tablets for children over 10 years old.

Body Weight (kg)	Approximate Age (years)*	Paracetamol Dose (mg)	Maximum Number of Effervescent Tablets per Dose	Minimum interval between doses (hours)	Maximum Daily Dose (tablets)
27 to < 40	10 to < 11	500	1	6	4 (2,000 mg)
40 to < 50	11 to < 12	500	1	4	6 (3,000 mg)
≥ 50	12 to ≤ 14	500	1 to 1.5	4 to 6	6 (3,000 mg)

* The approximate age ranges in relation to body weight are provided for guidance only. The ages should be used based on the local standard growth curves.

APOTEL effervescent granules

For adults and adolescents older than 14 years old, APOTEL effervescent granules should be administered in dosages of 10-15 mg/kg every 4 to 6 hours up to a maximum total daily dosage of 75 mg/kg/day. The maximum daily dose should not exceed 4 grams.

Table 3: Dosage of APOTEL effervescent granules for adults with body weight equal with or higher than 50 kg and adolescents over 14 years old.

APOTEL product	Paracetamol dose (mg)	Maximum Number of Sachets per Dose	Minimum interval between doses (hours)	Maximum Daily Dose (sachets)
500 mg effervescent granules	500 mg	2	4 to 6 hours	8 (4,000 mg)
1,000 mg effervescent granules	1,000 mg	1	4 to 6 hours	4 (4,000 mg)

The approximate age ranges in relation to body weight are provided for guidance only. The ages should be used based on the local standard growth curves.

Do not use these tablets in the dosage stated in table 3 in adults or children with body weight less than 50 kg. This will lead to the intake of a higher dose than the recommended one (overdose) and may cause damage to the liver.

Table 4: Pediatric Dosage for APOTEL 80, 160 and 500 mg effervescent granules according to body weight

Body Weight (kg)	**Approximate Age (years)***	**Paracetamol dose (mg)**	**Maximum Number of 80 or 160 mg Sachets per Dose**	**Maximum Number of 500 mg Sachets per Dose**	**Minimum interval between doses (hours)**	**Maximum Daily Dose (sachets)**
< 8	< 1	Please consult a doctor				
8 to < 12	1 to < 2	120	1.5 of 80 mg	-	6	6 480 mg
12 to < 16	2 to < 3	160	2 of 80 mg	-	6	9 720 mg
16 to < 20	3 to < 7	240	3 of 80 mg or 1.5 of 160 mg	-	6	12/6 960 mg
20 to < 27	7 to < 10	240	3 of 80 mg or 1.5 of 160 mg	-	4	18/9 (1,440 mg)
27 to < 40	10 to < 11	500	-	1	6	4 (2,000 mg)
40 to < 50	11 to < 12	500	-	1	4	6 (3,000 mg)
≥ 50	12 to ≤ 14	500-750	-	1-1.5	4 to 6	6 (3,000 mg)

* The approximate age ranges in relation to body weight are provided for guidance only. The ages should be used based on the local standard growth curves.

APOTEL suppositories

In children and adolescents younger than 15 years old, the maximum daily dosage of paracetamol suppositories is *60 mg/kg/day* at 4 different times, approximately 15 mg/kg every 6 hours.

In adults and adolescents older than 15 years old, the maximum daily dosage of paracetamol suppositories is *75 mg/kg/day* at 4 different times, approximately 15 mg/kg every 6 hours. The maximum daily dose should not exceed 4 grams.

Adults and children older than 12 years old: 0.5-1g, 3-4 times per day
Children 6-12 years old: 250-500 mg, 3-4 times per day
Children 1-5 years old: 125 -250 mg 3-4 times per day

Due to the risk of local toxicity, suppositories should not be used more than four times a day and more than 2 suppositories should not be administered at the same time. The duration of treatment via the rectal route must be as brief as possible.
The use of suppositories is not recommended to patients suffering from diarrhea.

APOTEL syrup/APOTEL elixir

In children younger than 8 years old, the maximum daily dosage of paracetamol is 60 mg/kg/day at 4 different times, approximately 10-15 mg/kg every 6 hours.

Table 5: Pediatric Dosage for APOTEL 120 mg/5 ml syrup and APOTEL 120 mg/5 ml elixir according to body weight

Body Weight (kg)	**Approximate Age (years)***	**Paracetamol Dose (mg)**	**Number of ml per Dose**	**Minimum interval between doses (hours)**	**Maximum Daily Dose (ml)**
< 8	< 1	Please consult a doctor			
8 to < 12	1 to < 2	120	5	6	20 (480 mg)
12 to < 16	2 to < 3	180	7.5	6	30 (720 mg)
16 to < 20	3 to < 5	240	10	6	40 (960 mg)
20 to < 24	5 to < 6	300	12.5	6	50 (1,200 mg)
24 to ≤ 28	6 to ≤ 8	360	15	6	60 (1,440 mg)

* The approximate age ranges in relation to body weight are provided for guidance only. The ages should be used based on the local standard growth curves.

For children 8-12 years old there are alternative pharmaceutical forms and dosages available.

APOTEL oral drops

In children younger than 8 years old, the maximum daily dosage of paracetamol is 60 mg/kg/day at 4 different times, approximately 10-15 mg/kg every 6 hours.

Table 6: Pediatric Dosage of APOTEL 100 mg/ml oral drops, solution according to body weight

Body Weight (kg)	**Approximate Age (years)***	**Paracetamol Dose (mg)**	**Number of ml (drops) per Dose**	**Minimum interval between doses (hours)**	**Maximum Daily Dose in ml (drops)**
< 8	< 1	Please consult a doctor			
8 to < 12	1 to < 2	120	1.2 (48)	6	4.8 (192) (480 mg)
12 to < 16	2 to < 3	180	1.8 (72)	6	7.2 (288) (720 mg)
16 to < 20	3 to < 5	240	2.4 (96)	6	9.6 (384) (960 mg)
20 to < 24	5 to < 6	300	3 (120)	6	12 (480) (1,200 mg)
24 to ≤ 28	6 to ≤ 8	360	3.6 (144)	6	14.4 (576) (1,440 mg)

* The approximate age ranges in relation to body weight are provided for guidance only. The ages should be used based on the local standard growth curves.

For children 8-12 years old there are alternative pharmaceutical forms and dosages available.

Renal impairment

APOTEL is contraindicated in patients with severe renal failure.

The minimum interval between each administration in patients with severe renal insufficiency must be APOTEL must be modified according to the following regimen:

Creatinine Clearance	**Interval between doses**
CL ≥ 50 mL/min	4 hours
CL 10-50 mL/min	6 hours
CL < 10 mL/min	8 hours

See also section 5.2 Pharmacokinetic properties, Special populations, Renal impairment.

Hepatic impairment

In patients with impaired hepatic function, the dose should be reduced or the dosing interval should be prolonged. Maximum daily dose should not exceed 60 mg/kg/day (should not exceed 2 g/day) in the following cases:

• Adults weighing less than 50 kg

• Chronic or decompensated liver disease, especially in patients with mild to moderate hepatocellular insufficiency

• Gilbert's syndrome (familial hyperbilirubinemia)

• Chronic alcoholism

• Chronic malnutrition (low reserves of hepatic glutathione)

• Dehydration.

See also section 5.2 "Pharmacokinetic properties, Special populations, Hepatic impairment"

Elderly

Usually, no dosage adjustment is required in elderly patients.

Method of administration

✓ ***APOTEL 500 & 1000 mg effervescent tablets***

✓ ***APOTEL 80, 160 & 500 mg effervescent granules***

Each APOTEL effervescent tablet and/or sachet with effervescent granules is dissolved in a glass of water before intake.

✓ ***APOTEL 1000 mg effervescent granules***

Each sachet of APOTEL 1000 mg effervescent granules is dissolved in half a glass of warm water before intake.

4.3. Contraindications

⏩ Hypersensitivity to active substance, to hydrochloric propacetamol (prodrug of paracetamol) or any of the excipients stated in section 6.1.

⏩ Severe hepatic-cellular failure or non-decompensated active liver disease.

⏩ Severe renal failure

⏩ In renal lithiasis *(only effervescent tablets)*.

4.4. Special warnings and precautions for use

To avoid the risk of overdose, confirm that other medications administered at the same time (including prescription and over-the-counter) do not contain paracetamol (see section 4.5).

Paracetamol should be used with caution in the following cases:

• Hepatocellular failure (including the Gilbert syndrome (familial hyperbilirubinemia) (also see sections 4.2 and 5.2)

• Severe renal failure (creatinine clearance ≤ 30 mL/min) (also see sections 4.2 and 5.2)

• Deficiency of glucose-6-phosphate dehydrogenase (G6PD) (may lead to hemolytic anemia)

• Chronic alcoholism, excessive consumption of alcohol (3 or more alcohol drinks each day)

• Anorexia, bulimia or cachexia, chronic malnutrition (low reserves of hepatic glutathione)

• Dehydration, hypovolemia

• Women during pregnancy and lactation.

Caution is required in children to avoid exceeding the recommended dose. Children are more sensitive in case of an overdose.

In case of chronic administration of the medicine or in high doses, hepatic function should be monitored.

Caution is advised when flucloxacillin is administered simultaneously with paracetamol, due to the increased risk of high anon gap metabolic acidosis (HAGMA). Patients with high risk for HAGMA are mostly those with severe renal dysfunction, sepsis or malnutrition, particularly when the highest daily doses of paracetamol have been used.

Following the simultaneous administration of flucloxacillin and paracetamol, close monitoring is advised to detect acid-base disturbances, particularly HAGMA, including a urine test for 5-oxoproline.

✓ ***APOTEL 500 mg effervescent tablets***

This medicinal product contains 292.70 mg sodium per tablet, equivalent to 14.6% of the WHO recommended maximum daily intake of 2 g sodium through diet by adults.

It also contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/or be given this medicinal product.

✓ ***APOTEL 1000 mg effervescent tablets***

This medicinal product contains 381.2 mg sodium per tablet, equivalent to 19.1% of the WHO recommended maximum daily intake of 2 g sodium through diet by adults.

It also contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/or be given this medicinal product.

✓ ***APOTEL 80 mg effervescent granules***

This medicinal product contains 35.67 mg sodium per sachet, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium through diet by adults.

It also contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/or be given this medicinal product.

✓ ***APOTEL 160 mg effervescent granules***

This medicinal product contains 71.35 mg sodium per tablet, equivalent to 3.6% of the WHO recommended maximum daily intake of 2 g sodium through diet by adults.

It also contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/or be given this medicinal product.

✓ ***APOTEL 500 mg effervescent granules***

This medicinal product contains 49.78 mg sodium per tablet, equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium through diet by adults.

It also contains sorbitol and sucrose. Patients with hereditary fructose intolerance (HFI) should not take/or be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effects.

Patients with rare hereditary problems of glucose intolerance, glucose-lactose malabsorption or sucrase-isomaltase deficiency should not take this medicine.

✓ ***APOTEL 1000 mg effervescent granules***

This medicinal product contains 99.54 mg sodium per tablet, equivalent to 5% of the WHO recommended maximum daily intake of 2 g sodium through diet by adults.

It also contains sorbitol and sucrose. Sorbitol may cause gastrointestinal discomfort and mild laxative effects (in individual with body weight less than 67 kg). Patients with hereditary fructose intolerance (HFI) should not take/or be given this medicinal product.

Patients with rare hereditary problems of glucose intolerance, glucose-lactose malabsorption or sucrase-isomaltase deficiency should not take this medicine.

✓ ***APOTEL 120 mg/5 ml syrup***

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially "sodium-free".

✓ ***APOTEL 100 mg/ml oral drops, solution***

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially "sodium-free".

This drug contains sodium metabisulphite.

It may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicine contains 60 mg of propylene glycol per each ml of solution. Simultaneous administration with any substrate of alcohol dehydrogenase, such as ethanol,

may cause severe adverse reactions in neonates and children younger than 5 years old.

✓ ***APOTEL 120 mg/5 ml elixir***

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg/ml, i.e. it is essentially "sodium-free".

It also contains sorbitol and sucrose.

Patients with hereditary fructose intolerance (HFI) should not take/or be given this medicinal product.

Patients with rare hereditary problems of glucose intolerance, glucose-lactose malabsorption or sucrase-isomaltase deficiency should not take this medicine.

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

Salicylamide may extend the half-life (t½) of paracetamol elimination. Cholestyramine decreases the absorption of paracetamol while metoclopramide and domperidone increase the absorption rate of paracetamol.

Caution is advised in concomitant use of hepatic enzyme inducer medication (e.g. phenobarbital, isoniazid, carbamazepine, rifampicin etc.) or with drugs that can have hepatotoxic actions (e.g. NSAIDs, interferons), as it increases the risk of hepatic damage.

Patients who receive barbiturates, tricyclic antidepressants and consume alcohol may present disorders of the metabolism of high paracetamol doses and its plasma half-life may be increased.

Probenecid may cause an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction in the paracetamol dose should be considered if it is to be administered concomitantly with probenecid.

Concomitant administration of paracetamol with coumarins, including warfarin, may lead to minor adjustments in the values of the International Normalized Ratio (INR). In this case, an increased monitoring of INR values is required during concomitant use, as well as for one week following the paracetamol treatment termination.

Paracetamol reduces the bioavailability of lamotrigine. However, the clinical significance of this is not clear.

Chronic consumption of alcohol may increase the hepatotoxicity of paracetamol in case of overdose.

The concomitant administration of phenytoin may lead to increased effectiveness of paracetamol and increased risk of hepatotoxicity. Patients who receive treatment with phenytoin should avoid high and/or chronic doses of paracetamol. Patients should be monitored for symptoms of hepatotoxicity.

Chronic administration of antiepileptics or oral administration of steroid contraceptives affect hepatic enzymes and may prevent therapeutic plasma levels of paracetamol by increasing its first pass metabolism or elimination.

Flucloxacillin: Caution is advised when paracetamol is administered concomitantly with flucloxacillin, as concomitant administration has been associated with metabolic acidosis with high anon gap metabolic acidosis (HAMGA), particularly in patients with risk factors (see section 4.4).

⇒ Investigations: Paracetamol can lead to false blood uric acid results using the phosphotungstic acid method and glucose results using the oxidase-peroxidase method.

4.6. Fertility, pregnancy and lactation

• *Pregnancy:*

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If the use of paracetamol is clinically needed, it can be used during pregnancy. However, it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

• *Breast-feeding:*

Paracetamol is eliminated in breast milk and has been detected in concentration with a 1:1 ratio with those in plasma. Rash has been reported in breast-feeding infants. However, paracetamol is considered compatible with breast-feeding.

4.7. Effects on ability to drive and use machines

No such effect has been reported.

4.8. Adverse reactions

At therapeutic doses, almost no adverse effects occur.

➔ Rare hypersensitivity reactions that manifest with skin rash or erythema, requiring treatment discontinuation.

➔ During chronic use or with the intake of large doses, the following have been reported: mild gastric disturbances, hemolytic anemia, agranulocytosis, methemoglobinemia, skin rashes, urticaria, fever, hypoglycemia, CNS stimulation or somnolence, thrombocytopenic purpura.

➔ Prolonged intake of high doses may cause nephropathy and rarely pancreatitis.

The following adverse effects have been reported during follow-up after the product's release. However, their incidence is not known:

System Organ Classification	Adverse reaction
Blood and lymphatic system disorders	Thrombocytopenia Thrombocytop enia, Leukopenia
Immune system disorders	Anaphylactic cataplexia/reaction Hypersensitivity
Vascular disorders	Hypotension (as a symptom of anaphylaxis)
Gastrointestinal disorders	Diarrhea Abdominal pain
Hepatobiliary disorders	Hepatic failure, hepatic necrosis, Hepatitis
Skin and subcutaneous tissue disorders	Urticaria, Erythema , Rash Acute generalized exanthematous pustulosis (AGEP), Toxic epidermal necrolysis Stevens Johnson syndrome, Angioedema Pruritus
Investigations	Increased hepatic enzymes Decreased International Normalized Ratio, increased International Normalized Ratio

Paracetamol may cause severe skin reactions which may be deadly, such as acute generalized exanthematous pustulosis, Stevens-Johnson syndrome and toxic epidermal necrolysis. Patients should be advised of the symptoms of severe skin reaction and the use of the medicine must be terminated upon the first occurrence of a skin rash or any other symptom of hypersensitivity.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions directly via the National Organization for Medicines, Mesogeion 284, GR-15562 Cholargos, Athens, Tel: +30 21 32040380/337, Fax: +30 21 06549585, Website: http://www.eof.gr

4.9. Overdose

An overdose may be the result of unintentional or intentional intake of a large amount of paracetamol or prolonged intake of high doses. The consequences may be very serious. The intake of 10 to 15 g paracetamol by adults may cause severe hepatocellular necrosis and in more rare cases renal tubular necrosis.

The symptoms of overdose develop within 24 hours and progress in severity. They include nausea, vomiting, hyperhidrosis, lethargy and abdominal pain. Hepatic injury may develop up to 4 to 6 days after ingestion, while it usually reaches peak severity in 3 to 4 days after ingestion. It may result in hepatic failure with encephalopathy, coma and death. Acidosis, cerebral edema, hemorrhage, hypoglycemia, hypotension, infection and renal failure may also develop.

In the laboratory investigations, increased levels of transaminases, bilirubin and prothrombin time prolongation, which is a reliable index of hepatic function progress and should be regularly monitored, are observed. Acute renal failure may occur due to acute tubular necrosis, even without the presence of hepatic lesion. Myocardium damage and pancreatitis may also develop.

The possibility of a toxic effect is increased in alcoholics, in patients receiving liver enzyme-inducing drugs and in cachexia.

Paracetamol toxicity is due to the production of one of its metabolites, N-acetyl-p-benzoquinone imine (NAPQI), which is detoxified by glutathione binding and eliminated after conjugation with mercaptopurine and cysteine. In case of overdose, glutathione stores are depleted and free NAPQI binds with the sulfhydryl groups in the hepatocytes, which are destroyed.

Substances such as acetylcysteine and methionine that restore glutathione stores are used as antidotes in paracetamol intoxication.

An overdose should be treated immediately in the hospital. Gastric lavage if done within 2 hours from ingestion removes the drug residues from the stomach. Activated charcoal administration interferes with the absorption of paracetamol from the intestine. The use of general support measures is essential. The administration of the antidote starts immediately, as long as the ingested dose exceeds 125 mg/kg body weight in adults and above 200 mg/kg body weight in children, and it may continue or not, depending on the results of paracetamol level measurements in plasma.

The levels should be measured 4 hours after ingestion and it should be done up to 16 hours after that. The values of the patient's plasma paracetamol levels are compared with a standardized nomogram of the levels to time of ingestion *(see chart)*. The administration of the antidote is necessary when the patient's levels exceed the risk threshold. In general, it is considered that a single ingestion of more than 10 g paracetamol can cause clinically evident hepatotoxic damage. Severe fatal damage usually occurs after ingestion of more than 25 g. Paracetamol concentrations in plasma are associated with hepatic damage severity. Levels exceeding 300 μg/ cm^3 4 hours after ingestion are indicative of serious injury development. Levels below 150 μg/ cm^3 mean that the onset of hepatocellular damage is unlikely.

Acetylcysteine is administered by either the oral route of the intravenous route. Despite being more effective when its administration starts within 8 hours from the intake, it should be administered even past 24 hours from the intake.

Initially 150 mg/kg body weight are administered diluted in 200 ml^3 glucose 5% during a 15-20-minute infusion, followed by an infusion of 50 mg/kg body weight in 500 cm^3 glucose 5% in the following 4 hours and then 100 mg/kg body weight in 1000 cm^3 glucose 5% for the next 16 hours.

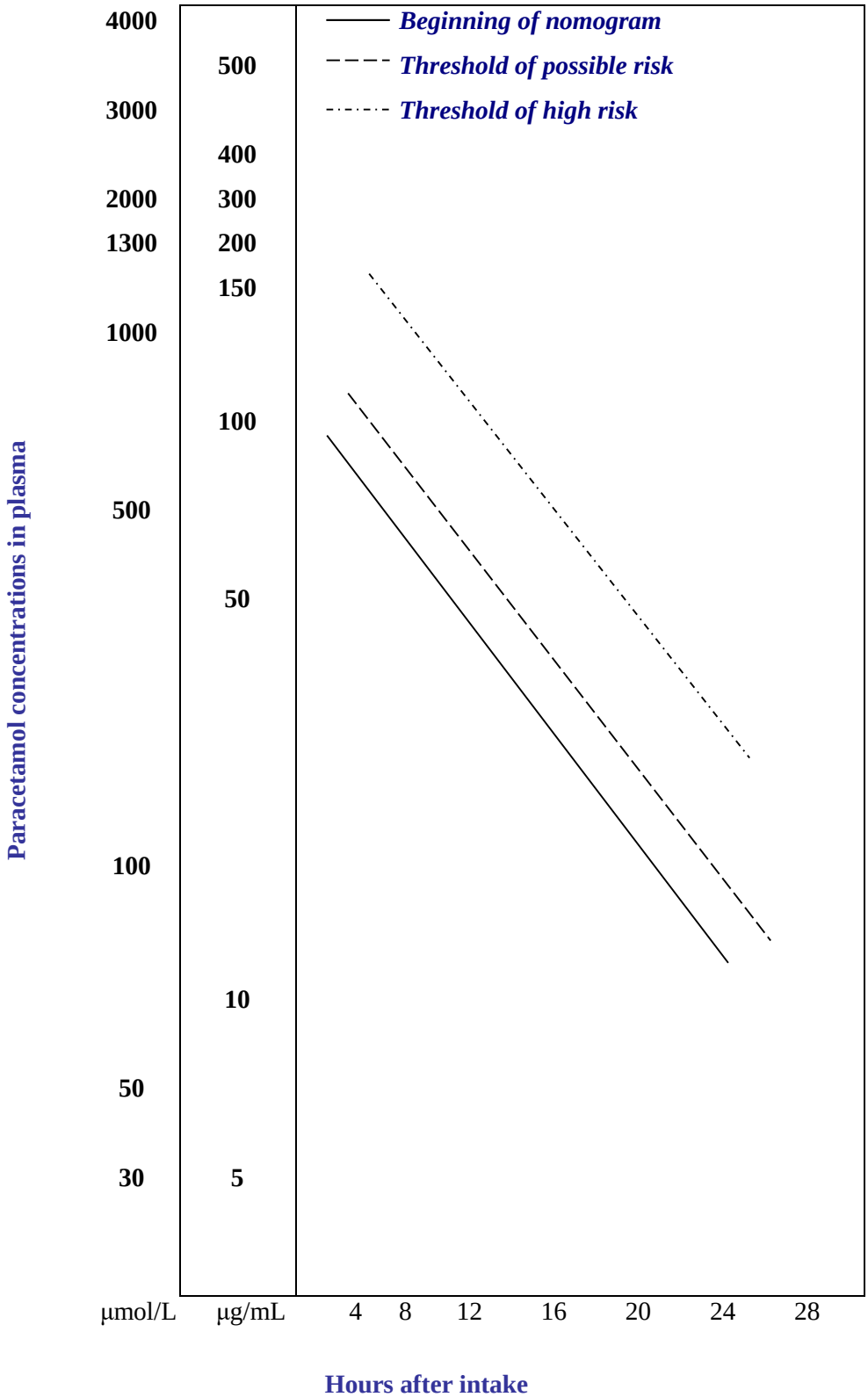
Total administration time 20 hours. If an anaphylactic reaction occurs, it should be treated with antihistamines and the administration of acetylcysteine can continue at a lower rate.

Initially 140 mg/kg body weight are administered orally and then 70 mg/kg body weight every 4 hours, for 17 times.

Methionine must be administered at the latest 10 hours after ingestion, otherwise its effectiveness is reduced. Oral administration of 2.5 g every 4 hours and for 4 times.

In the meantime, if the measured levels of paracetamol are below the risk threshold, the administration of the antidote is discontinued.

Failure of antidote treatment is an indication for liver transplantation.


Beginning of nomogram
Threshold of possible risk
Threshold of high risk
Paracetamol concentrations in plasma
4000
3000
2000
1300
1000
500
100
50
30
500
400
300
200
150
100
50
10
5
µmol/L
µg/mL
4
8
12
16
20
24
28
Hours after intake

The RUMACH MATTHEW Nomogram to determine the risk of hepatocellular damage according to the plasma concentrations of paracetamol. **Valid only for a single dose of paracetamol.** For high risk individuals, the risk starts already from the solid line.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, ATC Code: N02BE01

Paracetamol is the main active metabolite of phenacetin, but without its side effects. It has analgesic and antipyretic properties comparable to those of acetylsalicylic acid and mild anti-inflammatory properties. It is a mild inhibitor of prostaglandin biosynthesis, although it has been shown that it is more effective against CNS enzyme than the peripheral ones. Its antipyretic action is produced by a direct effect on the hypothalamic heat-regulating centers. Its mechanism of analgesic action is not known.

Single or repeated dosing has no effect on the cardiovascular or respiratory systems. Unlike acetylsalicylic acid, paracetamol does not interfere with prothrombin time, it has no anti-platelet effect and it does not cause ulcerations in the gastrointestinal tract. Its anti-inflammatory action is still under study.

5.2. Pharmacokinetic properties

Absorption:

Orally given paracetamol is absorbed rapidly and completely. Maximum plasma concentrations are reached 30 to 60 minutes after the intake.

Distribution:

Paracetamol is rapidly distributed throughout all tissues.

Concentrations are comparable in blood, plasma and saliva. The usual plasma concentrations to achieve analgesia range from 5 to 20 mcg/ml. Good relationship between its plasma levels and its analgesic effect. Plasma protein binding ranges between 20% and 50% in toxic concentrations.

It crosses the placenta and is excreted into milk.

Binding to plasma proteins is low.

Biotransformation:

Paracetamol is metabolized mainly in the liver. About 4% is metabolized by hepatic cytochromes P-450 and it is oxidized in a toxic metabolite, which is detoxified by selective binding with hepatic glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid.

The two most important metabolism routes are by conjugation to form glucuronide and sulphate conjugates to be eliminated in the urine.

This latter route is quickly saturated after the administration of amounts exceeding the therapeutic doses.

A very small quantity is metabolized via the mixed function oxidases of the liver and kidneys to the hydroxylated metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is toxic for the cells, but with the recommended doses, it is detoxified by glutathione and eliminated after conjugation with mercaptopurine and cysteine.

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

Elimination:

Elimination takes place mainly in the urine in the form of inactive glucuronide (60-80%) and sulphate (20-30%) conjugates and 5% is eliminated unchanged.

90% of the dose administered is excreted in 24 hours via the kidneys, mainly as glucuronide (60-80%) or sulfuric acid esters (20-30%) conjugates.

Less than 5% is excreted unchanged.

Mean elimination half-life is approximately 2 hours.

Special populations

Renal impairment

In case of creatinine clearance < 10 ml/min, the elimination of paracetamol and its metabolites is delayed. For glucuronide and sulfuric derivatives of conjugates, the elimination rate is slower in individuals with severe renal dysfunction versus healthy individuals. The minimum interval between each administration is 6 or 8 hours when paracetamol is administered to all patients.

Hepatic impairment

There is not counterindication for the use of paracetamol in therapeutic doses in patients with chronic, stable hepatic disease. Some clinical trials have showed a moderately affected metabolism of paracetamol in patients with chronic hepatic dysfunction, including alcoholic cirrhosis, as shown by the increased concentration of paracetamol in plasma and the larger half-life of elimination. In these reports, paracetamol's increased half-life in the plasma was

associated with reduced paracetamol metabolism ability in the liver. Consequently, paracetamol must be used with caution in patients with hepatic dysfunction and is contraindicated when a non-decompensated acute disease exists, particularly alcoholic hepatitis, due to the induction of CYP 2E1, which leads to increased formation of the hepatotoxic metabolite of paracetamol.

Elderly: The pharmacokinetic properties, the binding capacity and the metabolism of paracetamol are slightly or not modified in the elderly. Usually no dose adjustment is required in this population.

Pediatric population

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

Neonates, infants and children up to 10 years old excrete significantly less glucuronide and more sulphate conjugates than adults. Total excretion of paracetamol and its metabolites is the same for all ages.

5.3. Preclinical safety data

The effects of paracetamol on the diet of rats and mice in 0, 600, 3000 and 6000 ppm for 2 years. Paracetamol was found non-carcinogenetic in male mice as well as in male and female rats. Suspicion of carcinogenetic activity was noted in female rats based on the increase in the frequency of mononuclear cell leukemia.

In a comparative literature review on the genotoxicity and carcinogenicity of paracetamol, it was shown that genotoxic effects of paracetamol were seen only with dosages exceeding the recommended range and resulted in strong liver and bone marrow toxicity. Genotoxic threshold value could not be reached in therapeutic dosages of paracetamol. Animal studies did not indicate carcinogenicity potential at non-hepatotoxic dose levels. Tumorigenic effects of paracetamol have been observed in older studies, only after the administration of very high, cytotoxic doses.

There are no conventional studies to assess toxicity on reproduction and development using the applicable acceptable standards.

6. PHARMACEUTICAL INFORMATION

6.1. List of excipients

✓ ***APOTEL 500 mg tablets***

magnesium stearate, maize starch, potassium sorbate, colloidal silica.

✓ ***APOTEL 125, 250 & 500 mg suppositories***

hard fat.

✓ ***APOTEL 500 & 1000 mg effervescent tablets***

500 mg:

sorbitol, acidic sodium carbonate, anhydrous sodium carbonate, lemon flavor, sodium saccharin, adipic acid, sodium dihydrogen citrate, magnesium sulphate, sodium cyclamate.

1000 mg:

sodium bicarbonate, anhydrous sodium carbonate, sodium saccharin, anhydrous sodium citrate, citric acid, lemon flavor (natural aromatic substances, maltodextrine, modified starch), sorbitol, magnesium sulphate, maltodextrine, povidone.

✓ ***APOTEL 100 mg/ml oral drops, solution***

propylene glycol, glycerol, ethanol, citric sodium, sodium saccharin, sodium metabisulphite, erythrosine CI 45430 E127, cherry brandy flavor, purified water.

✓ ***APOTEL 120 mg/5 ml elixir***

glycerol, propylene glycol, sorbitol solution, disodium edetate, sodium benzoate, sodium saccharin, sucrose, ethanol, orange flavor, banana flavor, mint oil, purified water, polyethylene glycol 400.

✓ ***APOTEL 500 mg coated tablets***

Core: maize starch, magnesium stearate, potassium sorbate, colloidal silica.

Coating: methyl cellulose E 50, titan dioxide E171 CI 77891, purified talc, purified water.

✓ ***APOTEL 120 mg/5 ml syrup***

liquid maltitol, polyethylene glycol 1540, sodium benzoate, butylated hydroxyanisole, citric acid, disodium edetate, sodium citrate dihydrate, cherry flavor, sodium chloride, azorubine carmoisine CI 14720 E122 pigment, sodium cyclamate, sodium saccharin, purified water.

✓ ***APOTEL 80, 160, 500 & 1000 mg effervescent granules***

80 & 160 mg:

mannitol, citric acid, acidic sodium carbonate, polyvidone, anhydrous sodium carbonate, sodium docusate, sorbitol, lemon flavor in powder, sodium saccharin, fumaric acid.

500 & 1000 mg:

ascorbic acid, anhydrous citric acid, acidic sodium carbonate, polyethylene glycol 6000, sodium saccharin, lemon flavor in powder, polyvidone, sucrose, sodium cyclamate, honey flavor in powder, caramel flavor, sorbitol.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

✓ ***APOTEL 500 mg tablets***

✓ ***APOTEL 500 mg effervescent tablets***

✓ ***APOTEL 100 mg/ml oral drops, solution***

✓ ***APOTEL 500 mg coated tablets***

✓ ***APOTEL 120 mg/5 ml syrup***

✓ ***APOTEL 1000 mg effervescent granules***

3 (three) years, on condition that the product is kept unopened, in its original packaging according to storage instructions.

✓ ***APOTEL 1000 mg effervescent tablets***

2 (two) years, on condition that the product is kept unopened, in its original packaging according to storage instructions.

✓ ***APOTEL 125, 250 & 500 mg suppositories***

2½ (two and a half) years, on condition that the product is kept unopened, in its original packaging according to storage instructions.

✓ ***APOTEL 120 mg/5 ml elixir***

✓ ***APOTEL 80, 160, 500 mg effervescent granules***

2 (two) years, on condition that the product is kept unopened, in its original packaging according to storage instructions.

6.4. Special precautions for storage

✓ ***APOTEL 500 mg tablets***

✓ ***APOTEL 500 mg effervescent tablets***

✓ ***APOTEL 500 mg coated tablets***

✓ ***APOTEL 120 mg/5 ml syrup***

✓ ***APOTEL 80, 160, 500 & 1000 mg effervescent granules***

Store below 25 °C.

✓ ***APOTEL 1000 mg effervescent tablets***

This pharmaceutical product does not require special temperature conditions for storage. Please keep it in its original packaging, to protect it from humidity.

✓ ***APOTEL 125, 250 & 500 mg suppositories***

✓ ***APOTEL 100 mg/ml oral drops, solution***

✓ ***APOTEL 120 mg/5 ml elixir***

Store below 30 °C.

6.5. Nature and contents of container

✓ ***APOTEL 500 mg/tab tablets***

Carton box that contains 20 tablets packaged in 2 blisters made of PVC and Aluminum foil with 10 tablets each.

✓ ***APOTEL 125, 250 & 500 mg suppositories***

Carton box that contains 5 suppositories packaged in a special casing made of PVC.

✓ ***APOTEL 500 & 1000 mg effervescent tablets***

500 mg:

Carton box that contains 12 effervescent tablets packaged in 3 aluminum foils each containing 4 tablets.

1000 mg:

1) Carton box that contains 8 effervescent tablets packaged in 2 foists of PE and aluminum sheets each containing 4 tablets.

2) Carton box that contains 8 effervescent tablets packaged in a tube of inflexible plastic, with a polyethylene cap with desiccant.

✓ ***APOTEL 100 mg/ml oral drops, solution***

Glass amber dropper vial with plastic cap, containing 30 ml of product. The product is contained in a cardboard box.

✓ ***APOTEL 120 mg/5 ml elixir***

Carton box that contains one 60 ml glass amber vial and sealed with an aluminum cap.

✓ ***APOTEL 500 mg coated tablets***

Carton box that contains 20 coated tablets packaged in 2 blisters made of PVC and Aluminum foil each with 10 tablets and one Package Leaflet.

✓ ***APOTEL 120 mg/5 ml syrup***

Carton box that contains one 120 ml glass amber vial and sealed with an aluminum cap.

✓ ***APOTEL 80, 160, 500 & 1000 mg effervescent granules***

Carton box that contains 10 sachets with effervescent granules packaged in sandwich PVC, paper and aluminum foil.

1000 mg:

Carton box that contains 20 rod-like sachets (sticks) with effervescent granules packaged in PET/Aluminium/PE film.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UNI-PHARMA KLEON TSETIS PHARMACEUTICAL LABORATORIES S.A.

14th km National Road Athens - Lamia 1

145 64 Kifissia

Tel: 210 8072512

Fax: 210 8078907

8. MARKETING AUTHORISATION NUMBER

✓ ***Effervescent tablets 1000 mg/tab***

70434/22.07.2021.

✓ ***Tablet 500 mg/tab***

✓ ***Suppositories 125, 250 & 500 mg/sup.***

✓ ***Effervescent tablets 500 mg/tab***

✓ ***Oral drops, solution 100 mg/ml***

✓ ***Elixir 120 mg/5ml***

✓ ***Syrup 120 mg/5ml***

✓ ***Effervescent granules 80, 160, 500 & 1000 mg/sachet***

70432/22-07-2021.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

✓ ***Tablet 500 mg/tab***

Date of first authorization: 03 September 1982.

Date of latest renewal: 22 May 2008.

✓ ***Suppositories 125, 250 & 500 mg/sup.***

Date of first authorization: 30 October 1989.

Date of latest renewal: 22 May 2008.

✓ ***Effervescent tablets 500 & 1000 mg/tab***

500 mg:

Date of first authorization: 16 January 1990.

Date of latest renewal: 22 May 2008.

1000 mg:

Date of first authorization: 10 October 2002.

Date of latest renewal: 22 May 2008.

✓ ***Oral drops, solution 100 mg/ml***

Date of first authorization: 02 November 1989.

Date of latest renewal: 22 May 2008.

✓ ***Elixir 120 mg/5ml***

Date of first authorization: 02 November 1989.

Date of latest renewal: 22 May 2008.

✓ ***Coated tablet 500 mg/tab***

Date of first authorization: 10 May 1996.

Date of latest renewal: 22 May 2008.

✓ ***Syrup 120 mg/5ml***

Date of first authorization: 02 April 1996.

Date of latest renewal: 22 May 2008.

✓ ***Effervescent granules 80, 160, 500 & 1000 mg/sachet***

Date of first authorization: 16 January 1990.

Date of latest renewal: 22 May 2008.

1000 mg:

Date of first authorization: 02.10.2013

Date of latest renewal: 19.07.2019.

10. DATE OF REVISION OF THE TEXT

22.07.2021.