APOTEL

1. NAME OF THE MEDICINAL PRODUCT

APOTEL®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(Each ampoule contains 1 g Paracetamol).

Paracetamol 1g/6.7ml

For excipients see 6.1

3. PHARMACEUTICAL FORM

Solution for intravenous infusion.

4. CLINICAL DATA

4.1. Therapeutical Indications

APOTEL® is indicated for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

4.2. Posology and method of Administration

ATTENTION! APOTEL® is to be administered by intravenous infusion. It is usually dissolved in 100 ml Sodium Chloride 0.9% Sterile Solution (or alternative solutions) or according to doctor's decision.

ALTERNATIVE SOLUTIONS: 0.9% sodium chloride, Lactated Ringer's, 3.33% Dextrose/0.3% NaCl, 5.0% Dextrose.

APOTEL® is stable for 4 hours in intravenous admixtures with these alternative solutions.

A) ***Adolescents and adults who weigh more than 50 kg:***

1 g of paracetamol per dose up to four times a day. The ampoule content is dissolved in Sodium Chloride 0.9% Sterile Solution (or alternative solutions), usually in a 100 ml vial, and is administered immediately.

The minimum interval between each administration must be at least 4 hours.

The maximum daily dose must not exceed 4 g.

B) *<u>Pediatric dosing</u>*

Age group	Children, adolescents and adults weighing 33 to 50 kg	Children weighing 10 to 33 kg (approx 1-11 years old)	Full-term newborns, infants and children weighing up to 10 kg. (approx. up to 1 year old).
Dose (mg per kg of body weight)	15 mg/kg up to four times a day. The minimum interval between each administration must be at least 4 hours.		7.5 mg/kg up to four times a day. The minimum interval between each administration must be at least 4 hours.
Instructions	<u>For a dose of 15mg/kg:</u> 0.1 ml of APOTEL® dissolved in 1.5 ml of Sodium Chloride 0.9% Sterile Solution (or alternative solutions) per Kg of body weight. Another way is to dissolve the ampoule content into a 100 ml of Sodium Chloride 0.9% Sterile Solution (or alternative solutions) and administer 1.5 ml of the resulting solution per Kg of body weight		0.05 ml of APOTEL® dissolved in 0.75 ml Sodium Chloride 0.9% Sterile Solution (or alternative solutions) per Kg of body weight. Another way is to dissolve the ampoule content into a 100 ml Sodium Chloride 0.9% Sterile Solution (or alternative solutions) and administer 0.75 ml of the resulting solution per Kg of body weight.
Maximum daily dose	60 mg/Kg of body weight Maximum 3 g.	60 mg/Kg of body weight Maximum 2 g	30 mg/Kg of body weight.

There is no information available concerning safety and effectiveness for premature infants *(See 5.2 Pharmacokinetic Properties)*.

<u>C. Serious renal insufficiency:</u> When paracetamol is administered in patients with severe renal insufficiency (creatinine clearance ≤30 ml/min), the minimum interval between each administration must be at least 6 hours and a reduced total daily dose of paracetamol may be warranted.

In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione) and dehydration: The maximum daily dose must not exceed 3g.

<u>Solution preparation for intravenous infusion - Way of administration:</u>

The ampoule content is dissolved into a 100 ml of Sodium Chloride 0.9% Sterile Solution (or alternative solutions) or according to doctor's decision. The 100 ml produced solution is administered by intravenous infusion, in a time interval of 15 min.

4.3. **Contraindications**

APOTEL® is contraindicated in patients with:

- Hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the product's excipients.
- The product is contraindicated during pregnancy, due to the Glycerol Formal excipient which is implicated in teratogenicity in animals.
- Cases of severe hepatocellular insufficiency.

4.4. **Special Warnings and Precautions during Administration**

Warnings

❖ It is recommended to use a suitable analgesic oral treatment as soon as this administration route is possible.

❖ In order to avoid the risk of overdose, one should check that the other medicinal products administered along with APOTEL® do not contain paracetamol or propacetamol.

❖ Doses higher than the recommended ones entails risk for hepatic injury, including the risk of severe hepatotoxicity and death. Do not exceed the maximum recommended daily dose of paracetamol. Clinical symptoms and signs of liver damage are usually first seen after two days of drug administration, with a peak seen usually after 4 to 6 days.

❖ Treatment with antidote should be given as soon as possible *(See 4.9 Overdose)*.

❖ Caution is required regarding administration during lactation since there are no studies on the effects of Glycerol Formal in lactated women.

Precautions during Administration

❖ Paracetamol has been associated with a risk of rare but serious skin reactions. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal.

Reddening of the skin, rash, blisters, and detachment of the upper surface of the skin can occur with the use of drug products that contain paracetamol. These reactions can occur with first-time use of paracetamol or at any time while it is being taken.

Anyone who develops a skin rash or reaction while using paracetamol should stop the drug and seek medical attention right away. Anyone who has experienced a serious skin reaction with paracetamol should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.

Health care professionals should be aware of this rare risk and consider paracetamol along with other drugs already known to have such an association, when assessing patients with potentially drug induced skin reactions.

Precautions for use

Paracetamol should be used with caution in the following cases:

❖ Hepatocellular insufficiency, or active hepatic disease,

❖ serious renal insufficiency (creatinine clearance ≤ 30 ml/min) *(See 4.2 Dosage and Way of Administration and 5.2 Pharmacokinetic Properties)*,

❖ chronic alcoholism,

❖ chronic malnutrition (low levels of hepatic glutathione),

❖ Severe hypovolemia (e.g., due to dehydration or blood loss).

4.5. **Drug Interactions and other forms of interaction**

⇒ Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.

⇒ Salicylamide may prolong the elimination t1/2 of paracetamol.

⇒ Caution should be paid to the concomitant intake of enzyme-inducing substances (See 4.9 Overdose).

Effects of other Substances on Paracetamol

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of paracetamol and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, because excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of paracetamol.

Chronic oral paracetamol use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) values in some patients who have been stabilized on sodium warfarin as an anticoagulant. As no studies have been performed evaluating the short-term use of APOTEL® in patients on oral anticoagulants, increased monitoring of INR values should be conducted in such circumstances.

4.6. **Pregnancy and Lactation**

• *Pregnancy:*

Clinical experience of intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus / newborn infant. Prospective data on pregnant women exposed to overdoses did not show an increase in malformation risk.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals.

However, studies with the oral route did not show any malformation of foetotoxic effects.
The product is contraindicated during pregnancy, due to the Glycerol Formal excipient which is implicated in teratogenicity in animals.

• *Lactation:*
After oral administration, paracetamol is excreted in small quantities into breast milk. No undesirable effects on nursing infants have been reported. Consequently, **APOTEL®** may be used in breast-feeding women.
Caution is required regarding administration during lactation since there are no studies on the effects of Glycerol Formal in lactated women.

4.7. **Effect on the ability to drive or use machinery**
No such effect has been reported.

4.8. **Adverse Reactions**
As all paracetamol products, adverse reactions are rare (>1/10000 to <1/1000) or very rare (<1/10000). These are described below:

Organic System	**Rare** (>1/10000 to	**Very Rare** (<1/10000)	**Isolated reports**
General disorders	Malaise	Hypersensitivity Reactions	
Cardiovascular ***disorders***	Hypotension		
Hepatobiliary disorders	Increased levels of hepatic transaminas		
Blood and lymphatic system disorders			Thrombocytopenia Leucopenia Neutropenia

Very rare cases of hypersensitivity reactions ranging from dyspnoea, hypotension and skin rash or urticaria to anaphylactic shock have been reported. Clinical signs include swelling of the face, mouth and throat, respiratory distress, urticaria, rash and pruritis. Discontinue **APOTEL®** immediately if symptoms associated with allergy or hypersensitivity occur.
Isolated reports of thrombocytopenia have been observed.
Cases of erythema, flushing, pruritus and tachycardia have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffect@moh.gov.il

4.9. **Overdose**

In acute paracetamol overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. Plasma paracetamol levels > 300 mcg/ml at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/ml or
< 37.5 mcg/ml at 12 hours after ingestion.

There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly patients and young children, patients with liver disease, in cases of chronic alcoholism, patients with chronic malnutrition and patients receiving enzyme inducers. Overdosing can be fatal in these cases.
Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, abdominal pain, diaphoresis, and general malaise.

Overdose of 7.5 g or more of paracetamol in a single administration in adults or 140 mg/Kg of body weight in a single administration in children, causes hepatic cytolysis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy, which may lead to coma and death.

Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration.
Clinical symptoms of liver damage are usually evident initially after two days, and reach a maximum after 4 to 6 days.

Emergency measures

- Immediate hospitalization.
- Before beginning treatment, take a tube of blood for plasma paracetamol assay, as soon as possible after the overdose.
- The treatment includes administration of the antidote, N-Acetylcysteine (NAC), by the IV or oral route, if possible before the 10th hour. NAC can, however, give some degree protection even after 10 hours, but in these cases, prolonged treatment is given.
- Symptomatic treatment.
- Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours. In most cases, hepatic transaminases peak after 4 to 6 days and return to normal in one to two weeks, with full restitution of liver function. In very rare cases, however, liver transplantation may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

Therapeutical Category: Analgesic and Antipyretic
ATC Code: N02BE01

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

APOTEL provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.
APOTEL reduces fever within 30 minutes after the start of administration with duration of the antipyretic effect of at least 6 hours.

5.2. Pharmacokinetic Properties

Adults:

Absorption:

The pharmacokinetic properties of paracetamol are linear up to 2 gr after a single administration and after repeated administration, during 24 hours.
The maximum plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion of 1 g paracetamol is approximately 30 μg/ml.

Distribution:

The volume of distribution of paracetamol is approximately 1 L/kg.
Paracetamol is not extensively bound to plasma proteins. Following infusion of 1 gr paracetamol, significant concentrations of paracetamol (approx. 1.5 μg/ml) were observed in the cerebro spinal fluid, as and from the 20th minute following infusion.

Metabolism:
Paracetamol is metabolized mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation.
The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine), which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, during massive overdosing, the quantity of this toxic metabolite is increased.

Elimination*:*
The metabolites of paracetamol are mainly excreted in the urine.
90% of the dose administered is excreted in 24 hours, mainly as glucuronide (60-80%) and sulphate (20-30%) conjugates.
Less than 5% is eliminated unchanged.
Mean plasma half-life is 2.7 hours and total body clearance is 18 L/h.

Newborns, 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 that is slightly shorter (1.5 to 2 hours) than in adults. In neonates, the plasma half-life is longer than in infants, i.e. around 3.5 hours. Newborns, 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.

Special Populations:
Renal Insufficiency
In cases of severe renal impairment (creatinine clearance 10-30 ml/min), the elimination of paracetamol is slightly delayed, the Elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤30 ml/min), to increase the minimum interval between each administration to 6 hours. *(See 4.2 Posology and Method of Administration).*

Elderly subjects:
The pharmacokinetic properties and the metabolism of paracetamol are not modified in elderly patients. No dose adjustment is required in this population.

5.3. Pre-clinical data relative to safety
Preclinical data reveal no special hazard for humans beyond the information included in other sections of this SPC.
Glycerol Formal has shown teratogenic effects in animals. No teratogenic effects have been observed in humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients
- Glycerol formal

- Ethanol
- Sodium metabisulfite
- Disodium phosphate dodecahydrate
- Disodium edetate
- Water for injection

6.2. **Incompatibilities**

APOTEL® should not be mixed with other medicinal products.

6.3. **Shelf Life**

The expiry date of the product is indicated on the packaging materials

Shelf life after reconstitution: 4 hours.

6.4. **Special precautions for storage**

Do not store above 25°C.

6.5. **Nature and contents of container**

Each Cardboard box contains 3 brown Type I glass ampoules of 6.7 ml.

6.6. **Special precautions for disposal and other handling**

Before administration, **APOTEL®** should be visually inspected for any particulate matter and discoloration. **APOTEL®** is intended for single use only. Any unused solution or waste material should be discarded in accordance with local requirements.

7. MANUFACTURER:

UNI-PHARMA KLEON TSETIS PHARMACEUTICAL LABORATORIES S.A.
14th Km. National Road 1,GR-145 64 Kifissia, Greece.

8. IMPORTER AND LICENSE HOLDER:

Easy Care Ltd.
P.O.B 48577, TEL-AVIV 6148403 ISRAEL

9. REGISTRATION NUMBER

150-98-33541

APO-LFP-0718-03

The content of this leaflet was approved by the Ministry of Health in 11/2013 and updated according to the guidelines of the Ministry of Health in 07/2018