SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
PAROKAN 10 mg/mL Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Substance:

Paracetamol	10 mg/mL

Excipients:

Disodium hydrogen phosphate dihydrate	0.0831 mg/mL
Mannitol	38.5 mg/mL

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM
Solution for infusion.
Clear and light-yellowish solution.

4. CLINICAL PARTICULARS
4.1. Therapeutical indications
PAROKAN is indicated for the treatment of pain or hyperthermia in emergency cases that the intravenous route is deemed necessary and/or use of other administration routes is not available (particularly after surgical interventions, for treatment of medium-level pain or short-term fever).

4.2. Posology and method of administration
Switching to a suitable oral analgesic as soon as the patient is able to take oral is recommended.
This drug can be used for acute pain or fever in single or repeated dosages.

Posology/Frequency and Duration of administration:
Paracetamol solution is administered as intravenous infusion within 15 minutes.

Dosage will be adjusted according to the weight of the patient. Recommendations related to dosage adjustment are given in the table below.

Body weight of the patient	Single dose	Maximum daily dose
≤ 10 kg	**7,5 mg/kg** paracetamol/ administration (0,75 mL solution/kg)	- Four times daily maximum - Intervals of at least 4 hours must be given between the administrations - **The daily maximum dosage of 30 mg/kg** must not be exceeded.
> 10 kg and ≤ 33kg	**15 mg/kg** paracetamol/ administration (1,5 mL solution/kg)	- Four times daily maximum - Intervals of at least 4 hours must be given between the administrations - **The daily maximum dosage of 60 mg/kg** must not be exceeded (maximum daily dosage **2g**.)
> 33kg and ≤ 50kg	**15 mg/kg** paracetamol/ administration (1,5 mL solution/kg)	- Four times daily maximum - Intervals of at least 4 hours must be given between the administrations - **The daily maximum dosage of 60 mg/kg** must not be exceeded (maximum daily dosage **3g**)
> 50kg	**1 g** paracetamol/ administration (1 vial of 100 mL)	- Four times daily maximum - Intervals of at least 4 hours must be given between the administrations - **The daily maximum dosage of 4 g** must not be exceeded

***Preterm newborns:** There are no available safety and effectiveness data for preterm newborns (see: section 5.2).

****Maximum daily dosage**: As shown in the table above, the maximum daily dosage relates to patients that do not use any other products. All the paracetamol dosages administered through all the routes (oral, rectal, intravenous, etc.) must be taken into consideration.

Since the 100 mL (1000 mg) vial can cause dosage errors (administration of overdose); it must not be used as a whole for patients under 50 kg.

When giving doses less than 100 mL, the drug should be withdrawn from the vial and given separately.

Pediatric dosages up to 60 ml must be administered with a syringe within a period of 15 minutes.

Infusion must be made without hanging the vial for patients with body weights < 10 kg.

Method of administration:
Take care when prescribing and administering PAROKAN to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and death. It must be ensured that the required dose is correctly stated and administered. When writing prescriptions, include both the total dose in mg and the total dose in volume.

Paracetamol solution is administered as intravenous infusion within 15 minutes.

With the purpose of avoiding dosage errors in newborns and infants (≤ 10 kg) and not to confuse mg with mL, it is recommended that the volume to be administered in milliliters (mL). The PAROKAN volume (10 mg/mL) administered to this weight group must never exceed 7,5 mL per dosage. Very low volumes will be required for the newborns and infants (≤ 10 kg).

To measure the dosage with the required volume based on the body weight of the child, 5-mL or 10-mL syringes must be used.

PAROKAN can also be administered by diluting for pediatric dosage. However, only 0.9% sodium chloride or 5% glucose solutions can be used up to 1: 10 (1 aliquot of paracetamol within 9 aliquots of diluent). The diluted solution must be used within one hour (including the infusion time) after preparation.

As with any solution for infusion presented in a glass vial, close monitoring is recommended, especially at the end of the infusion. The need for close monitoring at the end of the perfusion is important to prevent air embolism, especially if central venous infusion is performed.

Additional information on special populations:
Renal impairment:
In patients with serious renal impairment (creatinine clearance ≤30 mL/min), intervals of 6 hours between each administration is recommended (See: Section 5.2).

Hepatic impairment:
In patients with chronic or active liver diseases, particularly in those with hepatocellular insufficiency, chronic malnutrition (low liver glutathione reserve) and dehydration, the daily 3 g/day dosage must not be exceeded (See: Section 5.2).

Pediatric population:
PAROKAN is suitable for adults, adolescents and children weighing more than 30 kg in 100 ml vials. The recommended dose is 10-15 mg / kg / dose every 6 hours (maximum 500 mg at a time in children over 30 kg), with a maximum daily dose of 60 mg / kg (maximum 2 grams per day in children over 30 kg). The maximum dosage interval should be 4 hours and should not be given more than 4 times a day.

Geriatric population:
No dosage adjustment is required for the geriatric population (See: Section 5.2).

Alcohol: The daily paracetamol dosage must not exceed 2000 mg in individuals taking alcohol because of hepatotoxicity risk.

4.3. Contraindications
PAROKAN is contra-indicated for the following conditions:

- In those allergic against paracetamol, proparacetamol hydrochloride (pre-drug of paracetamol) or other components of the drug.
- In cases of serious hepatic impairment or during active liver diseases.

4.4. Special warnings and precautions for use
Risk of medication errors: Take care to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and death.

It is recommended that a suitable oral analgesic would be shifted to as soon as the patient becomes able to take oral dugs. It must be checked if other drugs administered contain paracetamol to eliminate the risk of over- dosage.

Dosages exceeding the recommended amounts have the risk of serious liver damage. The clinical signs of liver damage appear generally the least 2 days later and the latest 4-6 days later. Treatment with antidotes must be started within the as soon as possible (see: section 4.9).

In those who first use paracetamol or have a history of previous use, skin rash, rash or a skin reaction may occur in the first dose of use or in repeated doses. In this case, it is necessary to contact the doctor and discontinue the use of the drug and switch to an alternative treatment. A person who has a skin reaction with paracetamol should not use this drug or any other drug containing paracetamol again. This can cause skin reactions, including severe and potentially fatal Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).

Paracetamol must be used carefully in the following conditions:

- Liver impairment

- Serious renal impairment (creatinine clearance ≤30 mL/min) *(See: Sections 4.2 and 5.2).*
- Glucose -6-phosphate dehydrogenase (G6PD) deficiency (can cause hemolytic anemia).
- Chronic alcoholism, excessive alcohol consumption (3 glasses or more daily alcoholic drink),
- Anorexia, bulimia or cachexia, chronic malnutrition (low levels of hepatic glutathione reserves),
- Dehydration, hypovolemia.

It should be used with caution under the supervision of a doctor in patients with anemia, liver and kidney dysfunction.
Causes severe liver toxicity in acute high doses.
May cause liver damage in adults in chronic daily doses.
It should be used with caution in alcoholic liver patients.

Due to the risk of hepatotoxicity in people who drink alcohol, the daily dose of paracetamol should not exceed 2000 mg.

This medicinal product contains less than 1 mmol (23 mg) sodium per 100 mL; so, it actually "does not contain sodium".

4.5. Interactions with other medical products and other forms of interaction
PAROKAN may increase the risk of undesirable effects when co-administered with other drugs.

Concurrent use with phenytoin can decrease the effectiveness of paracetamol and can increase the risk of hepatotoxicity. Administration of paracetamol in high and/or chronic dosages must be avoided in patients receiving phenytoin. Patients must be followed-up for hepatotoxicity.

Probenecid reduces the clearance of paracetamol approximately 2-fold by inhibiting its conjugation with glucuronic acid. Reducing the paracetamol dosage must be considered in treatment with probenecid.

Salicylamide can increase the elimination half-life of paracetamol. It is recommended that the combined dosage of paracetamol and salicylates for short-term use should not exceed the recommended dosages of paracetamol and salicylate alone. Diflunisal can increase the plasma concentration of paracetamol by 50% and can increase the hepatotoxicity risk related to paracetamol.

Care must be taken while concurrent use of enzyme inducers. Such substances include, but are not limited with barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin + clavulanic acid and ethanol.

Anticonvulsants such as phenytoin, barbiturates, carbamazepine may increase paracetamol-induced liver toxicity due to the increased conversion of paracetamol to hepatotoxic metabolites. The risk of

hepatic toxicity due to paracetamol increases in patients who take paracetamol above the recommended doses during anticonvulsant use.

Chronic alcoholics should be cautioned about regular and excessive use of paracetamol or avoiding chronic alcohol consumption, as there is some evidence that excessive alcohol consumption increases the risk of hepatotoxicity associated with paracetamol.

Concomitant use of paracetamol with high doses of anticoagulants (coumarin or indandione derivatives) for a long time may increase the anticoagulant effect, possibly due to decreased hepatic synthesis of procoagulant factors. If prothrombin time increases when prolonged, high-dose paracetamol therapy is initiated or terminated, anticoagulant dose adjustment may be required. This is not the case for rarely used or chronically used doses below 2 g / day.

Although the exact mechanism of its interaction is not known, concomitant use of isoniazid with paracetamol may increase the risk of hepatotoxicity.

Anticoagulants: Paracetamol injection (4 g / day, at least 4 days) combined with oral anticoagulants may cause deviations in INR values. Therefore, INR values should be closely monitored during the concomitant use of the drug and until 1 week after the completion of treatment with Paracetamol injection.

4.6. Pregnancy and lactation

General advice

Pregnancy category: B

Women with childbearing potential/Contraception

There is no adequate data related use of PAROKAN on women with potential of giving birth.

Pregnancy:

For paracetamol intravenous use, no clinical data on exposure in pregnancies are available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy / embryonal / fetal development / birth or postnatal development.

Caution should be exercised when administered to pregnant women.

It is recommended that PAROKAN be used during pregnancy only in cases where the benefit is high against possible risks.

In case of pregnancy, the recommended posology and duration should be strictly followed. Prospective data on pregnancies exposed to overdose do not show an increased risk of malformation**.**

Lactation:

After oral administration, paracetamol is excreted in a small amount of breast milk (it passes into milk). No undesirable effects on nursing infants have been reported. PAROKAN must be used carefully in lactating mothers.

The reproductive capability/Fertility
Reproduction studies have not been conducted in animals with the intravenous form of paracetamol. There are insufficient data to show whether paracetamol has any effect on fertility.

4.7. Effects on ability to drive and use machines
It is not known whether or not PAROKAN affects driving or machine-using skills. However, it can cause nausea or vomiting in some individuals (See: Section 4.8). Therefore, patients must be warned.

4.8. Undesirable effects
Clinical experience
Like in other drugs containing paracetamol, the adverse effects reported in the clinical studies on PAROKAN are either rare or very rare.
Frequencies are defined as follows:
Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (estimation based on the existing data is impossible).

Blood and lymphatic system diseases
Very rare: Thrombocytopenia, Leucopenia, Neutropenia.

Cardiac disorders
Rare: Hypotension

Hepatobiliary disorders
Rare: Increase in liver transaminase levels

General disorders and diseases related to the administration site
Rare: Malaise
Very rare: Hypersensitivity reaction

Post-marketing experience
The adverse effects listed below have been reported during the post-marketing experience; however, their frequencies are unknown.

Blood and lymphatic system disorders
Unknown: Thrombocytopenia

Immune system disorders
Unknown: Anaphylactic shock, anaphylaxis, hypersensitivity reaction, angioneurotic edema (Quincke's edema)

Cardiac disorders
Unknown: Tachycardia

Gastrointestinal disorders
Unknown: Nausea, vomiting

Hepatobiliary disorders
Unknown: Fulminate hepatitis, hepatic necrosis, hepatic impairment, increase in liver enzymes

Skin and subcutaneous tissue disorders
Rare: Skin rash, pruritus, urticarial, allergic edema and angioedema, acute generalized exanthematous pustulosis, erythema multiform, Stevens-Johnson Syndrome and toxic epidermal necrolysis (including fatal results).

General disorders and diseases related to the administration site
Unknown: Reaction in the administration site

Reporting of the side effects:
If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment

Toxicity is possible if 7.5 g or more is taken as a single dosage in adults and with 140 mg/kg in children; acute or fulminate liver impairment, hepatocellular insufficiency, metabolic acidosis and hepatic cytolysis characterized with encephalopathy that causes complete and irreversible hepatic necrosis can be seen. Furthermore, the harmful effects of over-dosage are greater in those with alcoholic liver disease without cirrhosis. The half-life of paracetamol, which is about 2 hours in normal adults, will increase to 4 hours or more in case of paracetamol over-dosage together with hepatocellular injury. Decrease in $^{14}CO_2$ excretion has been reported after ^{14}C-aminopyrine. This establishes a better relation between the over-dosage of paracetamol and hepatocellular damage as compared to paracetamol concentration or half-life or conventional hepatic function tests. Renal impairment can result in relation with acute tubular necrosis developing after fulminate liver impairment related to paracetamol. Nevertheless, this incidence is not greater in this group of patients than in those having fulminate liver impairment related to other reasons. Rarely, renal tubular necrosis only with minimal liver toxicity can occur 2 to 10 days later than taking of drug. It has been reported that chronic alcohol intake had contributed to the development of acute pancreatitis in one patient who had taken over-dosage of paracetamol. In addition to acute over-dosage of paracetamol, liver damage and nephrotoxic effects have also been reported following paracetamol intake in daily excessive amounts.

Symptoms and signs: Paleness, anorexia, nausea, vomiting and abdominal pain are the most frequent symptoms of paracetamol over-dosage. Hepatic necrosis is the dose-related complication of paracetamol over-dosage. Hepatic enzyme concentrations can be raised and prothrombin time can be extended within 12-48 hours; however, clinical symptoms may not be seen for 1 to 6 days following the intake of the drug.

Treatment: Paracetamol over-dosage must be treated immediately to protect the patient against delayed hepatotoxicity. For this, following the reduction of absorption (with gastric lavage or active coal), N-acetylcysteine intravenously or oral methionine must be administered. If the patient is vomiting, or if already treated with active coal, methionine must not be used. The peak paracetamol concentrations can be delayed for up to 4 hours following the over-dosage. Therefore, measurement of paracetamol levels continued for at least 4 hours after the drug intake. Additional treatment (additional oral methionine or intravenous N-acetylcysteine) must be evaluated under the light of paracetamol content in blood and the period that had lapsed till the intake of drug. The fulminate liver impairment treatment that had developed following the over- dosage of paracetamol can require specialty. Liver transplantation can be required in very serious cases.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics
ATC code: N02BE01

Although the mechanism of analgesic and antipyretic effects of paracetamol is not clearly known, it is thought that it shows its effects with central and peripheral routes.

Paracetamol shows its analgesic effect within 5-10 minutes following administration. The peak analgesic effect is reached within 1 hour, and this effect generally lasts for 4-6 hours.

It reduces fever within 30 minutes after administration of paracetamol and its antipyretic effect lasts for at least 6 hours.

5.2. Pharmacokinetic properties

Mechanism of action:

Absorption:

Bioavailability of paracetamol following infusion of 1 g paracetamol is similar to the bioavailability following the infusion of 2 g proparacetamol (contains 1 g paracetamol).

The peak plasma concentration (C_{max}) following 1 g paracetamol intravenous infusion within 15 minutes is approximately 30µg/mL.

Distribution:
The distribution volume of paracetamol is approximately 1 L/kg and mostly does not bind to plasma proteins. Significant paracetamol levels (approximately 1,5 mcg/mL) have been observed in the cerebrospinal fluid after infusion of 1 g paracetamol starting from the 20th minute of infusion.

Biotransformation:
Paracetamol is metabolized within liver by two major hepatic pathways: glucuronic acid conjugation and sulfuric acid conjugation. The latter is rapidly saturated with dosages exceeding the therapeutic dosages. A small fraction (< 4%) is metabolized to N-acetyl-benzoquinone-imine, which is a reactive intermediate product by cytochrome P450. This intermediate product is rapidly detoxified by reducing glutathione under normal conditions, and excreted with urine after being conjugated with cysteine and mercapturic acid. However, the amount of this metabolite increases in severe intoxications.

Elimination:
Paracetamol metabolites are excreted mainly through urine. 90 % of the administered dosage is excreted as glucoronate conjugates (60-80%) or as sulfate conjugates (20-30%) within 24 hours. Less than 5% is eliminated unchanged.

The plasma half-life is 2.7 hours and the total body clearance is 18 L/hour.

Linearity/Nonlinear status:
Pharmacokinetics of paracetamol is linear up to 2 g following single administration or administrations repeated within 24 hours.

Characteristics of patients
Renal İmpairment:
Elimination of paracetamol delays partially in patients with serious renal impairment (creatinine clearance ≤10-30 mL/min), and elimination half-life becomes 2.5-3 hours. Elimination of glucoronate and sulfate conjugates in patients with serious renal impairment will be 3 folds slower as compared to healthy individuals. Therefore, in patients with serious renal impairment (creatinine clearance ≤10-30 mL/min), it is recommended that administrations will be made with intervals of at least 6 hours (see: Section 4.2).

Hepatic impairment:
Paracetamol has been studied in patients with hepatic impairment. In a study, daily 4 g paracetamol was administered to six subjects with chronic stable liver impairment for 5 days. Plasma concentrations of paracetamol, which were analyzed at the midpoint of the 3rd and 4th 1 g dosages, ranged between 4.5 µg/mL and 26.7 µg/mL, which are rather below the toxic levels. No marked

paracetamol accumulation was observed, and no changes were observed in the clinical statuses or laboratory tests of the patients. The mean elimination half-life is not markedly different from those reported for healthy individuals and is about 3,4 hours. In the same study, 20 additional subjects with chronic stable liver impairment were randomized in a double-period crosswise study, and received 4 g dosage for 13 days. Increases in liver function tests (LFT) were observed in one subject; however, once this episode was recovered, no abnormalities were seen in the following to administrations. It was concluded that this increase was not related to the drug, and use of therapeutic paracetamol dosages was not contra-indicated in patients with chronic liver impairment.
Some clinical studies have shown that metabolism of paracetamol is slightly impaired in patients with chronic liver impairment including alcoholic cirrhosis. This has been shown with the increase in paracetamol plasma concentrations and elongation of elimination half-life. These reports have stated that the increase in the plasma half-life of paracetamol is related to the synthesis capacity of liver. In conclusion, paracetamol must be used carefully in patients with liver impairment and is contra-indicated in the presence of active disease including alcoholic cirrhosis related to the induction of CYP2E1.

Pediatric population:
Although the pharmacokinetic parameters of paracetamol observed in infants between 0-1 years of age and children resemble those observed in adults, the plasma half-lives in these populations are 1.5-2 hours shorter. The plasma half-life in the newborns is about 3.5 hours longer than those observed in infants between 0-1 years of age.

Newborns, infants between 0-1 years of age and children up to 10 years of age eliminate less glucoronate and more sulfate conjugates as compared to adults. Total elimination of paracetamol and metabolites are the same at every age.

Geriatric population:
Pharmacokinetic and metabolism of paracetamol do not change in the geriatric population. Dose adjustment is not required in these patients.

5.3. Preclinical safety data
Carcinogenesis, mutagenesis, fertility insufficiency

Effects of paracetamol on the diets of mice and rats have been studied with dosages of 0, 600, 3000 and 6000 PPM for 2 years. Paracetamol was found non-carcinogenetic in male and female mice like in male 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 toxicity
Preclinical data have not shown any damage in humans outside those indicated in the other sections of the Summary of Product Characteristics. The local tolerance studies carried out on rats and rabbits have shown that PAROKAN is well tolerated.

Delayed type contact hypersensitivity has been observed guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Mannitol
Cysteine hydrochloride monohydrate
Disodium hydrogen phosphate dihydrate
Sodium hydroxide/Hydrochloric acid(for pH adjustment)
Water for injection

6.2. Incompatibilities
PAROKAN must not be mixed with other drugs. (See: section 4.5)

6.3. Shelf life
24 months.

From the microbiologic perspective, unless the risk of contamination can be eliminated by the use of opening, the product must be used immediately after opening. If not used immediately, then the user shall be responsible for the periods and conditions of storage during the period of use.

The solution must be used immediately following the dilution with 0.9% sodium chloride.

The period of usability for PAROKAN for solutions opened or diluted is 1 hour at the most, including the infusion period.

6.4. Special precautions for storage
Keep at room temperature under 25°C and within the original packaging.
Do not keep in refrigerator, do not freeze it.

6.5. Nature and contents of container
100 mL Type II clear glass vial, Bromo butyl stopper and aluminum / plastic flip-off cap.
Packaging size: Boxes of 1 or 12 vials.

6.6. Special precautions for disposal and other handling

The product must be checked for visible particles and color change before use. For single use. The unused portion of solutions must be discarded.

The unused products and waste materials must be destructed according to the "Regulation Related to the Control of Medical Wastes" and the "Regulation Related to the Control of Packaging Materials and Packaging Wastes".

7. MARKETING AUTHORIZATION HOLDER

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