SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PAROKAN 10 mg/ml Vial Containing Solution For IV Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Paracetamol 10 mg/ml

Excipient:

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,
Colorless or light yellow clear solution

4. CLINICAL PROPERTIES

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 period 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/ application (0.75 ml solution/kg)	- Four times daily maximum - Intervals of at least 4 hours must be given between the applications - **The maximum dosage of 30 mg/kg** must not be exceeded
> 10 kg and ≤ 33kg	**15 mg/kg** Paracetamol/ application (1.5 ml solution/kg)	- Four times daily maximum - Intervals of at least 4 hours must be given between the applications - **The maximum dosage of 60 mg/kg** must not be exceeded (maximum daily dosage **2g**.)
> 33kg and ≤ 50kg	**15 mg/kg** Paracetamol/ application (1.5 ml solution/kg)	- Four times daily maximum - Intervals of at least 4 hours must be given between the applications - **The maximum dosage of 60 mg/kg** must not be exceeded (maximum daily dosage **3g**)
> 50kg	**1 g** Paracetamol/ application (1 vial of 100ml)	- Four times daily maximum - Intervals of at least 4 hours must be given between the applications - **The 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.

The drug must be drawn from the vial to administer dosages less than 100 ml.

Pediatric (for children) 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.

Route 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. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume. Take care to ensure the dose is measured and administered accurately.

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 little 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 population. However, only 0.9% sodium chloride or 5% dextrose 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. The diluted solution must be used within one hour following preparation (infusion time included).

Like in any other drug available within glass vials, close follow-up particularly after infusion is recommended. The requirement of close follow-up is particularly important as regards the air embolism when infusion is made through the central venous route.

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

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

Pediatric population: PAROKAN, 10 ml vial is suitable for adults, adolescents and children weighing more than 33 kg.

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

Alcohol: The daily paracetamol dosage must not exceed 2 g in individuals taking alcohol regularly 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 failure 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 4-6 days later, 2 days the least. Treatment with antidotes must be started within the as soon as possible (see: section 4.9).

Skin redness, rash or skin reaction may occur in first use of Paracetamol or patients with already in use paracetamol history, in the first dose or repeated doses of use. In this case must be contacted with the doctor, discontinue of drug use and switched to an alternative treatment. People which observed skin reactions with other drugs containing acetaminophen, should not use this medication more or paracetamol. In this case may cause skin reactions included serious and 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 failure
- Serious renal failure (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 gluthation reserves),

- Dehydration, hypovolemia.

It must be used carefully under the control of the doctor in patients with anemia, liver or renal dysfunctions.

It can cause serious hepatic toxicity with acute high dosages.

It can cause hepatic damage in adults with chronic daily dosages.

It should be used with caution in patients with alcoholic liver.

The daily paracetamol dosage must not exceed 2 g in individuals taking alcohol regularly because of hepatotoxicity risk.

This medical product contains 1 mmol (less than 23 mg) sodium in each 100 mL. No adverse effects related to sodium are expected at this dosage.

4.5. Interactions with other medical products and other forms of interaction

PAROKAN may increase the risk of undesirable effects when coadministered 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 decreases the clearance of paracetamol about two times 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 given to the concurrent use of enzyme inducers. Such substances include, but are not limited with barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin + clavulonic acid, and ethanol.

Anticonvulsant drugs including phenytoin, barbiturates and carbamazepine can increase the hepatotoxicity of paracetamol in relation with the increased transformation into hepatotoxic metabolites. The risk of hepatic toxicity will increase in patients who take paracetamol with

dosages exceeding the recommended dosages during anticonvulsant use.

Since there are some evidences that alcohol consumption in excessive amounts increases the risk of hepatotoxicity related to paracetamol, chronic alcoholics must be warned against regular and excessive paracetamol intake, or else avoiding consumption of alcohol in excessive amounts.

Concurrent use of paracetamol for long periods with anticoagulants (coumarin or indandione derivatives) can increase the anticoagulant effect, very probably through the decrease of hepatic synthesis of pro-coagulant factors. If prothrombin time increase is monitored at the beginning or termination of paracetamol therapy, dose adjustment of anticoagulants may be required. This requirement does not apply to occasional use or chronic uses under 2 g/day.

Although the mechanism of interaction is not known clearly, use of isoniazid together with paracetamol can result in the increase of hepatotoxicity risk.

Anticoagulants: Use of paracetamol injections (4 g/days, at least 4 days) can cause deviations in INR values. Therefore, INR values must be monitored closely throughout the period of the concurrent use of the two drugs, and 1 week later than the treatment with Paracetamol injections is complete.

4.6. Pregnancy and lactation

General

Pregnancy category: B

Women with potential of giving birth /Contraception

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

Pregnancy

There isn’t any clinical experience of intravenous administration of paracetamol.
Reproductive studies with the paracetamol did not show any adverse effect in animals.
Caution should take when using in pregnant.

PAROKAN should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.
The prospective data related to women who were exposed to over-dosage during pregnancy do not indicate any increase in malformation risk.

Lactation

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. PAROKAN must be used carefully in lactating mothers.

The reproductive capability/Fertility
Studies on reproduction have not been performed on animals. It is not available any data about whether or not paracetamol has an 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
Unknown: Thrombocytopenia, Leucopenia, Neutropenia.

Cardiac disorders
Rare: Hypotension

Hepatobiliary disorders
Rare: Increase in liver transaminase levels

General disorders and those 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 failure, increase in liver enzymes

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

General disorders and administration site conditions
Unknown: Reaction in the application site

4.9. Overdosage
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 failure, 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 failure can result in relation with acute tubular necrosis developing after fulminate liver failure related to paracetamol. Nevertheless, this incidence is not greater in this group of patients than in those having fulminate liver failure 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 failure treatment that had developed following the over-dosage of paracetamol can require specialty. Liver transplantation can be required in very serious cases.

5. PHARMACOLOGIC PROPERTIES

5.1. Pharmacodynamic properties

Pharmacoterapeutical 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.

Paracetamol brings fever down within 30 minutes 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 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 therapeutical 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 gluthatione under normal conditions, and excreted with urine after being conjugated with cysteine and mercapturine. However, the amount of this metabolite increases in severe intoxications.

Elimination:
Paracetamol metabolites are excreted mainly through urine. Ninety percent of the administered dosage is excreted as glucuronate 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 Failure: Elimination of paracetamol delays partially in patients with serious renal failure (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 failure will be 3 folds slower as compared to healthy individuals. Therefore, in patients with serious renal failure (creatinine clearance ≤30 ml/min), it is recommended that administrations will be made with intervals of at least 6 hours (see: Section 4.2).

Liver failure: Paracetamol has been studied in patients with liver failure. In a study, daily 4 g paracetamol was administered to six subjects with chronic stable liver failure 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. In the same study, 20 additional subjects with chronic stable liver failure 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 therapeutical paracetamol dosages was not contra-indicated in patients with chronic liver failure.

Some clinical studies have shown that metabolism of paracetamol is slightly impaired in patients with chronic liver failure 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 failure 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 glucuronate 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. Preclinic safety data

Carcinogenesis, mutagenesis and 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 carsinogenicity 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 therapeutical dosages of paracetamol.

Animal toxicity

Preclinical data have not shown any damage in humans outside those indicated in the other sections of the Summary Product Characteristics. The local tolerance studies carried out on rats and rabbits have shown that PAROKAN is well tolerated.

No delayed type contact hypersensitivity has been observed guinea pigs.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Mannitol
Cysteine hydrochloride monohydrate
Disodium phosphate dihydrate
Sodium
hydroxide/hydrochloride
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 within one hour following the dilution with 0.9% sodium chloride or 5% dextrose.

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 below 30°C and within the original packaging.
Do not keep in refrigerator, do not freeze it.

6.5. Nature and contents of container

100-ml colorless Type II glass vials with PP flip-off caps, bromobutyl stopper and Al hoods placed on silicone elastomer rubber stops.
Packaging size: boxes containing 12 vials.

6.6. Special precautions for disposal

The product must be checked for visible particles and color change before use. It must be used all at once. 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 AUTHORISATION HOLDER

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