# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT
PIROFEN 250 mg/5 mL oral suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each measuring spoon (5 mL) contains;
**Active substance:**
Paracetamol…….250 mg

**Excipients:**
Sorbitol liquid…….1895 mg
Sucrose……210 mg
Methyl parahydroxybenzoate……..4 mg
Sunset yellow……..0.0033 mg
Avicell RC*……..…45 mg
(microcrystalline cellulose/sodium carboxy methyl cellulose)

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM
Oral suspension
Banana-scented, yellowish-colored, homogeneous suspension

## 4. CLINICAL PARTICULARS
### 4.1 Therapeutic indications
Indicated for the symptomatic treatment of mild to moderate pain and fever.

### 4.2 Posology and method of administration
**Posology/frequency and duration of administration:**
It should not be used at doses higher than the recommended dose.

Treatment should be carried out at the lowest effective dose for the shortest possible time.

Recommended administration is 10-15 mg/kg/dose every 6 hours (maximum 500 mg at a time for children over 30 kg) with a maximum daily dose of 60 mg/kg (maximum 2 grams per day for children over 30 kg).

The minimum dosing interval should be 4 hours and it should not be given more than 4 times a day.

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

It should not be used for longer than 3 consecutive days without the advice of a physician.

**Method of administration:**
For oral administration. The thick consistency of PIROFEN ensures that the medicine does not spill from the spoon and facilitates its application.

The bottle should be shaken very well before use.

PIROFEN is used undiluted.

**Additional information on special populations**
**Renal impairment:**
It should be used with caution in patients with renal impairment, in accordance with the recommendation of a doctor. It is contraindicated in patients with severe renal impairment.

**Hepatic impairment:**
It is contraindicated in patients with severe hepatic impairment (Child Pugh score >9).

It should be used with caution in patients with mild to moderate hepatic impairment, in accordance with the recommendation of a doctor.

**Pediatric population:**
PIROFEN is intended for use by individuals over 6 years of age.

**Geriatric population:**
Usual adult dose is appropriate for healthy and active elderly patients; however, dose strength and dosage frequency should be reduced in frail and inactive elderly patients (see section 5.2).

**4.3 Contraindications**
PIROFEN is contraindicated,
- In case of hypersensitivity to paracetamol or any other constituents or,
- In case of severe hepatic impairment (Child Pugh score>9) or severe renal impairment (GFR<60 mL/min).

**4.4 Special warnings and precautions for use**
PIROFEN contains paracetamol. Do not use it together with other products containing paracetamol. Concurrent use with other products containing paracetamol may lead to overdose.

Paracetamol overdose may cause liver failure, which may lead to liver transplantation or death (see section 4.9).

The risk of paracetamol-induced liver damage increases when used by patients with underlying liver disease.

Patients diagnosed with liver or kidney impairment should seek medical advice before taking this medicine.

Cases of liver dysfunction/failure have been reported in patients with decreased glutathione levels (e.g., patients who are severely malnourished, anorexic, have a low body mass index, chronically heavy alcohol drinkers, or sepsis).

Use of paracetamol in patients with decreased glutathione levels may increase the risk of metabolic acidosis.

Paracetamol should be used with caution under medical supervision in patients with anemia, lung disease, hepatic or renal dysfunction. For patients with pre-existing hepatic disease, liver function

evaluations may be necessary at periodic intervals during high-dose or long-term therapy.

In those who use paracetamol for the first time or have a history of previous use, skin redness, rash or a skin reaction may occur with the first dose or repeated doses. In this case, it is necessary to contact the doctor, discontinue the use of the drug and switch to an alternative treatment. This medicine or any other paracetamol-containing medicine should not be used again in an individual who has had a skin reaction with paracetamol.

Cases of serious cutaneous adverse reactions (scars) such as Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), erythema multiforme (EM) and fixed drug eruption (FDE) have been reported in patients treated with paracetamol-containing drugs. Since scars may be life-threatening or fatal, paracetamol treatment should be discontinued immediately and appropriate treatment given.

Dose adjustment should be made and the patient should be monitored uninterruptedly.

Acute high doses cause serious liver toxicity.

Chronic daily doses may cause liver damage in adults.

Due to the risk of hepatotoxicity, paracetamol should not be taken in higher doses or for longer periods than recommended. Patients with mild to moderate hepatic impairment (Child-Pugh score <9) should use paracetamol with caution.

Serum alanine aminotransferase (ALT) level may increase during the administration of therapeutic doses of paracetamol.

Concomitant use of therapeutic doses of paracetamol and drugs that increase hepatic oxidative stress and reduce hepatic glutathione reserve, various conditions such as alcoholism, sepsis or diabetes mellitus may lead to an increased risk of hepatic toxicity.

Paracetamol should be used with caution in those with glucose-6-phosphate dehydrogenase deficiency. Rare cases of hemolysis may be observed.

Long-term use of high doses of paracetamol may cause renal damage.

In general, uninterrupted use of paracetamol, especially in combination with other analgesics, may lead to permanent renal damage and risk of renal failure (analgesic nephropathy).

Use of paracetamol by patients with Gilbert's syndrome may cause clinical symptoms such as jaundice and more pronounced hyperbilirubinemia. Therefore, these patients should use paracetamol with caution.

Concomitant intake of paracetamol along with moderate amounts of alcohol may lead to an increased risk of hepatic toxicity. It should be used with caution in patients with alcoholic liver.

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

If new symptoms occur within 3-5 days or if pain and/or fever do not subside, patients are advised to

discontinue use of paracetamol and consult a doctor.

This medicine contains 1895 mg sorbitol liquid per 5 mL. The additive effect of concomitant administration of sorbitol (or fructose) containing products and dietary intake of sorbitol (or fructose) should be taken into account. The sorbitol content in medicinal products intended for oral use may affect the bioavailability of other concomitantly administered medicinal products intended for oral use. Patients with hereditary fructose intolerance should not be given/take this medicine. Sorbitol can cause gastrointestinal discomfort and a mild laxative effect.

Since PIROFEN contains sucrose, patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not use this medicine.

Because of methyl parahydroxybenzoate ingredient, it may cause allergic reactions (possibly delayed).

Since PIROFEN contains sunset yellow as a coloring ingredient, it may cause allergic reactions.

This medicine contains less than 1 mmol (23 mg) sodium per 5 mL, meaning it is essentially "sodium-free."

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

Medicines that slow gastric emptying, such as propantheline, may cause slow absorption of paracetamol and thus delay its effect.

Medicines that accelerate gastric emptying, such as metoclopramide, may cause rapid absorption of paracetamol and therefore a quicker onset of action.

The use of drugs that induce hepatic microsomal enzymes such as anticonvulsants and oral contraceptives may increase the extent of metabolism of paracetamol resulting in reduced plasma concentrations of the drug and a faster elimination rate.

Certain hypnotics and antiepileptic drugs (glutethimide, phenobarbital, phenytoin, carbamazepine etc.) or drugs that cause hepatic microsomal enzyme induction in the liver, such as rifampicin, may cause liver damage if used concurrently with doses of paracetamol that would essentially be harmless when used alone. In case of excessive alcohol consumption, taking paracetamol even in therapeutic doses may also cause liver damage.

Chronic alcohol intake may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolize large doses of paracetamol, the plasma half-life of which can be prolonged.

Use of paracetamol in combination with chloramphenicol may prolong the half-life of chloramphenicol and therefore increase the risk of toxicity of this medicine.

Paracetamol (or its metabolites) interacts with enzymes involved in the synthesis of vitamin K-dependent coagulation factor. Interactions between paracetamol and warfarin or coumarin derivatives may lead to an increase in the "international normalized ratio (INR)" and an increase in the risk of bleeding. Therefore, patients using oral anticoagulants should not use paracetamol for long periods without medical supervision and control.

Tropisetron and granisetron, which are 5-hydroxytryptamine (serotonin) type 3 receptor antagonists, may completely suppress the analgesic effect of paracetamol through pharmacodynamic interaction.

Concomitant use of paracetamol and azidothymidine (AZT-zidovudine) increases the tendency for neutropenia. Therefore paracetamol should not be taken with AZT unless on medical advice.

Combination therapy with more than one analgesic should be avoided. Little evidence is available to suggest that this provides an additional benefit to the patient; in fact, it often causes undesirable effects to increase.

The absorption rate of paracetamol may be increased by metoclopramide or domperidone and decreased by cholestyramine.

St. John's Wort (*Hypericum perforatum*) may reduce blood levels of paracetamol.

When taken with food, the absorption rate of paracetamol may decrease.

**Additional information on special populations**
No interaction studies have been conducted.

**Pediatric population:**
No interaction studies have been conducted.

**4.6 Fertility, pregnancy and lactation**
**General advice**
Pregnancy category: B

**Women of childbearing potential/Birth control (Contraception)**
Caution should be exercised when prescribing the medicine to women of childbearing potential.

**Pregnancy**
For paracetamol, no adequate clinical data on exposure during pregnancy are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy/embryonal/fetal development/parturition or postnatal development.

The safety of paracetamol during pregnancy has not been established. Paracetamol crosses the placenta and reaches a fetal concentration similar to maternal concentration. However, short-term maternal intake of therapeutic doses of paracetamol has not been associated with teratogenic effects in humans.

**Breast-feeding**
Paracetamol is excreted in breast milk, but not in clinically significant quantities at recommended doses. Available published data do not contraindicate breast-feeding.

**Reproduction ability/fertility**
In chronic toxicity studies conducted in animals, paracetamol has been reported to cause testicular atrophy and inhibit spermatogenesis. No trials examining its effects on human fertility are available.

## 4.7 Effects on ability to drive and use machines

Dizziness or somnolence may occur in some patients due to the use of paracetamol. Patients using paracetamol should be careful during activities that require alertness.

## 4.8 Undesirable effects

Adverse drug reactions identified during clinical trials and post-marketing experience are listed below in the following order of frequency.

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

**Infections and infestations**
Common: Infection (2.9%)

**Blood and lymphatic system disorders**
Very rare: Agranulocytosis, thrombocytopenia (isolated reports)

**Immune system disorders**
Rare: Eruption, urticaria, angioedema
Very rare: Anaphylactic shock, positive allergy test**, immune thrombocytopenia***

**Nervous system disorders**
Common: Headache (5.1%), dizziness (3.58%), somnolence (6.97%), paresthesia (5.4%)

**Ear and labyrinth disorders**
Uncommon: Balance disorder (1%)

**Vascular disorders**
Very rare: Purpura

**Respiratory, thoracic and mediastinal disorders**
Common: Upper respiratory tract infection (2.7%)
Very rare: Bronchospasm*

**Gastrointestinal disorders**
Common: Nausea (2.3%), diarrhea (4.7%), dyspepsia (2.3%), flatulence (2.3%), abdominal pain (3.9%), constipation (3.9%), vomiting (7.8%)
Uncommon: Gastrointestinal hemorrhage (0.13%)

**Hepatobiliary disorders**
Very common: ALT levels above the upper limit of normal (17.4%)
Common: ALT levels 1.5 times of the upper limit of normal (4.2%)
Very rare: Hepatic dysfunction

**Skin and subcutaneous tissue disorders**
Rare: Skin rash, pruritus, urticaria, allergic edema, acute generalized exanthematous pustulosis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (including fatal consequences)
Scarring (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis and fixed drug eruption (see section 4.4)

**Renal and urinary disorders**
Not known: Nephrotoxic effects following therapeutic doses of paracetamol are uncommon. Papillary necrosis has been reported with long-term administration.

**General disorders and administration site conditions**
Common: Facial edema (4.5%)
Uncommon: Peripheral edema (1%)
Very rare: Fever, asthenia

**Surgical and medical procedures**
Uncommon: Post-tonsillectomy hemorrhage (0.5%)
Common: Post-extraction hemorrhage (3.3%)

*Bronchospasm: Seen in 20% of asthmatic patients sensitive to acetylsalicylic acid or other NSAIDs.
**Oral provocation test with paracetamol: Positive in 15.5% of patients with paracetamol-related allergic symptoms (eruption, urticaria, anaphylaxis).
***Immune thrombocytopenia: In the presence of paracetamol and paracetamol sulfate, antibodies bind to GPIIb/IIIa and GPIb/IX/V receptors of platelets. In a literature review involving 2000 patients comparing paracetamol with placebo and nonsteroidal anti-inflammatory drugs, following discontinuation of paracetamol treatment, no difference was observed between paracetamol and placebo in terms of the frequency of adverse effects and discontinuation of treatment. In a second literature review involving 2100 patients comparing paracetamol with nonsteroidal anti-inflammatory drugs, discontinuation of treatment was observed more frequently in the paracetamol group due to insufficient effect of the drug. One in every 10 patients receiving paracetamol treatment interrupted the treatment, and one in every 15 patients stopped the treatment because they concluded that the effect of the drug was insufficient. Compared to NSAIDs, the rate of treatment discontinuation due to undesirable effects is lower. According to clinical laboratory assessments, the undesirable effects of paracetamol used at therapeutic doses in clinical trials and the changes in laboratory values were found to be no different from those of placebo. Changes in biochemical values related to liver function indicate that the drug is taken at toxic doses. If the drug is taken at toxic doses, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) begin to rise within 24 hours and peak after 72 hours. Elevation of any of these above 1000 units is descriptive for hepatotoxicity. Besides that, bilirubin and creatinine are elevated and glucose is decreased. Findings indicating poor prognosis are arterial pH falling below 7.3, creatinine rising above 3.4 mg/dL, prothrombin time exceeding 100 seconds, and serum lactate level rising above 3.5 millimole/L. Differences in susceptibility to the adverse and toxic effects of paracetamol have not been reported depending on gender, race, height, weight, body structure, lifestyle and location. Apart from these, risk factors that increase susceptibility to the toxic effects of paracetamol are included in the drug interactions section (see section 4.5).

Children under 6 years of age are less susceptible to toxic effects of paracetamol. It has been suggested that elevated glutathione reserves and high detoxification rate play a role in this.

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of the disease improved after paracetamol withdrawal.

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 via the national reporting system.

**4.9 Overdose and management**

Paracetamol overdose can result in liver failure, which may lead to liver transplantation or fatal outcomes. Acute pancreatitis has often been observed in association with hepatic dysfunction and liver toxicity.

In addition, paracetamol overdose may cause signs and symptoms of acute renal impairment. Signs and symptoms may include increases in serum urea, creatinine and potassium levels, increased blood pressure, confusion, nausea and vomiting. However, renal injury may be secondary to liver injury or may be the only or primary toxic finding within 24 to 72 hours after paracetamol overdose.

Toxicity is possible for adults who have taken more than 10 grams of paracetamol. If the patient has risk factors (see below), ingestion of 5 grams or more of paracetamol may lead to liver damage.

*Risk factors:*

If the patient,

- Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes

Or

- Regularly consumes ethanol in excess of recommended amounts

Or

- Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, and cachexia.

The harm of overdose is greater in patients with non-cirrhotic alcoholic liver disease. Liver damage following overdose is relatively rare in children. In cases of paracetamol overdosage with liver cell damage, the half-life of paracetamol, which lasts around 2 hours in normal adults, is usually extended to 4 hours or longer. A decrease in $^{14}CO_2$ elimination after $^{14}C$-aminopyrine has been reported. This shows a better relationship between paracetamol overdose and liver cell damage compared to plasma paracetamol concentration or half-life or conventional liver function test measurements.

Renal failure may occur due to acute tubular necrosis following fulminant hepatic failure due to paracetamol. However, this group is not frequent in patients when compared with patients with fulminant hepatic failure due to other reasons for the incidence. Rarely, renal tubular necrosis may occur only after minimal hepatic toxicity, 2-10 days after taking the drug. It has been reported that chronic alcohol intake in a patient who received an overdose of paracetamol contributed to the development of acute pancreatitis. In addition to acute overdose, liver damage and nephrotoxic effects have been reported after excessive daily intake of paracetamol.

*Symptoms and signs:*

Pallor, anorexia, nausea and vomiting are common early symptoms of paracetamol overdose. Hepatic necrosis is a dose-related complication of paracetamol overdose. Hepatic enzymes can rise and prothrombin time is prolonged within 12 to 48 hours, but clinical symptoms may not be apparent within 1 to 6 days of drug ingestion. This may include hepatomegaly, liver tenderness, jaundice, acute hepatic failure and hepatic necrosis. Abnormalities of glucose metabolism and metabolic acidosis

may occur. Blood bilirubin, hepatic enzymes, INR, prothrombin time, blood phosphate and blood lactate may be increased. In severe poisoning may progress to hepatic failure, encephalopathy, hemorrhage, hypoglycemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria might develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

*Management:*
Immediate treatment is essential in the management of paracetamol overdose in order to protect the patient against delayed hepatotoxicity even if in the absence of symptoms. Therefore, it may be necessary to administer intravenous N-acetylcysteine or oral methionine.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol; however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required, the patient should be given intravenous N-acetylcysteine in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction or risk of kidney damage beyond 24 hours from ingestion should be discussed with the national poisons information center.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, Anilides
ATC code: N02BE01

Paracetamol is an analgesic and antipyretic agent. Therapeutic effects of paracetamol are thought to be due to inhibition of prostaglandin synthesis as a result of inhibition of cyclooxygenase enzyme. There is evidence showing that paracetamol is a more effective inhibitor on central cyclooxygenase than peripheral cyclooxygenase. Paracetamol has analgesic and antipyretic properties but exhibits only weak anti-inflammatory properties. This may be explained by the fact that inflammatory tissues contain higher levels of cellular peroxides compared to other tissues, and these cellular peroxides prevent cyclooxygenase inhibition of paracetamol.

### 5.2 Pharmacokinetic properties

**General characteristics**

Absorption:
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Absorption of paracetamol occurs primarily by passive transfer from the small intestines. Gastric emptying is a rate-limiting step for the absorption of orally administered paracetamol. Peak plasma paracetamol concentration generally occurs between 30 and 90 minutes after ingestion, depending on the formulation. Because paracetamol undergoes first-pass metabolism at a variable rate, it is not fully present in the systemic circulation after oral intake. Oral bioavailability in adults appears to be dependent on the amount of paracetamol administered. Oral bioavailability is 63% after a 500 mg dose, increasing to approximately 90% after a 1 or 2 g (tablet form) dose.

Distribution:
Paracetamol distributes equally into most body fluids, with an estimated volume of distribution of

0.95 L/kg. Following therapeutic doses, paracetamol is not significantly bound to plasma proteins. The distribution kinetics (Vd/F) in children is similar to that in adults.

Biotransformation:
The plasma half-life of paracetamol after therapeutic doses is 1.5-2.5 hours. Paracetamol is metabolized in the liver. The major metabolite excreted in urine is glucuronide and sulfate conjugate. About 10% of paracetamol is converted via a minor pathway to acetamidoquinone, a reactive metabolite by the cytochrome P-450 mixed-function oxidase system (mainly CYP2E1 and CYP3A4). This metabolite is rapidly conjugated with reduced glutathione and excreted as cysteine and mercapturic acid conjugates. Ingestion of large amounts of paracetamol may decrease hepatic glutathione, leading to excessive accumulation of hepatocyte acetamidoquinone, which covalently binds to vital hepatocellular macromolecules. This leads to hepatic necrosis, which can be seen in case of overdose.

Main paracetamol metabolite in children (3-10 years) and newborns (0-2 days) is paracetamol sulfate.

Elimination:
Following a single dose (1000 mg i.v.), total body clearance of paracetamol is about 5 mL/min/kg. Renal clearance of paracetamol depends on urine flow rate but not on pH. Less than 4% of the applied drug is excreted as unchanged paracetamol. In healthy individuals, approximately 85-95% of the therapeutic dose is excreted through urine within 24 hours.

There is no age-related difference between children and adults in terms of the total elimination rate of paracetamol.

Linearity/non-linearity:
Binding of reactive paracetamol metabolites to liver cell proteins causes hepatocellular damage. At therapeutic doses, these metabolites are bound by glutathione, forming nontoxic conjugates. However, in case of massive overdose, the liver's store of SH-donors (which facilitate and promote glutathione formation) is depleted, toxic metabolites of the drug accumulate in the liver and liver cell necrosis develops which progresses to deterioration in liver function and gradually to hepatic coma. Its pharmacokinetics are linear when used in accordance with the posology.

**Characteristic features of patients**
Renal impairment:
The mean plasma half-life between 2 and 8 hours is the same in normal and renal failure patients, but the elimination rate is reduced in renal failure between 8 and 24 hours. In chronic renal failure, significant accumulation of glucuronide and sulfate conjugates occurs. Some additional elimination of accumulated paracetamol conjugates may occur in patients with chronic renal failure with limited regeneration of the parent compound. In chronic renal failure, it is recommended to extend paracetamol dose intervals. Since paracetamol plasma levels may decrease during hemodialysis, additional doses of paracetamol may be required to maintain therapeutic blood levels.

Hepatic impairment:
The mean plasma half-life in patients with mild liver disease is similar to that in normal individuals, but is significantly prolonged (about 75%) in severe hepatic impairment. However, the clinical significance of the half-life extension is unclear because drug accumulation and hepatotoxicity have not been demonstrated and glutathione conjugation is not reduced in patients with liver disease. Administration of 4 g paracetamol daily for 13 days to 20 patients with chronic stable liver disease

did not cause deterioration in liver function. Paracetamol has not been proven harmful when taken at recommended doses in mild liver disease. However, in severe hepatic impairment, the plasma paracetamol half-life is significantly prolonged.

Children:
Studies have shown that paracetamol sulfate is the major metabolite of paracetamol in newborns aged 0-2 days and children aged 3-10 years. Data in adults and children 12 years of age and older indicate that the major metabolite is the glucuronide conjugate. However, there is no significant age-related difference in the overall paracetamol elimination rate or the total amount of drug excreted in the urine.

Elderly:
Differences observed in pharmacokinetic parameters between young and elderly healthy volunteers are not considered clinically important. However, there is evidence to suggest that serum paracetamol half-life is significantly increased (approximately 84%) and paracetamol clearance is reduced (approximately 47%) in frail, sedentary and elderly patients compared to healthy young individuals.

### 5.3 Preclinical safety data
Mild toxicity was detected following oral administration of paracetamol in adult rats. In young rats, it was found to be more toxic due to the immaturity of the hepatic enzyme system. Acute toxicity symptoms have included vomiting. With chronic administration, effects such as reduced weight gain, diuresis, aciduria, dehydration, and susceptibility to infections have been observed.

In rats, a potential genotoxicity was observed at the hepatotoxic dose level and this finding was explained not as a direct DNA damage but as an indirect consequence of hepatotoxicity/myelotoxicity.

No increased embryotoxic or teratogenic risk has been observed following extensive use in humans. Paracetamol is frequently taken during pregnancy, and no negative effects have been observed on either the course of pregnancy or the unborn child.

Chronic toxicity studies in animals have reported that paracetamol causes testicular atrophy and inhibits spermatogenesis.

## 6. PHARMACEUTICAL PARTICULARS
### 6.1 List of excipients
Sorbitol liquid (non-crystalline) (E420)
Sucrose
Glycerol
Methyl parahydroxybenzoate (E218)
Polysorbate 80
Xantham gum
Avicell RC (microcrystalline cellulose/sodium carboxy methyl cellulose)
Sucralose
Banana flavor
Quinoline yellow (E104)
Sunset yellow (E110)
Purified water

### 6.2 Incompatibilities

Not applicable.

**6.3 Shelf life**
24 months

**6.4 Special precautions for storage**
Store at room temperature below 25°C.

Shake the bottle vigorously before each use.

PIROFEN suspension should not be reconstituted.

**6.5 Nature and contents of container**
As the primary packaging material of our product, 28 PP honey-colored glass bottles containing 150 mL suspension and 28/20 mm plastic cap were used. These bottles are packaged in cardboard boxes. A cardboard box includes one bottle, a 5 mL transparent measuring spoon with liner for 1.25 mL, 2.5 mL and 5 mL, and one package leaflet.

**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 AUTHORIZATION HOLDER**
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**8. MARKETING AUTHORIZATION NUMBER(S)**
2022/786

**9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**
Date of first authorization : 22.12.2022
Date of latest renewal :

**10. DATE OF REVISION OF THE TEXT**