SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Paramolan 24 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 24 mg of paracetamol as active substance.

Excipients with known effect:
Each ml of oral solution contains 280 mg of sorbitol (E420), 30 mg of propylene glycol (E1520), 13.2 mg of sucrose, 1.8 mg of methyl parahydroxybenzoate (E218), red dye (E122) and benzoate sodium (E211) in amounts less than 0.22 mg, and 0.2 mg of propyl parahydroxybenzoate (E216).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

4. CLINICAL INFORMATION

4.1 Therapeutic indications

Paramolan is indicated for the treatment of mild to moderate pain, sore throat (excluding tonsillitis), as well as mild to moderate headaches.

Paramolan is also indicated for the treatment of fever lasting no longer than 3 days, and for the symptomatic treatment of colds and flu-like syndromes.

4.2 Posology and method of administration

The packaging of Paramolan oral solution includes a measuring spoon for a more accurate administration of the dose. This measuring spoon measures 5 ml (120 mg of paracetamol) or 2.5 ml (60 mg of paracetamol) of solution.

Posology

For information purposes only, and unless otherwise indicated by a doctor, may be administered as follows:

Paediatric population:
3 months to 1 year: 2.5 ml to 5 ml (1/2 to 1 measuring spoon), up to 4 times a day;
1 years to 6 years: 5 ml to 10 ml (1 to 2 measuring spoons), up to 4 times a day;
6 years to 12 years: 10 ml to 20 ml (2 to 4 measuring spoons), up to 4 times a day.

Adults: 20 ml (4 measuring spoons), up to 6 times a day.

Attention: do not exceed the recommended daily doses.

The minimum interval between doses should not be less than 4-6 hours.

In case of renal insufficiency, a dose reduction or longer intervals between doses may be required.

In case of hepatic insufficiency, the half-life of paracetamol is increased in patients with paracetamol-induced liver disease. No information is available about dosage adjustments in patients with other types of severe liver disease.

Paramolan oral solution should not be used in combination with other medicines containing paracetamol.

4.3 Contraindications

- Hypersensitivity to the active substance (paracetamol) or to any of excipients listed in section 6.1.

- Severe liver disease.

4.4 Special warnings and precautions for use

At therapeutic doses, paracetamol is relatively nontoxic. However, allergic skin reactions may occur, including anaphylactic reactions.

Cases of hepatic necrosis have been reported in patients taking high doses of paracetamol. In patients with cardiac, respiratory, hepatic or renal insufficiency, or anaemia, this product should only be administered under medical supervision, and for short periods.

In self-medication of pain, this medicine should not be used for longer than 10 days in adults, or longer than 5 days in children, unless prescribed by a doctor, since intense and prolonged pain may require medical assessment and treatment.

This medicine should also not be used for self-medication of high fever (temperature higher than 39ºC), fever lasting longer than 3 days, or recurring fever, unless prescribed by a doctor, since these situations may require medical assessment and treatment.

This medicine should not be used in combination with other medicines containing paracetamol in their composition.

Prolonged treatment with analgesics, particularly when several types of analgesics are administered concomitantly, may cause irreversible renal lesions, entailing the risk of development of renal insufficiency (analgesic nephropathy).

It should also be used with caution in patients with harmful alcohol consumption, chronic malnutrition (due to low reserves of glutathione) and dehydration.

Paracetamol administration may interfere with the determination of uric acid levels in blood by the phosphotungstic acid method and determination of glycaemia by the glucose oxidase-peroxidase method.

This medicine contains:
- Sodium benzoate (E211): this medicine contains less than 0.22 mg of sodium benzoate per ml of oral solution;
- Red dye (E122), which can cause allergic reactions;
- Parabens (methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216)), which can cause allergic reactions (possibly delayed);
- Propylene glycol (E1520): this medicine contains 30 mg of propylene glycol for each ml of oral solution. Concomitant administration with any alcohol dehydrogenase substrate, such as ethanol, may induce adverse effects in children under 5 years of age. The administration of propylene glycol to pregnant or breast-feeding patients should be considered on a case-by-case basis. Medical monitoring is required in patients with impaired renal or hepatic function, as several adverse events attributed to propylene glycol have been reported, such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction;
- Sucrose: patients with rare hereditary problems of fructose intolerance, malabsorption of gluco-galactose or sucrase-isomaltase insufficiency should not take this medicine;
- Sorbitol (E420): this medicine contains 280 mg of sorbitol for each ml of oral solution. Consideration should be given to the additive effect of concomitant administration of products containing sorbitol (or fructose) and the intake of sorbitol (or fructose) in the diet. Patients with Hereditary Fructose Intolerance (IHF) should not be given this medicine. Sorbitol can cause gastrointestinal discomfort and have a mild laxative effect.

4.5 Interaction with other medicinal products and other forms of interaction

Cholestyramine decreases paracetamol absorption. Therefore, an interval of 1 hour between administration of these two medicines is required to achieve the maximum analgesic effect.

Metoclopramide and domperidone increase paracetamol absorption. However, these medicines may be used concomitantly with paracetamol.

Prolonged treatment with high doses of paracetamol may enhance the effects of warfarin.

The combination of paracetamol and anti-epileptics may cause or aggravate hepatic lesions.

The combination of paracetamol and rifampicin may cause or aggravate hepatic lesions.

In situations of chronic alcoholism, taking paracetamol may cause or aggravate hepatic lesions.

Paracetamol increases plasma chloramphenicol concentrations.

Do not administrate concomitantly with other medicines containing paracetamol, salicylates or other non-steroidal anti-inflammatory drugs.

The concomitant administration of paracetamol and AZT (zidovudine) may increase the incidence or aggravate neutropenia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Epidemiological and clinical evidence of paracetamol safety during pregnancy is available.

A large amount of data in pregnant women indicates the absence of malformations or fetal/neonatal toxicity. Epidemiological studies on the neurological development of children exposed to paracetamol in the womb have not shown conclusive results. When clinically necessary, paracetamol can be taken during pregnancy, however, it should be administered at the lowest effective dose over the shortest possible period and frequency.

Breastfeeding

Paracetamol is excreted in human milk, but not in clinically significant amounts.

Human studies have not identified any risk to breast-feeding or breastfed children.

4.7 Effects on ability to drive and use machines

Has no influence on the ability to drive and use machines.

4.8 Undesirable effects

At the normal therapeutic doses, paracetamol is usually well tolerated.
The effects listed below are classified with the following frequency convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000); unknown (cannot be calculated from the available data).

Blood and lymphatic system disorders
Very rare: thrombocytopenia, leukopenia, pancytopenia, neutropenia, bleeding, hemolytic anaemia, methaemoglobinaemia. These effects are related to prolonged administration of high doses.

Skin and subcutaneous tissue disorders
Rare: hypersensitivity reactions (urticaria, pruritus) and oedema. The rash is usually of the erythema or urticaria type, although in some cases fever and mucosal lesions may occur.
These allergic reactions occur more frequently in patients with a history of hypersensitivity to salicylates. Treatment should be discontinued if allergic reactions occur.

Gastrointestinal disorders
Common: nausea, vomiting
Uncommon: diarrhoea, abdominal pain

Renal and urinary disorders
Unknown: dysuria, oliguria, haemoglobinuria

Metabolism and nutrition disorders
Unknown: hypoglycaemia

Hepatobiliary disorders
Unknown: jaundice, hepatic insufficiency.

General disorders and administration site conditions
Unknown: fever

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. Healthcare professionals are asked to report any suspected adverse reactions via INFARMED, I.P.:

INFARMED, I.P.
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisboa,
Tel: +351 21 798 73 73
Linha do Medicamento: 800222444 (gratuita)
Fax: +351 21 798 73 97
Sítio da internet: http://extranet.infarmed.pt/page.seram.frontoffice.seramhomepage
E-mail: farmacovigilancia@infarmed.pt

4.9 Overdose

Massive overdose of paracetamol can cause liver toxicity in some patients. In adults and adolescents hepatic toxicity has rarely been reported after ingestion of doses below 10 g. Deaths are rare (less than 3-4% of untreated cases) and have been little mentioned for overdoses of less than 15 g. In children, an acute overdose of less than 150 mg/kg was not associated with hepatotoxicity.

Hepatic lesions are likely to occur in adult patients taking paracetamol doses equal or higher than 10g. It is considered that excessive amounts of toxic metabolites (adequately metabolized when the recommended paracetamol doses are taken) bind irreversibly to hepatic tissues.

The symptoms of paracetamol overdose in the first 24 hours are: pallor, nausea, vomiting, anorexia and abdominal pain.

Hepatic lesions may become apparent 12 to 48 hours after ingestion of a toxic dose. Glucose metabolism abnormalities and metabolic acidosis may also occur.

Acute renal insufficiency with acute tubular necrosis may develop, even in the absence of severe hepatic lesions.

The occurrence of cardiac arrhythmias has been reported.

Treatment:

Adequate control of paracetamol overdose requires immediate treatment. Despite the absence of early symptoms, patients should be taken to hospital emergency services, for immediate treatment.

In case of acute intoxication, gastric emptying should be performed, by induction or aspiration. Forced alkaline diuresis may be required following correction of acidaemia through sodium bicarbonate infusion. Cardiac or renal insufficiency may require haemodialysis or peritoneal dialysis.

Patients ingesting a sufficient number of tablets (35 or more) within a 24-hour period should be treated for paracetamol poisoning.

Vigorous support treatment is required in case of severe intoxication. Basic measures may include blood and dextrose infusion. Gastric emptying should be considered, through aspiration or gastric lavage; administration of vegetable charcoal should be considered as an early treatment.
Acetylcysteine should be administered as an antidote, through intravenous infusion, at an initial dose of 150 mg/kg of body weight, for 15 minutes, followed by 50 mg/kg, for 4 hours, and 100 mg/kg, for the following 16 hours.

Alternatively, 2.5 g of methionine may be administered orally, every 4 hours, up to a total of 4 doses.

There is a risk that sulfhydryl compounds used as antidotes may aggravate hepatic lesions, if administered 10 hours after the overdose. Haemoperfusion may be advantageous if an excessive amount of time has elapsed after the intoxication, in order to allow the use of acetylcysteine or methionine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 2.10 - Central Nervous System. Analgesics and antipyretics.
ATC code: N02B E01

Mechanism of action

The antipyretic action of paracetamol should have a central origin. Heat loss is increased by the dilation of cutaneous vessels and perspiration. Paracetamol has little effect on the normal body temperature but is effective in mild hyperthermia. It is assumed that its action should be on the thalamus and hypothalamus, at the level of nerve endings transporting painful stimuli. The temperature control centre is located in the hypothalamus, where the centre of analgesic action also resides.

The peripheral action of paracetamol may be more important than the central action, as is typical of salicylates, although the differences and similarities between the mechanisms of action underlying the pharmacological activities of *p*-aminophenol derivatives and salicylates are not precisely known.

5.2 Pharmacokinetic properties

Paracetamol is well absorbed by the gastrointestinal tract, and the bioavailability is greater than 95%. Paracetamol is easily absorbed into the bloodstream, reaching therapeutic levels within 20-30 minutes, and the maximum activity is reached within 60 minutes of oral ingestion. Plasma elimination half-life is 2 hours and 30 minutes. Biotransformation occurs in the liver, where paracetamol becomes more soluble through the formation of sulphate and glucuronide conjugates. The elimination takes place by the renal route.

5.3 Preclinical safety data

In high concentrations, paracetamol is genotoxic, both *in vivo* and *in vitro*. The genotoxic activity of paracetamol depends on several mechanisms; however, non-toxic or therapeutic doses do not reach the required threshold for such mechanisms to be triggered.

Some evidence is found of the carcinogenic potential of paracetamol in mice and rats, at hepatotoxic doses (increased incidence of liver and bladder tumours). Long-term studies on food have shown that paracetamol is not carcinogenic in non-hepatotoxic doses, up to 300 mg/kg/day for rats and 1g/kg/day for mice. Given the current knowledge on hepatotoxicity, metabolism and threshold levels for the mechanisms associated with paracetamol genotoxicity, animal studies do not suggest the existence of a carcinogenic potential for paracetamol in humans, at non-hepatotoxic doses.

Pre-clinical data from conventional studies using currently accepted standards for reproductive and developmental toxicity are not available.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

- Macrogol 400
- Sorbitol 70% solution
- Propylene glycol (E1520)
- Methyl para-hydroxybenzoate (E218)

- Propyl para-hydroxybenzoate (E216)
- Sodium saccharin
- Apricot essence
- Nougat aroma
- Currant syrup concentrate (includes sucrose, red dye (E122) and sodium benzoate (E211))
- Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

100 ml type III amber glass bottles.

The packaging includes a measuring spoon in plastic material, with measurement of 5 ml or 2.5 ml.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

MEDINFAR CONSUMER HEALTH – PRODUTOS FARMACÊUTICOS, LDA.
Rua Henrique Paiva Couceiro, Nº 27
Venda Nova, 2700-451 Amadora
Portugal

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF MARKETING AUTHORISATION

10. DATE OF REVISION OF THE TEXT