

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINE

TIPTIPOT NOVIMOL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PARACETAMOL 100 MG/ML SUSPENSION

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Pink to red suspension with white particles and a strawberry odour.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Analgesic and antipyretic.

4.2 DOSE AND METHOD OF ADMINISTRATION

The generally accepted dosage is:

The dosage according to the child's weight is calculated as 15 mg/kg of the child's weight, per dose. In other words, 0.15 ml for every kg of the child's body weight.

Only if the child's weight is not known - the dosage will be determined according to age, as shown in the age table indicating dosage according to the child's age only.

Maximum number of doses per 24 hours	Dose in ml	Child's age
Up to 5 times	0.40	0-3 months
Up to 5 times	0.80	4-11 months
Up to 5 times	1.20	1-2 years
Up to 5 times	1.60	2-3 years
Up to 5 times	2.40	4-5 years

Doses should be taken/administered in intervals of at least 4 hours, as necessary, up to 5 doses in 24 hours.

Method of use: Shake well before use

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or any of its excipients listed in section 6.1.
- Patients suffering from severe haemolytic anaemia
- Severe hepatocellular insufficiency

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In rare cases of allergic reactions, administration should be discontinued and appropriate treatment should be instituted.

Use with caution in cases of chronic alcoholism, excessive alcohol intake (3 or more alcoholic drinks per day), anorexia, bulimia or cachexia, chronic malnutrition (low hepatic glutathione reserves), dehydration, hypovolaemia.

Paracetamol should be administered with caution to patients with mild to moderate hepatocellular insufficiency (including Gilbert's syndrome), severe hepatic impairment (Child-Pugh >9), acute hepatitis, under concomitant treatment with medicinal products that alter liver function, glucose-6-phosphate dehydrogenase deficiency, haemolytic anaemia.

High or prolonged doses of the product may lead to kidney and blood alterations, some of which severe; therefore, the administration in subjects with renal impairment should only be carried out if actually necessary and under direct medical supervision.

In the case of prolonged use, it is advisable to monitor hepatic and renal function and blood crisis.

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

During treatment with paracetamol, before taking any other medicinal product, check that it does not contain the same active substance, as when taken at high doses, paracetamol can result in severe adverse reactions.

Instruct the patient to contact the doctor before combining any other medicinal product (see section 4.5).

Important information on some excipients

TIPTIPOT NOVIMOL contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/ be given this medicine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The oral absorption of paracetamol depends on the rate of gastric emptying. Therefore, concomitant administration of medicinal products that slow (e.g. anticholinergics, opioids) or increase (e.g. prokinetics) the rate of gastric emptying may result in a decrease or increase in the bioavailability of the product, respectively.

Concomitant administration of cholestyramine reduces the absorption of paracetamol. The simultaneous intake of paracetamol and chloramphenicol can induce an increase in the half-life of chloramphenicol, with the risk of elevating its toxicity.

The concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants can induce slight variations in the INR values. In these cases, more frequent monitoring of INR values must be conducted during concomitant use and after its discontinuation.

Use with extreme caution and under strict supervision during chronic treatment with medicinal products that can determine the induction of hepatic monooxygenases or in case of exposure to substances that can have this effect (for example rifampicin, cimetidine, antiepileptics such as glutethimide, phenobarbital, carbamazepine). The same is true in cases of alcoholism and in patients treated with zidovudine.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

The administration of paracetamol can interfere with the determination of uricaemia (by the phosphotungstic acid method) and with that of blood sugar (by the glucose-oxidase-peroxidase method).

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy: A large amount of data on pregnant women indicates neither malformative nor foetal / neonatal toxicity. Epidemiological studies on neurological development in children exposed to paracetamol in uterus show inconclusive results. If clinically necessary, paracetamol can be used during pregnancy; however, it should be used at the lowest effective dose for the shortest possible time and with the lowest possible frequency.

Breast-feeding: It is advisable to take / administer this medicinal product only in cases of real need and under the direct supervision of the doctor.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TIPTIPOT NOVIMOL has no influence on the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The undesirable effects of paracetamol organised according to MedDRA System Organ Classification are indicated below. Insufficient data are available to establish the frequency of the individual effects listed.

<i>Blood and lymphatic system disorders</i>	Thrombocytopenia, leukopenia, anaemia, agranulocytosis
<i>Immune system disorders</i>	Hypersensitivity reactions (urticaria, laryngeal oedema, angioedema, anaphylactic shock)
<i>Nervous system disorders</i>	Vertigo
<i>Gastrointestinal disorders</i>	Gastrointestinal reaction
<i>Hepatobiliary disorders</i>	Abnormal liver function, hepatitis
<i>Skin and subcutaneous tissue disorders</i>	Erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis, rash
<i>Renal and urinary disorders</i>	Acute renal impairment, interstitial nephritis, haematuria, anuria
<i>Metabolism and nutrition disorders</i>	High anion gap metabolic acidosis

Description of selected adverse reactions

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients. Very rare cases of severe skin reactions have been reported.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il/>

4.9 OVERDOSE

There is a risk of intoxication, especially in patients with hepatic disease, in chronic alcoholism, in patients suffering from chronic malnutrition, and in patients receiving enzyme inducers. In such cases, overdose can be fatal.

Symptoms

In case of accidental intake of very high doses of paracetamol, acute intoxication is manifested by anorexia, nausea and vomiting, followed by a profound deterioration of the general condition; these symptoms usually appear within the first 24 hours. In case of overdose, paracetamol can cause hepatic cytolysis which can evolve towards massive and irreversible necrosis, with consequent hepatocellular insufficiency, metabolic acidosis and encephalopathy, which can lead to coma and death.

Simultaneously, an increase in the levels of hepatic transaminases, lactate dehydrogenase, and bilirubinaemia, and a reduction in prothrombin levels are observed, which can occur in the 12-48 hours following ingestion.

Treatment

The measures to be taken consist of early gastric emptying and hospitalization for appropriate treatment, by administering, as early as possible, N-acetylcysteine as an antidote: the dosage is 150 mg/kg i.v. in glucose solution in 15 minutes, then 50 mg/kg in the following 4 hours and 100 mg/kg in the following 16 hours, for a total of 300 mg/kg in 20 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Analgesics and antipyretics, anilides, ATC code: N02BE01

The analgesic effect of paracetamol is attributable to a direct action at the level of the Central Nervous System, probably mediated by the opioid and serotonergic system, as well as by an action of inhibition of the synthesis of prostaglandins at a central level.

Furthermore, paracetamol has a marked antipyretic activity.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Absorption of paracetamol by mouth is complete and rapid. The maximum concentrations in plasma are reached between 20 and 60 minutes after ingestion.

Distribution

Paracetamol is evenly distributed in all tissues. Concentrations in blood, saliva and plasma are comparable. Binding to plasma proteins is weak.

Biotransformation

Paracetamol is mainly metabolized in the liver. There are two main metabolic pathways: conjugation with glucuronic acid and sulfo-conjugation. The latter pathway is rapidly saturable at doses higher than therapeutic doses. A minor pathway, catalysed by cytochrome P450 (particularly CYP2E1), leads to the formation of a reactive intermediate, N-acetyl-p-benzoquinoneimine, which, under normal conditions of use, is rapidly detoxified from glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. Conversely, during severe intoxication, the amount of this toxic metabolite is increased.

Elimination

It is essentially urinary. 90% of the ingested dose is eliminated by the kidneys in 24 hours, mainly as glucuronide (60 to 80%) and as sulfur conjugates (20 to 30%). Less than 5% is eliminated unchanged. The elimination half-life is about 2 hours.

Renal impairment

In case of severe renal impairment (creatinine clearance less than 10 ml/min), the elimination of paracetamol and its metabolites is delayed.

5.3 PRECLINICAL SAFETY DATA

Acute and chronic toxicity studies showed no adverse effects. The oral LD50 for paracetamol ranges from 850 to over 3,000 mg/kg depending on the animal species used.

Conventional studies using currently accepted standards for assessing toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sorbitol Solution 70%, Glycerol, Xanthan Gum, Sucralose, Strawberry Cream Flavour, Sodium Benzoate, Citric acid, FD@ C Red No. 40, Purified Water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Amber glass bottle with childproof cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Not applicable

7 LICENCE HOLDER AND MANUFACTURER

CTS CHEMICAL INDUSTRIES LTD

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