SUMMARY OF PRODUCT CHARACTERISTICS

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1 NAME OF THE MEDICINAL PRODUCT

Tipol Junior 250mg granules in sachets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet contains 250 mg paracetamol.

Excipient(s):
Contains sorbitol (E420) 600 mg/sachet.
Contains sucrose 0.1 mg/sachet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules in sachets

White or almost white granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tipol Junior 250 mg is used for symptomatic treatment of mild to moderate pain and fever.

4.2 Posology and method of administration

Doses depend on body weight and age; a single dose ranges from 10 to 15 mg/kg body weight. The total daily dose ranges from 60-75 mg/kg.

The specific dose interval depends on the symptoms and the maximum daily dose. It should, however, not fall below 4 hours.

Don`t use Tipol Junior 250 mg longer than three days without medical advice.

Body weight (age)	single dose	max. daily dose
17 kg -25 kg (4 – 8 years)	250 mg Paracetamol (1 sachet)	1000 mg Paracetamol (4 sachets)

The sachets are not recommended in children younger than 4 years; children aged 4 – 8 years may be given 250 mg every 4 – 6 hours up to a maximum of 4 doses in 24 hours. Children aged 8 - 12 years may be given 500 mg every 4 - 6 hours up to a maximum of 1500 mg in 24 hours.

Method of administration

For oral use only. The granules should be taken directly into the mouth onto the tongue and should be swallowed without water.

Do not take Tipol Junior 250 mg at a fed state.

Special groups of patients

Impaired liver or kidney function

In patients with impaired hepatic or renal function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

Patients with impaired renal function
In patients with severe renal insufficiency (creatinine clearance < 10 ml/min), a dosing interval of at least 8 hours must be maintained.

Chronic alcoholism
Chronic alcohol consumption may lower the paracetamol toxicity threshold. In these patients, the length of time between two doses should be a minimum of 8 hours. 2 g paracetamol per day should not be exceeded.

Elderly patients
Dose adjustment is not required in the elderly.

For all indications:
Adults, the elderly and children aged over 12 years: The usual dose is 500 – 1000mg every 4 to 6 hours up to a maximum of 3g daily.
The dose should not be repeated more frequently than every four hours.

Renal Insufficiency
In case of renal insufficiency the dose should be reduced:

Glomerular filtration	Dose
10 – 50 ml/min	500 mg every 6 hours
< 10 ml/min	500 mg every 8 hours

The daily effective dose must be considered, without exceeding 60 mg/kg/day (without exceeding 3 g/day) in the following situations:
Adults weighing less than 50 kg,
Hepatocellular insufficiency (mild to moderate)
Chronic alcoholism
Dehydration
Chronic malnutrition
Impaired liver or kidney function
In patients with impaired hepatic or renal function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

4.3 Contraindications

Hypersensitivity to paracetamol or to any of the excipients.

Patients with severe hepatic dysfunction (Child-Pugh > 9).

4.4 Special warnings and precautions for use

In order to avoid the risk of overdose, it should be ensured that any concurrent medicinal product does not contain paracetamol.

Paracetamol should be administered only with particular caution under the following circumstances:

- hepatocellular insufficiency (Child-Pugh < 9)
- chronic alcohol abuse
- severe renal insufficiency (creatinine clearance < 10 ml/min [see section 4.2])
- Gilbert's syndrome (familial non-haemolytic jaundice)
- acute hepatitis
- concomitant treatment with medicinal products affecting hepatic functions
- glucose-6-phosphatedehydrogenase deficiency

- haemolytic anaemia

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

Following long-term, high-dose, incorrect use of analgesics, headaches may occur which may not be treated with higher doses of the medicinal product.

In general, habitual intake of analgesics, particularly a combination of several analgesic substances, can lead to permanent renal damage with the risk of renal failure (analgesic nephropathy).

Prolonged or frequent use is discouraged. Patients should be advised not to take other paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In children treated with 60mg/kg daily of paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Abrupt discontinuation following long-term, high-dose, incorrect use of analgesics may lead to headaches, fatigue, muscle pain, nervousness and autonomic symptoms. These withdrawal symptoms resolve within a few days. Until this time, further intake of analgesics should be avoided and not restarted without medical advice.

Caution should be exercised when paracetamol is used in combination with CYP3A4 inducers or use of substances that induce liver enzymes such as rifampicin, cimetidine, antiepileptics such as glutethimide, phenobarbital and carbamazepine.

Caution is advised in the administration of paracetamol to patients with severe renal insufficiency (creatinine clearance ≤ 30mL/min (see section 4.2)) or hepatocellular insufficiency (mild to moderate).

Alcohol should not be used during the treatment with paracetamol.

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. In patients with alcohol abuse the dose has to be reduced (see section 4.2). The total daily dose should not exceed 2 grams in such case.

In the case of high fever, or signs of secondary infection or persistence of symptoms beyond 3 days, a re-evaluation of treatment should be made.

Doses higher than recommended entail risk for very serious liver damage. Treatment with antidote should be given as soon as possible (see section 4.9).

Paracetamol should be used with caution in cases of dehydration and chronic malnutrition.

This medicinal product contains sorbitol and sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Intake of probenecid inhibits the binding of paracetamol to glucuronic acid, thus leading to a reduction in paracetamol clearance by a factor of approximately 2. In patients concurrently taking probenecid, the paracetamol dose should be reduced.

The metabolism of paracetamol is increased in patients taking enzyme-inducing medicinal products such as rifampicin and some antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). Isolated reports describe unexpected hepatotoxicity in patients taking enzyme-inducing medicinal products.

Concurrent administration of paracetamol and AZT (zidovudine) enhances the tendency to neutropenia. This medicinal product should therefore be co-administered with AZT only on medical advice.

Concurrent intake of medicinal products that accelerate gastric emptying, such as metoclopramide or domperidone, accelerate the absorption and onset of effect of paracetamol.

Concurrent intake of medicinal products that slow gastric emptying can delay the absorption and onset of effect of

paracetamol.

Colestyramine reduces absorption of paracetamol, and should therefore not be administered within an hour following paracetamol administration.

Repeated paracetamol intake for longer than one week enhances the effect of anticoagulants, particularly warfarin. Therefore long-term administration of paracetamol in patients who are being treated with anticoagulants should only take place under medical supervision. Occasional paracetamol intake has no significant effects on bleeding tendency.

Effects on laboratory tests

Paracetamol can interfere with laboratory tests for serum uric acid using phosphotungstic acid and blood sugar tests using glucose-oxidase-peroxidase. Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronid acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.

Paracetamol increases the plasmatic levels of acetylsalicylic acid and chloramphenicol.

4.6 Fertility, pregnancy and lactation

Pregnancy
Epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the fetus / newborn infant. Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk. Reproductive studies with the oral route did not show any malformation or foetotoxic effects.

Consequently under normal conditions of use, paracetamol can be use throughout the duration of pregnancy, after a benefit-risk assessment.

During pregnancy, paracetamol should not be taken for longs periods, at high doses or in combination with other medicinal products, as safety of use in such cases is not established.

Lactation
After oral use, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Therapeutic doses of this medicinal product may be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Paracetamol has no influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

<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)>

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders

Rare: anaemia, non-haemolytic anaemia; bone marrow depression, thrombocytopenia

Cardiac disorders:
Vascular disorders:

Rare: Oedema.

Gastrointestinal disorders

Rare: acute and chronic pancreatitis

Haemorrhage, abdominal pain, diarrhoea, nausea, vomiting, hepatic failure, hepatic necrosis, jaundice.

Skin and subcutaneous tissue disorders

Rare: pruritus, rash, sweating, purpura, angioedema, urticarial

Very rare cases of serious skin reactions have been reported.

Renal and urinary disorders

Rare: nephropathies and tubular disorders

Paracetamol has been widely used and reports of adverse reactions are rare, and are generally associated with overdose.

Nephrotoxic effects are uncommon and have not been reported in association with therapeutic doses, except after prolonged administration.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.
Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition. Overdosing may be fatal in these cases.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, and abdominal pain.

Overdose of paracetamol in a single administration in adults or in children causes liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk Factors include:

If the patient;

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

Or

b. Regularly consumes ethanol in excess of recommended amounts

Or

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

Emergency Procedure:

Immediate transfer to hospital

Blood sampling to determine initial paracetamol plasma concentration

Gastric lavage

IV (or oral if possible) administration of the antidote N-acetylcysteinea as soon as possible and before the 10th hour of the overdose

Symptomatic treatment should be implemented

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesics and antipyretics, anilides, ATC code: N02BE01

The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and, to a lesser extent, through a peripheral action by blocking pain impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat regulating centre to produce peripheral vaso-dilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

5.2 Pharmacokinetic properties

Absorption

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low. Time to peak concentration, 0.5 - 2 hours; peak plasma concentrations, 5 - 20 microgram (μg)/ml (with doses up to 50mg); time to peak effect, 1- 3 hours; duration of action, 3- 4 hours.

Metabolism

Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cystein and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination

Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form. Elimination half life is about 2 hours.

Physiopathological variations

Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly Subjects. The capacity for conjugation is not modified.

5.3 Preclinical safety data

In animal experiments regarding acute, subchronic and chronic toxicity of paracetamol in rats and mice, gastro-

intestinal lesions, blood count changes, degeneration of liver and renal parenchyma, even necroses were observed. The causes for these changes are attributed to the mechanism of action on the one hand and on the other to the metabolism of paracetamol.

Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic, i.e. non-toxic doses.

Long-term studies in rats and mice yielded no evidence on relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol passes through the placenta.

Animal studies yield no evidence on reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E 420)
Talc
Basic butylated methacrylate copolymer
Magnesium oxide light
Carmellose sodium
Sucralose (E955)
Magnesium stearate
Hypromellose
Stearic acid
Sodium laurilsulfate
Titanium dioxide (E 171)
Simeticone
Strawberry flavour (contains Maltrodextrin, Gum arabic (E414), Natural & Nature Identical Flavouring substances, Propylenglycol (E1520), Triacetin (E1518), 3 Hydroxy-2-methyl-4H-pyran-4-on (E636))

Vanilla flavour (contains Maltrodextrin, Natural & Nature Identical Flavouring substances, Propylenglycol (E1520), Sucrose)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Aluminium sachets.

2, 4, 6, 10, 12, 20, 24 sachets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Carysfort Healthcare Limited
93 Carysfort Park
Blackrock
Co. Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1684/4/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2011

10 DATE OF REVISION OF THE TEXT

October 2016