Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tipol Max 1000mg granules in sachets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One sachet contains 1000 mg paracetamol.

Excipient(s):
Contains sorbitol (E420) 806 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 Max 1000mg is used for symptomatic treatment of mild to moderate pain and fever.

4.2 Posology and method of administration

Posology
Paracetamol doses depend on body weight and age. A single dose ranges from 10-15 mg/kg body weight, given every 4 to 6 hours as required, and a maximum of 4 doses can be given in 24 hours.

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 Max 1000 mg longer than three days without medical advice.

The following table gives a guide to the recommended doses and dosing frequencies for Tipol Max 1000 mg granules based on age and weight.

Age (Body Weight)	Recommended Dose	Frequency
Children over 16 years and adults (Body weight 50kg and over)	1000 mg paracetamol (1 sachet)	Every 4-6 hours when necessary to a maximum of 4 doses in 24 hours

For children under 16 years other formulations and dose strengths are available.

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.

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.

The elderly
Experience has indicated that normal adult dosage is usually appropriate. However in frail, immobile, elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate.

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

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

The maximum daily dose should not exceed 60mg/kg/day (up to a maximum of 2g per day for adults) in the following situations, unless directed by a physician:

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 the active substances or to any of the excipients listed in section 6.1.
Use in children under 16 years of age.

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
- dehydration
- chronic malnutrition
- Glutathione deficiency
- weight less than 50kg
- elderly

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 is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

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. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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.

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

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

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feeding
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

Tipol Max 1000 mg has no or negligible 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 the national reporting system:
HPRA Pharmacovigilance
Website: www.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.

Biotransformation
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, catalysed 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

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

In animal experiments regarding acute, subchronic and chronic toxicity of paracetamol in rats and mice, gastrointestinal 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
N,2,3-Trimethyl-2-(propan-2-yl)butanamid
Cappuccino flavour (contains Maltrodextrin, Gum arabic (E414), Natural & Nature Identical Flavouring substances, Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Aluminium sachets.
2, 6, 10, 12 sachets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/333/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

June 2022