Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tipol 75 mg suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 75 mg of paracetamol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository.

White to ivory coloured suppository with an approximate length of 26 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief of mild to moderate pain and fever

To be administered to infants with a body weight of 3 kg or more.

4.2 Posology and method of administration

For rectal use only.

Doses depend on body weight and age; a single dose ranges from 10 to 15 mg/kg body weight to a maximum of 60 mg/kg for total daily dose.
The specific dose interval depends on the symptoms and the maximum daily dose. It should not fall below the interval stated under 'Interval between doses' (see dosing table).

The following doses are recommended:

Body Weight	Age	First Dose (Equivalent dose of paracetamol)	Interval between doses	Max. daily dose (Equivalent dose of paracetamol)
3-4 kg	<3 months	1 suppository (75 mg paracetamol)	8 to 12 hrs 1 suppository (75 mg paracetamol)	2 suppositories (150 mg paracetamol)
4-5 kg	<3 months	1 suppository (75 mg paracetamol)	6 to 8 hrs 1 suppository (75 mg paracetamol)	3 suppositories (225 mg paracetamol)
4 kg	>3 months	1 suppository (75 mg paracetamol)	6 to 8 hrs 1 suppository (75 mg paracetamol)	3 suppositories (225 mg paracetamol)
5-6 kg	>3 months	1 suppository (75 mg paracetamol)	6 hrs 1 suppository (75 mg paracetamol)	4 suppositories (300 mg paracetamol)

Infants up to 3 months of age, should only be treated with Tipol 75mg suppositories under the supervision of a physician.

Special patient groups

Tipol 75 mg suppository is not suitable for children less than a body weight of 3 kg, because of the dose of paracetamol.

Hepatic insufficiency and mild renal insufficiency
With patients suffering from liver or kidney disorders or Gilbert's syndrome, the dose must be reduced or the interval between doses must be extended.

Severe renal insufficiency
Severe renal insufficiency (creatinine clearance < 10 ml/min) requires dose intervals of at least 8 hours.

Patient groups at increased risk of toxic liver effects

Elderly patients, infants, patients with chronic nutritional disorders,patients who are underweight, patients with liver or renal disease, patients taking excess alcohol or patients using medicines which are enzyme inducers are more likely to develop liver toxicity from paracetamol use. Even relatively small overdoses of paracetamol in these patients can cause serious liver toxicity which can be fatal (see sections 4.4 and 4.9).

Method of administration

The suppositories are for rectal use and should be put deeply into the rectum after bowel movement. The suppositories could be warmed up in the hands or dipped for a short time into warm water to improve the sliding properties.

4.3 Contraindications

Tipol must not be used by patients with hypersensitivity to the active substance paracetamol or to any other of the excipients.

Severe hepatocellular insufficiency (Child- Pugh ≥ 9) .

4.4 Special warnings and precautions for use

To avoid the risk of overdose, it must be ensured that any concurrent medication does not contain paracetamol.

The medicinal product should only be used with special caution and under medical supervision in patients with

- liver function disorders (e.g. caused by hepatitis) because of the potential of increased risk of hepatotoxicity,
- chronic nutritional disorders or who are underweight
- severe renal impairment,
- Gilbert's syndrome.

In cases of high fever, signs of a secondary infection, or persistence of symptoms, further medical advice should be sought.

If analgesics are taken for extended periods of time or if these drugs are not used properly, they may cause headache which should not be treated with increased doses.

In general, the habitual use of analgesics, in particular those containing more than one active ingredient, may lead to permanent damage to the kidney, which might result in renal failure (analgesic nephropathy).

Paracetamol preparations should generally be taken for a few days only, and never in higher (than recommended) doses.

Immediate medical advice should be sought in the event of overdosage, because of the risk of irreversible liver damage.

This product should be used only when clearly necessary.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased bleeding; occasional doses have no significant effect.

Ingestion of probenecid inhibits the linkage of paracetamol to glucuronic acid, reducing paracetamol clearance by a factor of about 2. The dose of paracetamol should therefore be reduced if probenecid is given concurrently.

When administered concomitantly with medicinal products that cause an induction of the cytochrome P 450 enzyme system in the liver, such as certain hypnotics/sedatives and antiepileptics (phenobarbital, phenytoin, carbamazepine) and rifampicin, a potentially toxic metabolite is formed and liver impairment may occur with otherwise harmless doses of the active substance paracetamol (see section 4.9).

When paracetamol and chloramphenicol are taken at the same time, the excretion of chloramphenicol can be significantly delayed with the risk of severe toxicity.

Cholestyramine reduces the absorption of paracetamol. The rate of absorption of paracetamol may be increased by metoclopramide or domperidone.

Patients concomitantly receiving AZT (zidovudine) are more susceptible to develop a decrease in the number of white blood cells (neutropenia). That is why these active substances should be used in combination with paracetamol only on medical advice.

Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

The use of drugs that induce hepatic micosomal 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.

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).

Effect on laboratory tests:

Uric acid tests using phosphotungstic acid and the determination of blood glucose with glucose oxidase peroxidase may be influenced by paracetamol.

4.6 Fertility, pregnancy and lactation

Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, during pregnancy, paracetamol should not be taken for longer periods, at high doses or in combination with other medicinal products, as safety of use in such cases is not established.

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 used throughout the duration of pregnancy, after a benefit-risk assessment.

After oral administration paracetamol is excreted into breast milk in small quantities. No undesirable effects for nursing infants have been reported. Therapeutic doses of paracetamol may be used during breast-feeding

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The assessment of side effects is based on the following frequencies:

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 (frequencies cannot be estimated from the available data)

Hepatobiliary disorders
Rare: Increase in liver transaminase

Blood and lymphatic system disorders
Very rare: Changes in blood count like thrombocytopenia, agranulocytosis

Immune system disorders
Very rare: bronchospasm (analgesic asthma) in predisposed persons, hypersensitivity reactions from common skin rash to urticaria and anaphylactic shock.

Skin and subcutaneous tissue disorders
Very rare cases of serious 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms

Elderly people, infants, persons with liver disease, chronic alcohol abuse, chronic nutritional disorders, patients who are underweight and those concomitantly receiving other active substances which cause enzyme induction, are more at risk of intoxication. In such cases, overdosing may be fatal.

In general the symptoms occur within 24 hours: nausea, vomiting, anorexia, pallor and abdominal pain. Although discomfort may be relieved, mild abdominal pain indicative of hepatic damage will persist.

Overdosing of paracetamol as a single dose in adults or children can cause hepatonecrosis, which may lead to total irreversible hepatonecrosis and, subsequently, to hepatocellular insufficiency, metabolic acidosis and encephalopathy.

These conditions may result in coma and produce death. At the same time, increased concentrations of liver transaminases (AST, ALT), lactate dehydrogenase and bililrubin in combination with a prolonged prothrombin time were observed. These abnormalities may occur between 12 and 48 hours after administration of the drug. The clinical symptoms of hepatic damage are usually noted after two days and are most pronounced after 4 to 6 days.

Acute renal failure and acute tubular necrosis may occur even in the absence of severe hepatic damage. Myocardial abnormalities and pancreatitis are among other symptoms that are unrelated to hepatic damage and have been observed after overdosing with paracetamol.

Treatment of intoxication

If poisoning with paracetamol is suspected, the intravenous injection of SH group donators such as N-acetylcysteine in the first ten hours may be helpful. N-acetylcysteine may provide some protection even after 10 to 48 hours. Long-term administration is advisable in such cases. Paracetamol concentrations in plasma can be lowered by means of dialysis. The plasma paracetamol levels should be determined.

Other treatments of paracetamol poisoning are dependent upon the extent, stage and the clinical symptoms of the intoxication, in accordance with the methods used in intensive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, anilides
ATC-Code: N02BEO1

Paracetamol has an analgesic, antipyretic and very weak anti-inflammatory effect. The mechanism of action has not been fully explained. There is evidence of distinct inhibition of cerebral prostaglandin synthesis, whereas peripheral prostaglandin synthesis is only slightly inhibited. Paracetamol further inhibits the effect of endogenous pyrogens on the hypothalamic thermoregulation centre.

5.2 Pharmacokinetic properties

When administered rectally, paracetamol is absorbed up to 100 %; maximum plasma concentrations are attained with Tipol 75 mg suppositories after 1 -2 hours. Plasma protein binding is slight (up to 10 %), but may rise in the event of an overdose. Paracetamol is metabolised in the liver by conjugation to glucuronide or sulphate.

A small part (in therapeutic doses approximately 3 -10 %) is metabolised through the cytochrome P450 system and the reactive intermediate formed is bound primarily to glutathione and excreted as cystein or mercapturic acid conjugates through the kidneys. 2 -3 % of the therapeutic dose is excreted unchanged, approximately 80 -95 % is excreted as glucuronide or sulphate and a small amount as cystein or mercapturic acid conjugates. On average the elimination half-life is 2.5 to 5.0 hours. Complete excretion occurs within 24 hours as a rule.

The half life is longer in patients with liver and kidney function disorders, after an overdose and with new-born infants. The maximum effect and average period of action (4 -6 hours) correlate somewhat with the plasma concentration.

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, 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 (see above) on the one hand and on the other to the metabolism of paracetamol. The metabolites presumed to yield the toxic effects and the corresponding changes in organs have also been found in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. In case of subtoxic doses, signs of intoxication can occur after a 3-week intake. Therefore, paracetamol should not be taken over a longer period of time and not at higher doses.
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 the placenta.
Animal studies and experience in humans to date yield no evidence on reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Aluminium/polyethylene strips
Packs containing 10 suppositories
Hospital pack containing 100 (10 x 10) suppositories
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
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Clonmel, Co. Tipperary
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8 MARKETING AUTHORISATION NUMBER

PA0126/331/001

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Date of last renewal: 5th September 2018

10 DATE OF REVISION OF THE TEXT

August 2022