

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tipol 500 mg suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 500 mg of paracetamol.

Excipients(s) with known effect

Contains soya lecithin (13 mg).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository.

White to ivory coloured, odourless, torpedo-shaped suppository with an approximate length of 26 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderate pain and/or fever.

4.2 Posology and method of administration

Details on the posology are available in the following table. The dose of paracetamol depends on the patient's age and body weight. The single dose is usually between 10 - 15 mg/kg body weight, to a maximum up to 60 mg/kg body weight for a total daily dose.

The interval between doses depends on the symptomatology and the maximum daily dose. It should be at least six hours.

If symptoms are persisting for more than three days medical attention must be received.

Body weight (Age)	Single dose (equivalent dose of paracetamol)	Maximum daily dose (24 hours) (equivalent dose of paracetamol)
26 kg - 32 kg (8 – 11 years)	1 suppository (equivalent to 500 mg of paracetamol)	3 suppositories (equivalent to 1500 mg of paracetamol)
33 kg - 43 kg (11 – 12 years)	1 suppository (equivalent to 500 mg of paracetamol)	4 suppositories (equivalent to 2000 mg of paracetamol)
more than 43 kg (Children and youth from 12 years and adults)	1 or 2 suppositories (equivalent to 500 or 1000 mg of paracetamol)	8 suppositories (equivalent to 4000 mg of paracetamol)

The maximum daily dose (24 hours) must not be exceeded

Method of administration

Tipol suppositories should be put deeply into the rectum after bowel movement. They may be warmed up in the hands or dipped for a short time into warm water to improve their sliding properties.

Special groups of patients

Hepatic insufficiency and mild renal insufficiency

For patients with impaired liver and kidney function or Gilbert's syndrome the dose should be reduced or the interval between doses should be increased.

Severe renal insufficiency

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

Elderly population

Dose adjustment is not required in the elderly.

Children and adolescents with low body weight

Tipol 500 mg suppositories are not suited for children younger than 8 years or less than a body weight of 26 kg, because of the dose of paracetamol. For this patient group other pharmaceutical forms and strengths may be more appropriate.

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).

4.3 Contraindications

Tipol must not be used by patients with known hypersensitivity to paracetamol, soya or to any other excipients. Tipol contains soya which may cause allergic reactions. Tipol should not be used by patients with known hypersensitivity to soya or peanut.

Severe hepatocellular insufficiency (Child-Pugh \geq 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.

In the presence of the following disorders, paracetamol should be used with great caution (longer interval between doses or reduced dosage) and under careful supervision by a physician:

- hepatocellular insufficiency (Child-Pugh $<$ 9),
- chronic nutritional disorder
- underweight
- chronic alcohol abuse,
- severe renal insufficiency (creatinine clearance below 10 ml/min (see section 4.2)),
- Gilbert's syndrome (Meulengracht's disease).

High fever, evidence of secondary infection and symptoms persisting for more than three days should receive medical attention.

Medicinal products containing paracetamol should only be taken for a few days and not in large doses without a physician's or a dentist's advice.

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).

Headache, fatigue, muscular pain, nervousness and vegetative symptoms may occur after abrupt discontinuation of prolonged, improper use of large amounts of analgesics, and will subside after a couple of days. No analgesics should be taken within this period. The use of such medicinal products should not be resumed without a physician's advice.

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.

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.

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 potential toxic metabolite is formed and liver impairment may occur under the application of otherwise harmless doses of the active substance paracetamol. (see section 4.9).

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.

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.

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 microsomal 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 due to pyroglutamic 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

Pregnancy

Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, during pregnancy, paracetamol should not be used for prolonged periods of time, in high doses or in combination with other drugs, since its safety has not been established under these conditions.

Prospective data regarding overdose during pregnancy have not indicated an increased risk of malformations. Reproduction studies of orally given paracetamol have not demonstrated malformations or foetotoxicity.

Under normal circumstances paracetamol may be used throughout pregnancy after balancing the therapeutic benefits against the possible risks.

During pregnancy, paracetamol should not be used for prolonged periods of time, in high doses or in combination with other drugs, since its safety has not been established under these conditions.

Lactation

Small amounts of orally given paracetamol are excreted in human milk. No deleterious effects or adverse reactions during lactation have been observed. Thus, paracetamol may be given to nursing women in therapeutic amounts.

4.7 Effects on ability to drive and use machines

No unfavourable effects are to be expected.

4.8 Undesirable effects

The evaluation of side effects is based on the following incidence rates:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1,000$ to $< 1/100$

Rare: $\geq 1/10,000$ to $< 1/1,000$

Very rare: $< 1/10,000$

Not known: Frequency cannot be estimated from the available data.

Hepatobiliary disorders

Rare: Increase in liver transaminases

Blood and lymphatic system disorders

Very rare: Changes of blood count such as thrombocytopenia and agranulocytosis

Immune system disorders

Very rare: In predisposed persons, bronchospasm (asthma induced by analgesics).

Very rare: Hypersensitivity reactions like erythema including urticaria and anaphylactic shock. Very rare: Soybean lecithin may induce allergic reactions.

Skin and subcutaneous tissue disorders

Very rare cases of serious skin reactions have been reported.

Metabolism and nutrition disorders

Not known: 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.

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, people 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 bilirubin 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 donors 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: analgesics and antipyretics, anilides

ATC code: N02BE01

The analgesic and antipyretic mode of action of paracetamol is not well elucidated. The drug is supposed to have a central and a peripheral action.

However, it is well established that paracetamol inhibits the central prostaglandin synthesis to a far greater extent than the peripheral one. Furthermore, it counteracts the effect of the endogenous pyrogens on the hypothalamic heat-regulating centre.

5.2 Pharmacokinetic properties

Absorption

Orally given paracetamol is absorbed rapidly and completely; maximum plasma levels are reached after 30 to 60 minutes after taking.

Rectally given paracetamol is absorbed between 68 to 88 per cent; maximum plasma levels are first reached after 3 to 4 hours.

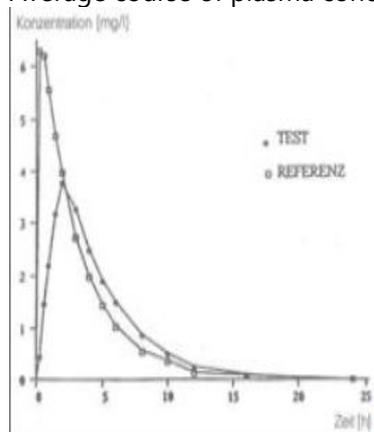
Bioavailability

A study performed in 1992 with 17 healthy volunteers showed the following results for a suppository with 500 mg as test preparation in comparison with a tablet 500 mg as reference standard:

	Test preparation	Reference standard
Peak plasma concentration C_{\max} [mg/ml]:	3.81 ± 1.42	7.31 ± 1.36
Time of peak plasma concentration t_{\max} [hr]:	2.0 ± 0.5	0.6 ± 0.3
Area under the plasma concentration-time curve AUC_{0-t} [mg/l x hr):	20.4 ± 7.9	22.5 ± 7.2

These values are expressed as a mean and a range.

Average course of plasma concentrations in comparison with a reference standard in a concentration-time diagram:



The relative bioavailability for Tipol 500 mg suppositories is 90.8 % in relation to the tablet formulation.

Distribution

Paracetamol is rapidly distributed throughout all tissues. The drug reaches comparable concentrations in blood, plasma and saliva. Binding to plasma proteins is of minor importance.

Metabolism

Paracetamol is metabolized chiefly in the liver via two major routes – by conjugation to glucuronic acid and to sulphuric acid. This latter route is quickly saturated after the administration of amounts exceeding the therapeutic dose. A small part of the drug is metabolized through the cytochrome P 450 (mainly CYP2E1), a catalyst leading to the formation of N-acetyl-p-benzoquinimine, a metabolite usually rapidly detoxicated by glutathione and bound to cysteine and mercapturic acid. A large amount of this toxic metabolite is found in the presence of massive paracetamol poisoning.

Elimination

Excretion takes place chiefly by way of the urine. Ninety per cent of the ingested amount is eliminated within 24 hours through the kidneys, mainly as glucuronides (60 to 80 per cent) and sulphate conjugates (20 to 30 per cent). Less than 5 per cent is excreted as such. The elimination half life is about two hours. Longer half lives were seen in patients with impaired liver and kidney function, after overdose and in the newborn. The maximum effect of the drug and its average duration of action (four to six hours) correlate more or less with its plasma concentration.

Renal insufficiency

The excretion of paracetamol and its metabolites is delayed in patients with severe renal failure (creatinine clearance below 10 ml/min).

Elderly patients

The capacity for conjugation remains unchanged.

5.3 Preclinical safety data

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

Animal studies of the acute, subchronic and chronic toxicity of paracetamol in rats and mice have revealed gastrointestinal lesions, changes to the blood count, degenerative changes to the hepatic and renal parenchyma and necroses. These changes are due to the mode of action and to the metabolism of paracetamol. The metabolites suspected of producing these toxic effects and the resulting organ changes, were encountered in humans as well. Very rare cases of reversible, chronic aggressive hepatitis were observed during the long-term administration (one year) of maximum therapeutic doses.

Symptoms of poisoning may occur after the ingestion of subtoxic doses over a period of three weeks.

Thus, paracetamol should not be given for prolonged periods or in large amounts.

Comprehensive studies failed to provide evidence that paracetamol carries a significant genotoxic risk, as long as the drug is given in therapeutic, i. e. non-toxic doses.

In long-term studies performed in rats and mice, no relevant tumorigenic effects were caused by paracetamol administered in doses that do not produce toxic effects on the liver.

Paracetamol crosses the placental barrier.

No evidence of foetal damage was noted in animal studies and in human therapy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat
Soya lecithin

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0126/331/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th September 2013

Date of last renewal: 5th September 2018

10 DATE OF REVISION OF THE TEXT

March 2025