

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

BRADOL 125 (Paediatric Paracetamol Oral Suspension BP 125mg/5ml)

2. Qualitative and quantitative composition

Each 5 ml contains:

Paracetamol BP 125 mg

3. Pharmaceutical form

Oral suspension

Pink coloured suspension.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of mild to moderate pain, including headache, migraine, neuralgia, toothache, sore throat, period pains, aches and pains.

For the reduction of fever and to be used as an adjunctive treatment to relieve symptoms of cold and flu.

4.2 Posology and method of administration

Posology

For oral administration only

It is important to **shake the bottle** for at least 10 seconds before use.

Child's Age	How Much	How often (in 24 hours)
6 – 8 years	One 5 mL spoonful (large end)	4 times
8 – 10 years	One 5.0 mL spoonful (large end) and one 2.5 mL spoonful (small end)	4 times
10 – 12 years	Two 5 mL spoonfuls (large end)	4 times
<ul style="list-style-type: none">• Do not give more than 4 doses in any 24 hour period• Leave at least 4 hours between doses• Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist		

- Do not give to children under the age of 6 years.

Children aged 12-16 years: Two - three 5mL spoonfuls (large end) up to 4 times a day

Adults and children over 16 years: Two - four 5mL spoonfuls (large end) up to 4 times a day.

4.3 Contraindications

Hypersensitivity to paracetamol and/or other constituents.

Patients with severe hepatic dysfunction.

4.4 Special warnings and precautions for use

Do not exceed the recommended dose. Taking more than the recommended dose (overdose) may cause liver damage. In case of overdose, get medical help straight away. Quick medical attention is critical for adults as well as children even if signs or symptoms are not noticed.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Chronic alcohol users should consult a doctor before use.

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.

Patients should be informed about the signs of serious skin reactions and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Taking this product with other paracetamol-containing medicines could lead to overdose and should therefore be avoided.

The label contains the following statement:

- Contains paracetamol.
- Do not give with any other paracetamol-containing products.
- For oral use only.
- Never give more medicine than shown in the table.
- Always use the spoon supplied with the pack. Do not overfill the spoon.

- Do not give more than 4 doses in any 24 hour period.
- Leave at least 4 hours between doses.
- Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist.
- As with all medicines, if your child is currently taking any medicine consult your doctor or pharmacist before taking this product.
- Do not store above 25°C. Protect from light. Store in the original package.
- Immediate medical advice should be sought in the event of an overdose, even if the child seems well, because of the risk of delayed serious liver damage.
- If symptoms persist consult your doctor.
- Keep out of the sight and reach of children.

The leaflet contains the following statements:

- Talk to a doctor at once if your child takes too much of this medicine, even if they seem well. This is because too much paracetamol can cause delayed, serious liver damage.
- Very rare cases of serious skin reactions have been reported. Symptoms may include:
 - Skin reddening
 - Blisters
 - Rash

If skin reactions occur or existing skin symptoms worsen, stop use and seek medical help right away.

Excipients in the formulation

This product contains:

- Small amounts of tartrazine and carmoisine in the flavouring. May cause allergic reactions.
- Methyl and propyl parahydroxybenzoates. These may cause allergic reactions (possibly delayed).
- Sucrose (2.5g per 5ml dose). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- Sorbitol. This medicine contains 682.0mg per 5ml dose. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. Sorbitol may cause gastrointestinal discomfort and have a mild laxative effect. It has a calorific value of 2.6kcal/g sorbitol.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

- Propylene Glycol. This medicine contains 163.9mg propylene glycol per 5ml dose. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

- This medicine contains less than 1 mmol sodium (23mg) per 5ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The hepatotoxicity of Paracetamol, particularly after overdose, may be increased by drugs which induce liver microsomal enzymes such as carbamazepine, barbiturates (e.g. phenobarbital), fosphenytoin, primidone, tricyclic antidepressants and alcohol.

Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. 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 speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

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

Antivirals: Regular use of Paracetamol possibly reduces metabolism of Zidovudine (increased risk of neutropenia).

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, especially in patients with risks factors (see section 4.4).

4.6 Fertility, Pregnancy and lactation

Fertility

There is no information relating to the effects of this medicine on fertility.

Pregnancy

A large amount of data on pregnant women indicate neither malformative, nor fetoneonatal 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.

When given to the mother in therapeutic doses (1 g single dose), paracetamol crosses the placenta into foetal circulation as early as 30 minutes after ingestion and is metabolised in the foetus by conjugation with sulfate and increasingly with glutathione.

Breast-feeding

Paracetamol is excreted in breast milk, but not in clinically significant quantities. Available published data do not contraindicate breast feeding.

4.7 Effects on ability to drive and use machines.

None

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and post marketing experience with paracetamol are listed below by System Organ Class (SOC)

The frequencies are defined according to the following convention:

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	(cannot be estimated from available data).

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available or 2) when incidence is unavailable, frequency category is listed as Not known.

System Organ Class (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Blood and lymphatic system disorders	Not known	Blood disorder (including thrombocytopenia and agranulocytosis) ¹
Immune System Disorders	Very rare Very rare	Anaphylactic reaction Hypersensitivity
Hepatobiliary disorders	Not known	Liver injury ²
Skin and Subcutaneous Tissue disorders	Very rare	Rash
	Not known	Fixed eruption
	Not known	Rash pruritic
	Not known	Urticaria
Renal and urinary disorders	Uncommon	Nephropathy toxic
	Not known	Renal papillary necrosis ³
Investigations	Not known	Transaminases increased ⁴

¹ Reported following paracetamol use, but not necessarily causally related to the drug

² Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year

³ Reported after prolonged administration

⁴ Low level transaminase elevations may occur in some patients taking therapeutic doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.

Very rare cases of serious skin reactions have been reported.

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of the disease improved after paracetamol withdrawal.

4.9 Overdose

Liver damage is possible in adults and adolescents (≥ 12 years of age) who have taken 7.5g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors

If the patient

a) Is on long term treatment with carbamazepine, phenobarbital, 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.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, hyperhidrosis, malaise, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. This may include hepatomegaly, liver tenderness, jaundice, acute hepatic failure and hepatic necrosis.

Abnormalities of glucose metabolism and metabolic acidosis may occur. Blood bilirubin, hepatic enzymes, INR, prothrombin time, blood phosphate and blood lactate may be increased.

In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria may develop even in the absence of severe liver damage.

Cardiac arrhythmias and pancreatitis have been reported.

Haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Haemolysis has been reported in patients with G6PD deficiency, with use of paracetamol in overdose.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of

overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required, the patient should be given intravenous N-acetylcysteine in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Analgesics and Antipyretics (Anilides)

ATC Code: N02 BE01.

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

Oral absorption is rapid and almost complete, it may be decreased if Paracetamol is taken following a high carbohydrate meal.

There is no significant protein binding with doses producing plasma concentrations below 60mcg (μg)/ml, but may reach moderate levels with high or toxic doses.

Approximately 90 - 95% of a dose is metabolised in the liver, primarily by conjugation with glucuronic acid, sulphuric acid and cysteine. An intermediate metabolite, which may accumulate in overdosage after primary metabolic pathways become saturated, is hepatotoxic and possibly nephrotoxic.

Half life is 1 to 4 hours; does not change with renal failure but may be prolonged in acute overdosage, in some forms of hepatic disease, in the elderly, and in the neonate; may be somewhat shortened in children.

Time to peak concentration, 0.5 - 2 hours; peak plasma concentrations, 5 - 20mcg (μg)/ml (with doses up to 650mg); time to peak effect, 1- 3 hours; duration of action, 3- 4 hours.

Elimination is by the renal route, as metabolites, primarily conjugates, 3% of a dose may be excreted unchanged.

Peak concentrations of 10 - 15mcg(μg)/ml have been measured in breast milk, 1 - 2 hours following maternal ingestion of a single 650mg dose. Half life in breast milk is 1.35 - 3.5 hours.

5.3 Preclinical safety data:

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

6. Pharmaceutical particulars

6.1 List of excipients

Menthol
Colloidal Anhydrous Silica
Liquid Essence Strawberry
Colour Erythrosine Supra ISI
Sodium Citrate
Sodium Benzoate
Sodium Methyl Hydroxybenzoate
Sodium Propyl Hydroxybenzoate
Sorbitol 70 % (non- crystallising)
Xanthan Gum (Transparent)
Polysorbate -80
Citric Acid
Sodium Saccharin
Glycerol Redistilled Anhydrous
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

60 ml Oral suspension filled in PET bottle and packed in unit carton with package insert.

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

07296/08622/NMR/2020

9. Date of first authorisation/renewal of the authorisation

Apr 13, 2022

10. Date of revision of the text

11.07.2023