SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Panadol 500 mg capsules, soft

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 500 mg paracetamol.

Excipients with known effect

Every capsule contains 108 mg of sorbitol liquid (partially dehydrated) and 20 mg of propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft.

White, oval (about 19 mm in length) soft gelatin capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicine is a mild analgesic and antipyretic, and is recommended for the treatment of most painful and febrile conditions, for example headache including migraine and tension headaches, toothache, rheumatic and muscle pains, lower back pain, dysmenorrhea, sore throat, and for relieving the fever, aches and pains of flu and colds. Also recommended for the symptomatic relief of pain due to non-serious arthritis.

4.2 Posology and method of administration

This medicine is suitable for adults and children aged 10 years and older.
Children should not be given this medicine, for more than 3 days without consulting a doctor.

Posology
For adults and children aged 16 years and older, the usual dosage is 1 to 2 capsules (500-1000 mg) at a time, up to four times daily as required, with a maximum of 8 capsules (4000 mg) every 24 hours.

Paediatric population
A suitable dosage form should be used. See the table below for doses for children.

Age (years)	Number of capsules at a time	Frequency of dosing	Maximum number of capsules per day	Maximum daily dosage (mg)
10-15	1	up to four times daily as required	4 whole capsules	2000
≥16	1-2	up to four times daily as required	8 whole capsules	4000

These doses should not be repeated more frequently than every four hours nor should more than four doses be given in any 24 hour period.

Instructions for use:

- The treatment should be kept as short as possible.
- The administration interval must be at least 4 hours.
- Do not exceed the recommended daily dose on account of the risk of severe hepatic damage (see section 4.4 and 4.9).
- Do not use in combination with other paracetamol-containing products.
- Depending on the recurrence of symptoms (fever and pain), repeated administration is allowed.
- If pain lasts for longer than 5 days or fever lasts for longer than 3 days or these symptoms become worse or if other symptoms occur, the treatment must be stopped, and a doctor must be consulted.

Method of administration:

Capsule
The capsules should be swallowed with enough water. The intake of paracetamol with food or drink doesn't influence the efficacy of the medicine.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

- The recommended dose should not be exceeded.
- Long-term or frequent use is not advised.
- Patients must be advised not to use any other paracetamol-containing products at the same time.
- In the case of a high fever, symptoms of secondary infection or the persistence of symptoms, it will be necessary to reconsider the treatment.
- The taking of several daily doses at once can cause severe damage to the liver. In such cases, a loss of consciousness will not occur. However, immediate medical help must be sought even if the patient feels well because of the risk of irreversible damage to the liver (see section 4.9). Long-term use can be harmful except under medical supervision.
- Caution is required when administering paracetamol to patients with moderate to severe renal insufficiency, mild to moderate hepatic insufficiency (incl. Gilbert's syndrome), severe hepatic insufficiency (Child-Pugh > 9), acute hepatitis, the concomitant administration of medicinal products which have an influence on hepatic function, glucose-6-phosphate dehydrogenase deficiency, haemolytic anaemia, alcohol abuse, dehydration and chronic malnutrition.
- The risk of an overdose is greater in patients with non-cirrhotic alcoholic liver conditions. Caution is required in the case of chronic alcoholism. The daily dose may not exceed 2 grams in this case. No alcohol may be used during treatment with paracetamol.
- Caution is required in the case of asthmatic patients who are sensitive to acetylsalicylic acid as mild bronchospasms have been reported as a cross-reaction after the use of paracetamol.
- For children a treatment of 60 mg/kg/day of paracetamol combined with another antipyretic is not allowed, unless due to a lack of efficacy.
- After the long-term use (> 3 months) of analgesics with intake every other day or more frequently, headache can occur or become worse. Headache which is caused by the excessive use of analgesics (drug-dependent headache) must not be treated by increasing the dose. In these cases, the use of analgesics must be stopped in consultation with a doctor.
- Patients should be advised to consult a doctor if they suffer from non-serious arthritis and need to take painkillers every day.
- Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol may increase the risk of metabolic acidosis (refer also to section 4.9). Use with caution in patients with glutathione depletion due to metabolic deficiencies.
- This medicine contains 20 mg propylene glycol in each soft capsule.
- This medicine contains 108 mg sorbitol liquid in each soft capsule. Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.
- 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 patients with malnutrition and 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 rate of absorption of paracetamol can be increased by metoclopramide or domperidone.
- Absorption can be reduced by cholestyramine. Therefore, ingestion of cholestyramine should not occur within one hour of the ingestion of paracetamol.
- The anticoagulatory effect of warfarin and other coumarins can increase during the long-term, regular use of paracetamol with an increase in the risk of bleeding as a result. There is no significant effect with the occasional taking of a dose.
- 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)

4.6 Fertility, Pregnancy and lactation

Pregnancy

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

Breastfeeding

Paracetamol is excreted into breast milk. No undesirable effects on nursing infants have been reported. Paracetamol 500 mg capsules, soft may be used in therapeutic dosages in breast-feeding women.

4.7 Effects on ability to drive and use machines

This medicine has no influence on the ability to drive and use machines.

4.8 Undesirable effects

At therapeutic doses few undesirable effects occur. Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system

class and frequency.

The frequency of undesirable effects is classified as follows: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000) and not known frequency (cannot be estimated from the available data).

System organ class	Undesirable effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis	Very rare
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes and angiodema. Very rare cases of serious skin reactions have been reported.	Very rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare
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.	Not known

*There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

Overdose

Liver damage is possible in adults who have taken 10g or more of paracetamol. 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:

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

Or

- Regularly consumes ethanol in excess of recommended amounts.

Or

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

Symptoms:

The first symptoms of paracetamol overdose are pallor, nausea, vomiting, anorexia and abdominal pain and these symptoms usually appear within 24 hours after intake. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. 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.

Immediate treatment:

Immediate hospitalization is essential for 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: Analgesics and antipyretics. Anilides, ATC code: N02BE01.

Paracetamol has both analgesic as well as antipyretic activity. However, it does not have anti-inflammatory activity. The mechanism of action of paracetamol has so far not been fully explained. The effect appears to be based on inhibition of the enzyme prostaglandin synthetase, but the lack of an anti-inflammatory effect cannot be explained by this. It is possible that the distribution of paracetamol over the body and hence the site of the inhibition of prostaglandin synthetase plays a role. Paracetamol has the advantage that number of side effects which are characteristic of NSAIDs are completely or largely absent in the case of paracetamol.

Paracetamol is, therefore, a good alternative to NSAIDs for combating pain and fever.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. The concentration in plasma reaches a peak in 30 to 60 minutes and the plasma half-life is 1 - 4 hours after therapeutic doses.

Distribution
Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; 20 to 30 % may be bound at the concentrations encountered during acute intoxication.

Biotransformation
Excretion of paracetamol is essentially through metabolization. Paracetamol is conjugated with glucuronic acid by uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1 (around 60 %), sulphate (around 35 %) by sulfotransferase (SULT) 1A1 and cysteine by N-acetylcysteine transferase (NAT) (around 3 %) in the liver of adults. With the help of cytochrome P-450 (CYP) 2E1 and 2D6, a small proportion of paracetamol (~5%) is converted in the body into a very reactive metabolite (N-acetyl-p-benzoquinonimine) which is normally quickly inactivated by conjugation with glutathione by Glutathione S-transferase (GST). Overdose can deplete glutathione stocks and thus result in acute hepatic damage.

Elimination
Following therapeutic doses 90 - 100% of the drug may be recovered in the urine within the first day. However, practically no paracetamol is excreted unchanged and the bulk is excreted after hepatic conjugation.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 400
Purified water
Propylene glycol
Silica, colloidal anhydrous

Capsule shell
Gelatin
Sorbitol, liquid, partially dehydrated
Purified water
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

White blister formed of PVDC/PVC-Alu/PET packed in a box.

Pack sizes of 8,10,12,16 capsules in blister packs.

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

Haleon UK Trading Limited.
The Heights,
Weybridge,
KT13 0NY,
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8 MARKETING AUTHORISATION NUMBER(S)

PL 44673/0233

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/06/2023

10 DATE OF REVISION OF THE TEXT

21/01/2025