Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Genmed 500 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of paracetamol.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, biconvex, round tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Posology:
For oral use only.
Doses depend on body weight and age; a single dose ranges from 10 to 15 mg/kg body weight (= b.w.) to a maximum of 60 mg/kg b.w. for total daily dose (also see section 4.4).

Adolescents 12 to 15 years of age (40 – 55 kg):
500 mg per intake, maximum 4-6 times per 24 hours, with an interval between administrations of minimum 4 hours.
The lower dosage frequency is intended for the adolescents at the lower limit of the age category.

Adults:
500 to 1000 mg per intake, maximum 3000 mg per 24 hours, with an interval between administrations of minimum 4 hours.

In cases of chronic alcoholism, the maximum dose should not exceed 2000 mg per 24 hours.
Paracetamol Genmed 500 mg tablets is not recommended in children below 12 years of age or who weigh less than 40 kg.

Method of administration:
The tablet should be swallowed with a large amount of water or, if desired, left to dissolve in plenty of water, which should be stirred well before drinking.

Instructions for use:
- The specific dose interval depends on the symptoms and the maximum daily dose. Depending on the reoccurrence of symptoms (fever and/or pain), repeated administration is allowed. It should, however, never fall below 4 hours.
- In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min.), the minimum interval between 2 administrations should be 8 hours.
- The daily effective dose must be considered, without exceeding 60 mg/kg/day (without exceeding 2 g/day) in the following situations:

- Adults and adolescents weighing less than 50 kg
- Hepatocellular insufficiency (mild to moderate)
- Chronic alcoholism
- Dehydration

If complaints persist for more than 3 days, get worse or other symptoms appear, the treatment should be stopped and medical advice should be sought.

4.3 Contraindications

Hypersensitivity to paracetamol or to any of the excipients.

4.4 Special warnings and precautions for use

The total dose of paracetamol should not exceed:
- 60 mg/kg/day for adolescents weighing less than 40 kg
- 3 g daily for adolescents and adults weighing more than 40 kg

The recommended dose should not be exceeded.
Prolonged or frequent use is discouraged.
Patients should be advised not to take other paracetamol-containing products concurrently.

Paracetamol should be used with caution in adults and adolescents weighing less than 50 kg.

Caution 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-chirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2 grams in such case.

Gilbert`s syndrome (Meulengracht`s disease)
Paracetamol is metabolized by enzymes which are deficient in some people with Gilbert's syndrome. Therefore, a subset of people with Gilbert's syndrome may have an increased risk of paracetamol toxicity.

In general, regular use of analgesics, especially combinations of various analgesic agents, has the potential to cause permanent renal damage including the risk of renal failure (analgesics nephropathy).

Abrupt discontinuation of long-term use of high-dosed analgesics, taken not as directed, may cause headache, tiredness, muscular pain, nervousness and vegetative symptoms. The withdrawal symptoms subside within a few days. In the meantime do not restart use of the analgesic and do not start a new therapy without medical advice.

In children treated with 60 mg/kg daily of paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

In cases of high fever, signs of a secondary infection, or persistence of the symptoms for more than three days, medical advice should be sought.

4.5 Interaction with other medicinal products and other forms of interactions

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged daily use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.

Use of substances that induce liver enzymes, such as barbiturates, can increase the hepatotoxicity of paracetamol overdose due to increased and more rapid formation of toxic metabolites.
Caution is advised during simultaneous administration of enzyme inducing agents (see section 4.9).

Probenecide blocks the binding of paracetamol to glucuronic acid reducing paracetamol clearance by a factor of about 2. If probenecide is taken concurrently the paracetamol dose should be reduced.

Salicylamide may prolong the elimination t1/2 of paracetamol.

Ethyl alcohol potentiates paracetamol toxicity, possibly by inducing hepatic production of paracetamol-derived hepatotoxic products.

Isoniazid reduces the paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver.

Paracetamol may decrease the bioavailability of lamotrigine, with possible reduction of its effect, due to a possible induction of its metabolism in the liver.

Interference with laboratory tests
Paracetamol may affect phosphotungstate uric acid tests and blood sugar tests by glucose-oxydase-peroxydase.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus/newborn infant. Reproductive studies 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.

Lactation:
Paracetamol is excreted in breast milk but not in a clinically significant amount. No negative effects on infants have been reported. Paracetamol may be used by breastfeeding women as long as the recommended dosage is not exceeded. In case of long term use caution should be exercised.

4.7 Effects on ability to drive and use machines

Paracetamol Genmed has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

At therapeutic doses few undesirable effects occur. However, in rare or very rare occasions the following undesirable effects have been reported:

Organ class	Rare ≥ 1 / 10,000 to < 1 / 1,000	Very rare < 1 / 10,000
Blood and lymphatic system disorders	- Agranulocytosis (after long-term use) - Thrombocytopenic purpura - Hemolytic anemia	
Renal and urinary disorders		Interstitial nephritis (after prolonged use of high doses)
General disorders and administration site conditions	- Allergic reactions such as exanthema, urticaria - fever	

Administration of 6 grams of paracetamol may already lead to hepatetic damage (in children: more than 140 mg/kg); higher doses cause irreversible hepatic necrosis.

4.9 Overdose

Paracetamol can result in poisoning, particularly in elderly subjects, young children, patients with liver diseases, in cases of chronic alcoholism, in patients suffering from chronic malnutrition and patients using liver enzyme inducing agents. Overdose may be fatal in these cases.

Liver damage is possible in adults who have taken 6 g or more of paracetamol, especially 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 symptoms of paracetamol overdosage in the first 24 hours are nausea, vomiting, anorexia, pallor and abdominal pain. 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.

Treatment:
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 local overdose treatment guidelines.
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 24 h from ingestion should be discussed with the National Poisons Information Service (NPIS) or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N02BE01
Pharmacotherapeutic category: Other analgesics and antipyretics, Anilides
Paracetamol is an effective antipyretic and analgesic agent. However, it has no antiinflammatory effect.

5.2 Pharmacokinetic properties

Absorption
After oral administration paracetamol is rapidly and almost completely absorbed. Peak plasma concentrations are reached after 30 minutes to 2 hours.

Distribution
The volume of distribution of paracetamol is approximately 1 L/kg bodyweight. At therapeutic doses protein binding is negligible.

Metabolism
In adults paracetamol is conjugated in the liver with glucuronic acid (~60%), sulphate (~35%) and cystein (~3%). In neonates and children <12 years sulphate conjugation is the main elimination route and glucuronidation is lower than in adults. Total elimination in children is comparable to that in adults, due to an increased capacity for sulphate conjugation.

Elimination
Paracetamol is excreted in urine, predominantly as the glucuronide and the sulphate conjugate, and approximately 5% unchanged. The elimination half life varies between 1 and 4 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.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to a prescriber, which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K-29/32 (E1201)
Microcrystalline cellulose (E460)
Maize starch
Stearic acid (E570)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Keep blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/Aluminium blisters in a cardboard box, containing 10, 12, 16, 20, 24, 30 or 50 tablets per box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Genmed B.V.
Rontgenlaan 37
2719 DX Zoetermeer
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1519/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 June 2010

10 DATE OF REVISION OF THE TEXT

September 2012