SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol Neogen 500 mg filmomhulde tabletten
Paracetamol Neogen 1000 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg: Each film-coated tablet contains 500 mg paracetamol
1000 mg: Each film-coated tablet contains 1000 mg paracetamol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

500 mg: White, film-coated, oval tablet, scored and marked "P 500" on one side.
1000 mg: White, film-coated, oval tablet that has a break line on one side and is plain on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

For the 500 mg strength
This product is indicated in adults and children weighing more than 30 kg (i.e. about 9 years).

For the 1000 mg strength
This product is indicated in adults and children weighing more than 55 kg (i.e. about 15 years).

4.2 Posology and method of administration

Posology

For the 500 mg strength:

Adults and children over 15 years (> 55 kg body weight)
1 to 2 tablets of 500 mg at a time, up to 6 tablets (3000 mg) per 24 hours. The dosing interval should be at least 4 hours.

Paediatric population

Children from 9 to 15 years

This pharmaceutical form is not considered suitable for children below the age of 6.

The posology depends on the child's bodyweight. The recommended dose is 60 mg/kg/day, not more than 3000 mg (3 g) per day:

- 30-40 kg (about 9-12 years): 1 tablet at a time (i.e. 500 mg), up to 3-4 times in 24 hours, with a dosing interval of 6-8 hours.
- 40-55 kg (about 12-15 years): 1 tablet at time (i.e. 500 mg), up to 4-6 times per 24 hours, with a dosing interval of 4-6 hours.

The lower frequency of administration is intended for children in the lower limit of the relevant weight group. Systematic administration, including during the night, helps to avoid pain and fever oscillations.

For the 1000 mg strength:

Adults and children above 15 years
½ to 1 tablet of 1000 mg at a time, 3 to 4 times a day, up to 3 tablets (3000 mg) per 24 hours.
The dosing interval should be at least 4 hours.
The 1000 mg strength is not considered suitable for children below the age of 15.

Warning: each tablet contains 1000 mg (1 g) of paracetamol. Do not take more than one tablet at a time.

Direction for use:
- Do not use in combination with other paracetamol-containing products.
- The indicated dose must not be exceeded due to risk of serious damage to the liver (see section 4.4 and 4.9).
- Depending on the onset of symptoms (fever and pain) repeated administration is allowed.
- If you do not feel better or if you feel worse after 3 days or if other symptoms occur, treatment should be discontinued and a physician should be consulted.
- The ingestion of paracetamol with food and drink does not affect the efficacy of the medicinal product.

Renal impairment
In case of renal insufficiency (renal failure), the dose should be reduced. For adults:

Glomerular filtration rate	Dose
10 – 50 ml/min	500 mg every 6 hours
< 10 ml/min	500 mg every 8 hours

Hepatic impairment
In patients with hepatic impairment or Gilberts syndrome, the dose must be reduced or the dosing interval prolonged.

The daily effective dose should not exceed 60 mg/kg/day (up to maximum 2000 mg/day) in the following situations:
- Adults weighing less than 50 kg
- Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial nonhaemolytic jaundice)
- Dehydration
- Chronic malnutrition
- Chronic alcoholism

Method of administration
The tablet should be swallowed with a large amount of water.

4.3 Contraindications

Hypersensitivity to paracetamol or to any of the excipients listed in section 6.1.

Use in children under 6 years of age.

4.4 Special warnings and precautions for use

Prolonged or frequent use is discouraged.

Due to the risk of overdose, caution should be exercised when using other medicinal products that also contain paracetamol.

Ingestion of doses higher than those recommended carries the risk of very serious liver damage. In such cases, immediate medical advice should be sought even if the patient feels well because of the risk of irreversible liver damage and treatment with an antidote should be given as soon as possible (see section. 4.9).

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

Benefits and risks must be weighed carefully with use in patients with hepatic and renal insufficiency (child-Pugh > 9), mild to moderate hepatic impairment (incl. Syndrome Gilbert), acute hepatitis, concomitant administration of drugs that affect the liver function, glucose -6-phosphatedehyrogenase deficiency or haemolytic anaemia.

If acute viral hepatitis is identified, treatment must be discontinued.

The hazards of overdose are greater in those with non-chirrhotic alcoholic liver disease.
Caution should be exercised in cases of chronic alcoholism. Alcohol must not be used during treatment period. The daily dose should not exceed 2000 mg in such case.

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

With long-term use (> 3 months) of any type of analgesic headache medication, the headaches may become worse and more frequent (mean-tested headache). If this condition develops or is suspected, the headache treatment should be discontinued in consultation with the doctor. Medication-overuse headache should be suspected in patients with frequent or daily headaches despite (or because of) the regular use of analgesics.

In patients with impaired nutritional status due to alcohol abuse, anorexia or poor nutrition, continuous use and maximum doses are not recommended due to the risk of toxic hepatic reactions.

Caution is advised in asthmatic patient sensitive to acetylsalicylic acid, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported.

In general, the habitual use of analgesics, especially the combination of different analgesic drug substances, can lead to lasting renal lesions with the risk of renal failure (analgesic nephropathy).

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.

Interference with serological testing
Paracetamol may affect phosphotungstate uric acid tests and blood sugar tests by glucoseoxydase-peroxydase.

4.5 Interaction with other medicinal products and other forms of interaction

Metoclopramide and domperidone may increase the rate of absorption of paracetamol (marginally clinically relevant).

Cholestyramine reduces the absorption of paracetamol. /.../ should be administered at least 1 hour before or 4 to 6 hours after cholestyramine.

Paracetamol is extensively metabolized in the liver and can therefore interact with medicinal products with the same metabolic pathway or induce/inhibit the same metabolic pathway.

Chronic use of alcohol or drugs with an enzyme-inducing effect like rifampicin, barbiturates, some anti-epileptic drugs Wort (e.g. phenytoin, carbamazepinem phenobarbital, pirimidone) and St. John's reduce the bioavailability of paracetamol through increased glucuronidation, increasing the risk of hepatotoxicity. Caution is therefore necessary with concomitant use of enzyme-inducing drugs.

When co-administered with probenecid, a dose reduction should be considered, as probenecid reduces paracetamol clearance by nearly half by inhibiting glucuronic acid conjugation. If probenecide is taken concurrently the paracetamol dose should be reduced.

Paracetamol can increase plasma concentration of chloramphenicol.

With chronic concomitant use of paracetamol and zidovudine, neutropenia often occurs and is probably due to the reduced metabolism of zidovudine.

Salicylamide may prolong the elimination t½ of paracetamol.

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.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged, regular daily intake of paracetamol. This leads to increased risk of bleeding; occasional intake had no significant effect.

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

Pregnancy
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal 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.

Breast-feeding
Paracetamol is excreted in breast milk but not in a clinically significant amount. No negative effects on infants have been reported. Paracetamol can be used during breast-feeding as long as the recommended dosage is not exceeded. In case of long term use caution should be exercised.

Fertility
No detrimental effects on fertility upon normal use of paracetamol are known.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Undesirable effects are generally rare. The most common undesirable effects are urticaria and increased liver transaminases, which are seen in 0.01% to 0.1% of treated patients.

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Rare	Agranulocytosis (long-term use), thrombocytopenia, thrombocytopenic purpura, leucopenia, haemolytic anaemia, Platelet disorders, stem cell disorders.
	Very rare	Pancytopenia.
Immune system disorders	Rare	Hypersensitivity (excluding angioedema).
	Very rare	Hypersensitivity (angioedema, ventilation difficult, hyperhidrosis, nausea, hypotension, shock, anaphylactic reaction), requiring discontinuation of treatment.
Metabolism and nutrition disorders	Very rare	Hypoglycaemia.
Psychiatric disorders	Rare	Depression NOS, confusion, hallucinations.
Nervous system disorders	Rare	Tremor NOS, headache NOS.
Eye disorders	Rare	Abnormal vision.
Cardiac disorders	Rare	Oedema.
Respiratory, thoracic and mediastinal disorders	Very rare	Bronchospasm in patients sensitive to aspirin and other NSAIDS.
Gastrointestinal disorders	Rare	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
Hepatobiliary disorders	Rare	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
	Very rare	Hepatotoxicity.
	Administration of 6 grams of paracetamol may already lead to hepatic damage (in children: more than 140 mg/kg); higher doses cause irreversible hepatic necrosis.	
Skin and subcutaneous tissue disorders	Rare	Pruritus, rash, sweating, purpura, angioedema, urticaria.
	Very rare	Serious skin reactions have been reported.
	Unknown	Acute generalised exanthemateus pustulosis, toxic necrolysis, drug-induced dermatosis, Stevens-Johnson-syndrome.
Renal and urinary disorders	Very rare	Sterile pyuria (cloudy urine) and renal side effects (severe renal impairment, nephrite interstitial, haematuria, anuresis).
General disorders and administration site	Rare	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug

conditions		interaction NOS.
Injury, poisoning and procedural complications	Rare	Overdose and poisoning.

NOS= Not otherwise specified.

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 <[To be completed nationally]>.

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 6000 mg (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
Acute paracetamol intoxication can progress in several phases.
The symptoms of paracetamol over dosage in the first two days are nausea, vomiting, anorexia, pallor and abdominal pain. Slight intoxication is limited to these symptoms.

When intoxication is more severe, subclinical symptoms as increased liver enzymes appear.
From 2 to 4 days after exposure, clinical symptoms of liver damage are manifest, such as painful hepatomegaly, jaundice, encephalopathy, coma and disturbed blood clotting, all secondary to liver insufficiency.

Insufficient kidney functioning (tubule necrosis) is rare. Severe intoxication may result in metabolic acidosis may occur.

Management
Immediate medical treatment should be sought.
Local treatment guidelines for paracetamol overdose should be followed.
Directly after intake of a paracetamol overdose, possibly leading to severe intoxication, absorption – decreasing therapy can be applied such as gastric lavage within one hour of intake or administration of activated charcoal.

Antidote treatment with N-acetylcysteine (NAC) is effective and should be started immediately, even in the absence of acute symptoms. For administration of NAC and further treatment, the concentration of paracetamol in blood should be determined. In general, intravenous administration of NAC is preferred and should be continued until paracetamol is no longer detectable. It is important to realize that intake of NAC up to 36 hours after intake can improve prognosis. Oral administration of NAC should not be combined with oral activated charcoal.

Liver tests have to be performed at the start of treatment and need to be repeated each 24 hours after treatment. In most cases, hepatic transaminases will return to normal levels within two weeks after intake of overdose with complete recovery of liver function. In rare cases, liver transplantation may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, anilides, ATC code: N02BE01.

Both peripheral and central analgesic effects are likely, as are antipyretic effects on the thermoregulatory centre of the hypothalamus. However, it has no anti-inflammatory effect. /.../ does not affect hemostasis, and does not irritate the gastrointestinal mucosa.

The main action of paracetamol is the inhibition of cyclo-oxygenase, an enzyme which is important for the prostaglandin synthesis. Central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this explains why paracetamol has an antipyretic and analgesic efficacy without a conspicuous peripheral anti-inflammatory activity.

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
Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma.

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

Biotransformation
In adults paracetamol is conjugated in the liver with glucuronic acid (~60%), sulphate (~35%) conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalysed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine (~3%) and mercapturic acid.

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
Elimination of paracetamol is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, predominantly as the glucuronide (60 to 80%) and the sulphate (20 to 30%) conjugates. Less than 5% is eliminated in unchanged form. The elimination half-life is about 2 hours.

In cases of renal or hepatic insufficiency, after overdose, and in neonates the elimination half-life of paracetamol is delayed. The maximum effect is equivalent with plasma concentrations.
For elderly patients, the capacity for conjugation is not modified.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. 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

Tablet core:
Starch, pregelatinised
Maize starch
Povidone
Stearic acid
Talc

Film-coating:
Opadry White (Y-1-7000), which contains:
Hypromellose
Macrogol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

500 mg: Blister packs (PVC/Aluminium). Package sizes: 10, 16, 20, 30, 50 and 100 tablets.
Plastic bottle (HDPE) with screw cap (PP). Package sizes: 50, 100, 200 and 300 tablets.

1000 mg: Blister packs (PVC/Aluminium). Package sizes: 8, 20 and 30 tablets.
Plastic bottle (HDPE) with screw cap (PP). Package sizes: 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Neogen N.V.
Square Marie Curie 50
1070 Anderlecht
België

8. MARKETING AUTHORISATION NUMBER(S)

500 mg: RVG 118557
1000 mg: RVG 118558

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 26 april 2016
Datum van laatste verlenging: 21 mei 2018

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 4.5: 2 mei 2022