Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Max 1000 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1000 mg paracetamol

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White to off-white, caplet-shaped tablet, debossed with scoreline between '10' and '00' on one side and scoreline between 'PA' & 'RA' on the other side.
(21.4 mm long x 9.0mm wide x 6.9 mm thick)
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of mild to moderate pain and fever.

4.2 Posology and method of administration

Doses depend on body weight and age; a single dose ranges from 10 to 15 mg/kg body weight to a maximum of 60 mg/kg for total daily dose.
The specific dose interval depends on the symptoms and the maximum daily dose. It should, however, not fall below 4 hours.

Body weight (age)	**Single dose**	**Max. daily dose (24 h)**
33 kg - 43 kg (children 11 - 12 years)	500 mg	2,000 mg
44 kg – 65 kg (adults and adolescents from 12 years of age)	500 mg	3,000 mg
>65 kg	1,000 – 500 mg	3,000 mg

The maximum daily dose of paracetamol must not exceed 3000mg

Don't use Paracetamol longer than three days without medical advice

Special groups of patients

Elderly population
There is no need for dosage reduction in the elderly.

Impaired liver or kidney function
In patients with impaired hepatic or renal function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

Patients with impaired renal function
Impaired kidney function
In patients with renal insufficiency, the dose should be reduced:

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

Children and adolescents with a low body weight
Paracetamol is not recommended for use in children below 11 years or below 33 kg body weight, as the dosage strength is not suitable for this age group. However, there are appropriate dosage strengths and/or formulations available for this age group.

Method of administration
Oral use

Swallow the tablet with a glass of water.

4.3 Contraindications

Hypersensitivity to paracetamol or to any of the excipients.

4.4 Special warnings and precautions for use

Do not exceed the stated dose.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

In general, medicinal products containing paracetamol should be taken for only a few days without the advice of a physician or dentist and not at high doses.

Children under 11 years of age: Not recommended without medical advice.

Patients should be advised not to take other paracetamol containing products concurrently.

Paracetamol should be used with caution in cases of dehydration and chronic malnutrition.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment or severe haemolytic anaemia. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. In patients with alcohol abuse the dose has to be reduced The daily dose should not exceed 2 grams in such case.
Caution should be exercised when paracetamol is used in combination with CYP3A4 inducers or use of substance that induce liver enzymes, such as (e.g. rifampicin, cimetidine, antiepileptics as glutetimmide, fenobarbital, carbamazepine).

Following long-term, high-dose, incorrect use of analgesics, headaches may occur which may not be treated with higher doses of the medicinal product.

In general, habitual intake of analgesics, particularly a combination of several analgesic substances, can lead to permanent renal damage with the risk of renal failure (analgesic nephropathy).
Prolonged or frequent use is discouraged. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately.
Prolonged use except under medical supervision may be harmful. In children treated with 60mg/kg daily of paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.
Abrupt discontinuation following long-term, high-dose, incorrect use of analgesics may lead to headaches, fatigue, muscle pain, nervousness and autonomic symptoms. These withdrawal symptoms resolve within a few days. Until this time, further intake of analgesics should be avoided and not restarted without medical advice.

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 daily use of paracetamol with increased risk of bleeding. The interaction is dose-dependent but may appear already at daily doses of 1.5-2g. Occasional doses have no significant effect.

Concurrent administration of paracetamol and AZT (zidovudine) enhances the tendency to neutropenia. This medicinal product should therefore be co-administered with AZT only on medical advice.
Concurrent intake of medicinal products that accelerate gastric emptying, such as metoclopramide, accelerates the absorption and onset of effect of paracetamol.

Concurrent intake of medicinal products that slow gastric emptying can delay the absorption and onset of effect of paracetamol.
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine. Intake of cholestyramine and paracetamol should be separated by at least one hour.

Probenecid reduces the clearance of paracetamol by almost 50%. Thus, the paracetamol dose may be halved during concomitant treatment.

Alcohol abuse increases the risk for paracetamol toxicity.

Enzyme inducing drugs such as rifampicin certain antiepileptic drugs, St John´s wort can give rise to reduced plasma concentrations and reduce the effectiveness of paracetamol. Furthermore, the risk of liver damage is expected to be larger in patients concomitantly treated with enzyme inducers and the maximum therapeutic dose of paracetamol.

Paracetamol may affect the plasma concentrations of chloramphenicol. Monitoring of the plasma concentrations is advised during chloramphenicol injection treatment.

Effects on laboratory test.
Intake of paracetamol can affect tests for uric acid using phosphotungstic acid and blood sugar tests using glucose-oxidase-peroxidase.

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 fetus / newborn infant. Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk. Reproductive studies with the oral route did not show any malformation or foetotoxic effects.
Consequently under normal conditions of use, paracetamol can be use throughout the duration of pregnancy, after a benefit-risk assessment.
During pregnancy, paracetamol should not be taken for longs periods, at high doses or in combination with other medicinal products, as safety of use in such cases is not established.

Lactation
After oral use, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Therapeutic doses of this medicinal product may be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Paracetamol has no influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

<Very common (≥1/10)>
<Common (≥1/100 to <1/10)>
<Uncommon (≥1/1,000 to <1/100)>
<Rare (≥1/10,000 to <1/1,000)>
<Very rare (<1/10,000)
Not known (cannot be estimated from the available data)>

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders
Rare: - anaemia, non-haemolysis and marrow depression; - marrow depression, – thrombocytopaenia

Cardiac disorders:
Vascular disorders:

Rare: Oedema.

Gastrointestinal disorders
Rare exocrine pancreas conditions, acute and chronic pancreatitis
Haemorrhage, abdominal pain, diarrhoea, nausea, vomiting, hepatic failure, hepatic necrosis, jaundice.

Skin and subcutaneous disorders
Rare: pruritus, rash, sweating, purpura, angiooedema, urticaria

Renal and urinary disorders
Rare: nephropathies, nephropathies and tubular disorders
Paracetamol has been widely used and reports of adverse reactions are rare, and are generally associated with overdose. Nephrotoxic effects are uncommon and have not been reported in association with therapeutic doses, except after prolonged administration.

4.9 Overdose

There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition. Overdosing may be fatal in these cases.

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).

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.

Risk factors:
If the patient
a. Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. Johns 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 deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms:
Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia 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 in the absence of severe liver damage. Cardiac arrythmias and pancreatitis have been reported.

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 concentrations 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 hours from ingestion should be discussed with the NPIS or a liver unit. Dialysis can reduce the plasma paracetamol concentration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANALGESICS ,OTHER ANALGESICS AND ANTIPYRETICS, Anilides, ATC Code : N02BE01

Paracetamol is an antipyretic and analgesic. Paracetamol produces antipyresis through action on the hypothalamic heat-regulation centre and analgesia by elevation of the pain threshold. Paracetamol has analgesic and antipyretic actions similar to aspirin, but it has no useful anti-inflammatory properties.

Paracetamol produces its analgesic effect from the inhibition of prostaglandin synthesis. Prostoglandins appear to sensitise pain receptors to mechanical stimulation or to other chemical mediators. Paracetamol lowers the body temperature in patients with fever but rarely lowers normal body temperature. This is again due to the inhibiton of synthesis and release of prostoglandins. The drug also acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow.

Paracetamol is generally well tolerated by patients hypersensitive to acetylsalicylic acid.

5.2 Pharmacokinetic properties

Paracetamol is reapidly and almost completely absorbed from the alimentary tract. Peak plasma concentrations occur after 30 minutes to two hours following oral dosing. Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucoronide and sulphate conjugates with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half life varies from about 1 – 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose dependent.

5.3 Preclinical safety data

In animal experiments regarding acute, subchronic and chronic toxicity of paracetamol in rats and mice, gastro-intestinal lesions, blood count changes, degeneration of liver and renal parenchyma, even necroses were observed. The causes for these changes are attributed to the mechanism of action on the one hand and on the other to the metabolism of paracetamol. Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic, i.e. non-toxic doses.
Long-term studies in rats and mice yielded no evidence on relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.
Paracetamol passes through the placenta.

Animal studies yield no evidence on reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate Type A
Povidone (K-30)
Pre-gelatinised maize starch
Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blisters
Pack sizes: 12, 16, 18, 24, or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pensa Pharma AB
Birger Jarlsgatan 22,
114 34 Stockholm,
Sweden

8 MARKETING AUTHORISATION NUMBER

PA 1647/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th December 2012

10 DATE OF REVISION OF THE TEXT

March 2014