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 of paracetamol

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to slightly yellow oblong tablets with smooth surface and a central break line. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of mild to moderate pain (such as headache, migraine, toothache, sore throat, backache, muscle pain, rheumatic pain, dysmenorrhoea) and/or fever.
Paracetamol Max 1000 mg Tablets is indicated in adults and adolescents aged 16 years and over, whose body weight is greater than 50 kg.

4.2 Posology and method of administration

Posology

Doses depend on body weight and age with a maximum of 60 mg/kg body weight for total daily dose, not exceeding 4000 mg daily.

Adults and adolescents over 16 years of age and >50 kg of body weight:

One tablet to be taken four times a day as required.

Paracetamol Max 1000 mg Tablets should not be given more frequently than every
4-6 hours, and not more than 4 doses (4000 mg) should be given in any 24 hour period.

Not to be given to children under 16 years of age.

Renal insufficiency
In case of renal insufficiency the dose should be reduced:

Glomerular flitration rate	**Dose**
10-50 ml/min	500 mg every 6 hours
< 10 ml/min	500 mg every 8 hours

Hepatic insufficiency
In patients with impaired hepatic or Gilbert’s syndrome, the dose must be reduced or the dosing interval prolonged.

The daily effective dose should not exceed 2000 mg/day in the following situations:

• Mild to moderate hepatic insufficiency, Gilbert's syndrome (familiar nonhaemolytic jaundice)
• Dehydration
• Chronic malnutrition
• Chronic alcoholism

Paracetamol Max 1000 mg Tablets is suitable for patients with renal and hepatic insufficiency when reduced dose is required, because the tablets can be divided into equal doses.

Intake of paracetamol with food and drink does not affect the efficacy of the medicinal product.

Method of administration
Paracetamol Max 1000 mg Tablets are for oral administration only. Tablet should be swallowed using a glass of water.

4.3 Contraindications

- Hypersensitivity to paracetamol or to any of the excipients.
- Children under 16 years of age.
- Adults and adolescents with a body weight less than 50 Kg.

4.4 Special warnings and precautions for use

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

Caution is advised in the administration of paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatic insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (Child-Pugh>9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic anaemia, alcohol abuse dehydration and chronic malnutrition (see section 4.2).

The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.
Caution should be exercised in case of chronic alcoholism. The daily dose should not exceed 2000 mg in such case.
Alcohol should not be used during the treatment with Paracetamol.

Do not exceed the stated dose.

This product should only be used when clearly necessary.

If symptoms persist consult your doctor.

Keep out of the reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of paracetamol depends on the gastric depletion rate. The gastric depletion rate can be altered by the concomitant use of other medications such as anticholinergic or opioid drugs (e.g. metoclopramide, domperidone or codeine) which increase paracetamol absorption. The absorption of paracetamol is reduced by concomitant administration of cholestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced (may lead to slight variations in INR values) with prolonged concomitant use of paracetamol (4 g per day for at least 4 days). This may increase the risk of bleeding therefore should be closely monitored.

Extreme caution and medical supervision is advised in prolonged use with drugs / substances which induce hepatic monooxygenases (e.g., cimetidine, zidovudine, rifampicin, isoniazid and antiepileptic agents glutethimide,

phenobarbital and carbamazepine).

Concomitant administration of paracetamol and chloramphenicol can prolong the half-life of chloramphenicol and increase its toxic effects.

Probenecid causes an almost two-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction in the paracetamol dose should be considered if it is to be used concomitantly with probenecid.

Salicylamide may prolong the elimination half-life of paracetamol

4.6 Fertility, pregnancy and lactation

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use. Paracetamol is excreted in breast milk, but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

4.7 Effects on ability to drive and use machines

Paracetamol Max 1000 mg Tablets have no known influence on the ability to drive and use machinery.

4.8 Undesirable effects

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

According to extensive post-marketing experience, the following undesirable effects can be listed:

Body System	**Undesirable effect**
Blood and lymphatic System Disorders	Thrombocytopenia Agranulocytosis
Immune System Disorders	Anaphylaxis Cutaneous hypersensitivity reactions including skin rashes, angioedema and Stevens Johnson syndrome/toxic epidermal necrolysis
Respiratory, thoracic and mediastinal disorders	Bronchospasm*
Hepatobiliary disorders	Hepatic dysfunction

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

4.9 Overdose

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g 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
Symptoms of paracetamol overdose 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 even in the absence of severe liver damage. Cardiac arrhythmias 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.

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 hours from ingestion should be discussed with a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics and antipyretics, anilides
ATC-code: N02BE01
The analgesic effect of paracetamol is ascribable to a direct action, probably mediated by the opioid and serotoninergic system, on the Central Nervous System and to inhibition of the prostaglandin synthesis on a central level. In addition, paracetamol has a marked antipyretic activity.

5.2 Pharmacokinetic properties

Absorption: paracetamol by the oral route is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in 30 to 60 minutes. Plasma half-life is 1-4 hours.

Distribution: paracetamol is distributed throughout most tissues. Concentrations are comparable in blood, saliva and plasma. Plasma protein binding is variable; 20 – 30% may be bound at the concentrations encountered during acute intoxication.

Metabolism: paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed by the cytochrome P450 (mostly CYP2E1), 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 cystein and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

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

Renal Insufficiency: in cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol metabolites is delayed.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Povidone K30
Povidone K90
Magnesium stearate
Silicone dioxide

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Package containing 6 scored tablets:
1 opaque blister made up of polyvinylchloride (PVC) thermoformed with an aluminium sheet coated with thermoforming film for polyvinylchloride (PVC) containing 6 tablets.

Package containing 8 scored tablets:
1 opaque blister made up of polyvinylchloride (PVC) thermoformed with an aluminium sheet coated with thermoforming film for polyvinylchloride (PVC) containing 8 tablets.

Package containing 12 scored tablets:
2 opaque blisters made up of polyvinylchloride (PVC) thermoformed with an aluminium sheet coated with thermoforming film for polyvinylchloride (PVC) containing 6 tablets each.

Package containing 16 scored tablets:
2 opaque blisters made up of polyvinylchloride (PVC) thermoformed with an aluminium sheet coated with thermoforming film for polyvinylchloride (PVC) containing 8 tablets each.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal products or waste materials should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aziende Chimiche Riunite Angelini Francesco
Viale Amelia 70
00181 Roma (RM)
Italy

8 MARKETING AUTHORISATION NUMBER

PA0959/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th March 2013

10 DATE OF REVISION OF THE TEXT

November 2013