REGAL PHARMACEUTICALS LIMITED
NAIROBI, KENYA

1.5.1 SUMMARY OF PRODUCT CHARACTERISTICS

APPLICATION DOSSIER FOR THE REGISTRATION OF CETAMOL TABLETS
RWANDA FOOD AND DRUGS AUTHORITY (RFDA)
RWANDA

1. Name of the medicinal product

Cetamol tablets

2. Qualitative and quantitative composition

Each tablet contains 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet

White, round, flat tablet, scored and impressed with P/500 on one side, and impressed with REGAL on the other side and free from visible impurities.

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.

Adults, the elderly and children 16 years and over (above 55 kg body weight):

Take 500 mg to 1000 mg at a time, up to 3000 mg per 24 hours.

The maximum daily dose of Paracetamol must not exceed 3000 mg.

Children 10 to 15 years of age (40-55 kg body weight)

Take 500 mg at a time, up to 2000 mg per 24 hours.

The daily dose must not exceed 2000 mg.

Not recommended for children under 10 years of age.

The dose should not be repeated more frequently than every 4 hours and not more than 4 doses should be taken in any 24-hour period

Direction for use:

• Paracetamol tablet is not suitable for children below 10 years.

• The dosing interval should be at least 4 hours.

• The indicated dose should not be exceeded due to risk of serious damage to the liver (see section 4.4 and 4.9).

• If pain for more than 5 days or fever for more than 3 days exists or get worse, or if any other symptom 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.

Special Populations:

• In case of renal insufficiency (renal failure), the dose should be reduced:

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

• In patients with impaired hepatic 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 2 g/day) in the following situations:

▪ Adults weighing less than 50 kg

▪ Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-hemolytic jaundice)

▪ Dehydration

▪ Chronic malnutrition

Method of administration

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

4.3 Contraindications
Hypersensitivity to the Paracetamol or to any of the excipients listed in section.

4.4 Special warnings and precautions for use
Prolonged or frequent use is discouraged.

Patients should be advised not to take other Paracetamol-containing products concurrently. Multiple daily doses or in the event of over dosage may cause severe damage to the liver; in such cases, immediate medical advice should be sought even if the patient feels well because of the risk of irreversible liver damage (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.

Caution is advised in the administration of Paracetamol to patients with severe renal or severe hepatic impairment (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, haemolyticanaemia, alcohol abuse, chronic dehydration and malnutrition.

The hazards of overdose are greater in those with Non-cirrhotic 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 2 grams in such case.

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.

After prolonged use (> 3 months) of analgesics intake every day or more often, headaches may occur or worsen. Headaches caused by overuse of analgesics should not be handled by increasing the dose. In those cases, the use of analgesics should be taken after consulting a doctor Caution is advised in asthmatic patient sensitive to acetylsalicylic acid, because bronchospasm with Paracetamol (cross-reaction) has been reported.

Self-medication with paracetamol should be limited when taking anticonvulsants because with the concomitant use of both, liver toxicity is potentiated and the bioavailability of paracetamol is reduced, especially when using high-doses of paracetamol (see section 4.5).

Interference with laboratory tests

Paracetamol may affect uric acid tests by wolframato phosphoric acid and blood sugar tests by glucose-oxydase-peroxydase

4.5 Interaction with other medicinal products and other forms of interaction
The speed of absorption of Paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. 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.

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 medicinal products which induce liver enzymes like rifampicin, barbiturates, some anti-epileptic drugs (e.g. carbamazepine, phenytoin, phenobarbital, primidone) and St. John's wort can increase the hepatotoxicity of Paracetamol as a result of an increased and fast formation of toxic metabolites. Caution is therefore necessary with concomitant use of enzyme-inducing drugs.

Probenecid blocks the binding of Paracetamol to glucuronic acid reducing Paracetamol clearance by a factor of about 2. If probenecid is taken concurrently the Paracetamol dose should be reduced.

Paracetamol can increase the 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 $t_{1/2}$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.

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.

Consequently under normal conditions of use, Paracetamol can be used throughout the duration of pregnancy.

Breastfeeding:

Following oral administration, small amounts of paracetamol are excreted into breast milk, however not in a clinical significant amount. To date, there are no known undesirable effects or side effects during breast-feeding. Paracetamol can be administered during lactation at therapeutic doses.

Fertility:

No detrimental effects on fertility upon normal use of Paracetamol are known

4.7 Effects on ability to drive and use machines
Paracetamol tablets has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
At therapeutic doses few undesirable effects occur.

The frequency of undesirable effects is classified as follows: 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).

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Rare	Agranulocytosis (long-term use), thrombocytopenia, thrombocytopenic purpura, leucopenia, haemolytic anemia, 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	Hypoglycemia
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	Hemorrhage NOS, abdominal pain NOS, diarrhea NOS, nausea, vomiting.
Hepatobiliary disorders	Rare Very rare	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
		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 Unknown	Serious skin reactions have been reported Acute generalized exanthematous 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, hematuria, enuresis)

General disorders and administration site conditions	Rare	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
Injury, poisoning and procedural complications	Rare	Overdose and poisoning

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.

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:

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.

Treatment:

Local treatment guidelines for Paracetamol overdose should be followed.

Directly after intake of a Paracetamol overdose, possibly leading to severe intoxication, absorptiondecreasing therapy can be applied such as gastric lavage within one hour of intake or administration of activated charcoal.

N-acetyl cysteine (NAC) can be administered as antidote. 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

Paracetamol is an effective antipyretic and analgesic agent. However, it has no anti-inflammatory effect.

The main action of Paracetamol is the inhibition of cyclooxygenase, an enzyme which is important for the prostaglandin synthesis. Central nervous system cyclooxygenase is more sensitive for paracetamol than peripheral cyclooxygenase 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.

Metabolism

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, catalyzed 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 mercaptopuric 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. Animal studies have not indicated any teratogenic potential

6. Pharmaceutical particulars

6.1 List of excipients
Starch

Sodium benzoate

Potassium sorbate

Gelatin

Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
48 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.