Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rowalief 500 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, caplet shaped, film-coated tablets with 'P', a bisect breakline and '500' on one side and 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 fever.

4.2 Posology and method of administration

Posology

Adults (including the elderly)
The usual dose is 500 mg to 1,000 mg every 4 to 6 hours as needed, to a maximum of 3 g daily. Maximum single dose is 1,000 mg.

The maximum daily dose must not be exceeded due to risk of serious hepatic damage (see sections 4.4 and 4.9).

Paediatric population (weighing 20-50 kg)
The recommended total daily dose of paracetamol is approximately 60 mg/kg divided in 4 or 6 separate doses, or approximately 15 mg/kg every 6 hours or 10 mg/kg every 4 hours. Maximum daily dose must not be exceeded due to risk of serious hepatic damage (see sections 4.4 and 4.9).

Paediatric dosage should be based on body weight and a suitable dosage should be used. Information on the age of children within each weight group given below is for guidance only.

Care must be taken not to exceed the maximum number of doses in a 24 hour period i.e. not more than 4 doses in a 24 hour period. Paracetamol should only be administered when clearly necessary and at the lowest efficacious dose.

Children and adolescents weighing 43-50 kg (about 12-15 years)
The usual dose is 500 mg every 4 hours as needed, to a maximum of 2.5 g daily.

Children weighing 34-43 kg (about 11-12 years)
The usual dose is 500 mg every 6 hours as needed, to a maximum of 2 g daily.

Children weighing 26-34 kg (about 8-11 years)
The usual dose is about 250 mg every 4 hours or 500 mg every 6 hours as needed, to a maximum of 1.5 g daily.

Children under 8 years

Rowalief 500 mg Film-coated tablets are not suitable for children under 8 years of age, 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.

Hepatic and Renal Impairment
In patients with impaired hepatic or renal function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged (see section 4.4).

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

These doses should not be repeated more frequently than every 4 hours and not more than 4 doses should be given in any 24 hour period.

Maximum duration of continued use without medical advice: 3 days

The lowest effective dose should be used for the shortest duration necessary.

Method of administration

For oral use.

The tablet should be swallowed with a glass of water.

4.3 Contraindications

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

Rowalief 500 mg Film-coated tablets are not suitable for use in children under 8 years of age. However, there are appropriate dosage strengths and/or formulations available for this age.

4.4 Special warnings and precautions for use

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

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 only be taken for a few days without the advice of a physician or a dentist and not at high doses.

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 (see section 4.2) 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 cases.

Caution should be exercised when paracetamol is used in combination with CYP3A4 inducers or use of substances that induce liver enzymes, such as rifampicin, cimetidine or antiepileptics (e.g. glutetimmide, fenobarbital or carbamazepine).

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of

paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

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.

Other notes:

Prolonged use of analgesics for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

In general terms, the habitual intake of analgesics particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure. Therefore it must be avoided.

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 must be avoided and not restarted without medical supervision.

Patients should be advised accordingly.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of paracetamol with:	**Possible side effects:**
AZT (Zidovudine)	The risk of developing neutropenia is increased. Paracetamol should therefore only be used concomitantly with AZT when supervised by a doctor.
Anticoagulants (Warfarin, Courmarin)	Prolonged regular daily use of paracetamol (from 1500 mg or greater) may enhance the effect of anti-coagulants, with increased risk of bleeding; occasional doses have no significant effect.
Medications which accelerate gastric emptying (e.g. Metoclopramide)	May increase the resorption rate and onset of action of paracetamol.
Cholestyramine	Reduces the resorption of paracetamol. Intake of cholestyramine and paracetamol should be separated by at least one hour.
Probenecid	Probenecid reduces the clearance of paracetamol by almost 50%. Thus, the paracetamol dose may be halved during concomitant treatment.
Medications which lead to an enzyme induction (e.g. rifampicin, primidone, cimetidine, barbiturates, certain antiepileptic drugs, St. John’s Wort)	Enzyme inducing drugs 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.
Potential hepatotoxic substances (e.g. alcohol)	Increase the risk of liver toxicity
Lamotrigine	Paracetamol may decrease the bioavailability of lamotrigine, with possible reduction of its effect, due to a possible induction of its metabolism in the liver.

Chloramphenicol	Paracetamol may increase the plasma concentrations of chloramphenicol. Monitoring of the plasma concentrations is advised during chloramphenicol injection treatment.
Salicylamide	Salicylamide may prolong the elimination $t_{1/2}$ of paracetamol.
Isoniazid	Reduces paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver.
Flucloxacillin	Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

Interference with laboratory tests

Paracetamol may affect phosphotungstic uric acid tests and blood sugar tests by glucose-oxydase-peroxidase.

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
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

Rowalief 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. Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: 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).

Blood and lymphatic system disorders Rare:	Anaemia, non-haemolysis and marrow depression, marrow depression, thrombocytopaenia
Immune system disorders Very rare:	Anaphylaxis Stevens Johnson syndrome
Metabolism and nutrition disorders Not known:	High anion gap metabolic acidosis
Cardiac disorders Rare:	Oedema
Vascular disorders	

Rare:	Oedema
Respiratory, thoracic and mediastinal disorders Very rare:	Bronchospasm in patients sensitive to acetylsalicylic acid and other NSAIDs
Gastrointestinal disorders Rare:	Exocrine pancreas conditions, acute and chronic pancreatitis, haemorrhage, abdominal pain, diarrhoea, nausea, vomiting, hepatic failure, hepatic necrosis, jaundice
Hepatobiliary disorders Very rare:	Hepatic dysfunction
Skin and subcutaneous tissue disorders Rare:	Pruritus, rash, sweating, purpura, angioedema, 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.

Description of selected adverse reactions

High anion gap metabolic acidosis
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

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 HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

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

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

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).

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
- 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.

Emergency Treatment

- Immediate hospitalisation.

- After overdosage a blood sample should be drawn to determine the paracetamol level as soon as possible.

- Rapid evacuation of the ingested product by means of gastric lavage, followed by administration of activated charcoal (adsorbens) and sodium sulphate (laxans).

- Dialysis may lower plasma concentration of paracetamol.

- Treatment consists of administration of the antidote N-acetylcystein (NAC), intravenously or orally, if possible before the tenth hour after intake. NAC may even offer protection after 10 hours but in such cases a prolonged treatment is given.

- Symptomatic treatment.

- Liver tests should be performed at the start of treatment and should be repeated every 24 hours. In most cases, the hepatic transaminases will return to normal within one to two weeks, with full recovery of liver function. However, in very rare cases a liver transplantation may be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 acetylsalicylic acid, but it has no useful anti-inflammatory properties.
Paracetamol produces its analgesic effect from the inhibition of prostaglandin synthesis. Prostaglandins appear sensitise pain receptors to mechanical stimulation or to other chemical mediators. Paracetamol lowers body temperature in patients with fever but rarely lowers normal body temperature. This again is due to the inhibition of synthesis and release of prostaglandins. 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

Absorption
Paracetamol is rapidly and almost completely absorbed from the alimentary tract. Peak plasma concentrations occur after 30 minutes to 2 hours following oral dosing.

Distribution
The volume of distribution of paracetamol is approximately 1 L/Kg body weight. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose dependant.

Biotransformation
Paracetamol is metabolised in the liver and excreted in the urine mainly as glucoronide and sulphate conjugates with about 10% as glutathione conjugates.

Elimination
Less than 5% is excreted as unchanged paracetamol. The elimination half life varies from about 1-4 hours.

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 were 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.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are notavailable.

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) includes:
Titanium dioxide (E171)
Macrogol
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package.

6.5 Nature and contents of container

Clear PVC/aluminium foil blister strips packed into cardboard cartons
White HDPE bottles and a PP screw closure

10, 12, 20, 24, 30, 50, 60 and 100 film-coated tablets for blisters,
30, 100 and 300 film-coated tablets for HDPE bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Limited
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0074/065/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th December 2012
Date of last renewal: 5th November 2017

10 DATE OF REVISION OF THE TEXT

June 2025