Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Padolieve Max 1000mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1000 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, caplet-shaped, biconvex, film-coated tablets that have a break line on one side and are 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
Padolieve Max 1000 mg Film-coated tablets are not suitable for children under 16 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.

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 (see section 4.4).

Patients with impaired renal function

Impaired renal 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

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.

Alcoholic patients: A maximum daily dose of 2 tablets per 24 hours must not be exceeded.

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.

Padolieve Max 1000 mg Film-coated tablets are not suitable for use in children under 12 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.

Patient groups at increased risk of toxic liver effects

Elderly patients, infants, patients with chronic nutritional disorders, patients who are underweight, patients with liver or renal disease, patients taking excess alcohol or patients using medicines which are enzyme inducers are more likely to develop liver toxicity from paracetamol use. Even relatively small overdoses of paracetamol in these patients can cause serious liver toxicity which can be fatal (see sections 4.4 and 4.9).

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).

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 interactions

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.

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.

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

Padolieve Max 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
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 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.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

4.9 Overdose

Immediate medical attention is required in the event of an overdose even if there are no significant early symptoms.

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 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 toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, and abdominal pain or patients maybe asymptomatic.

Overdose of paracetamol in a single administration in adults or in children causes liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk Factors include: If the patient;
a. Is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's 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 depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Emergency Procedure:
Immediate transfer to hospital
Blood sampling to determine initial paracetamol plasma concentration
Gastric lavage
IV (or oral if possible) administration of the antidote N-acetylcysteine as soon as possible in accordance with National treatment guidelines.
Symptomatic treatment should be implemented.

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.

Metabolism
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 not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Starch, pregelatinised
Maize starch
Povidone K-30
Stearic acid
Talc

Film-coating:
Opadry White (Y-1-7000) includes:
Titanium dioxide (E171)
Macrogol 400
Hypromellose 5cP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

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

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

5, 6, 10, 12, 20, 24, 30, 50 and 60 film-coated tablets for blisters,
30 and 100 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

Alter Pharma
Square Marie Curie 50
1070 Anderlecht
Belgium

8 MARKETING AUTHORISATION NUMBER

PA22983/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd October 2014
Date of last renewal: 19th August 2019

10 DATE OF REVISION OF THE TEXT

March 2021