Summary of Product Characteristics

1-NAME OF THE MEDICINAL PRODUCT (FPP)

Parol

Paracetamol

1.1 Strength

500 mg paracetamol/tablet

1.2 Pharmaceutical form

Tablet

2- QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative declaration

For the full list of excipients, see section 6.1

2.2 Quantitative declaration

Each tablet contains 500 mg of paracetamol.

3- PHARMACEUTICAL FORM

Tablet

White, round, biconvex, engraved tablet.

4- CLINICAL PARTICULARS

4.1 Therapeutic indications

Relieve of mild and moderate pain and reducing fever.

Parol® tablets are used for symptomatic treatment of pain associated with conditions such as headaches, toothaches, migraine, teething, neuralgia, post-traumatic, post-operative pains and musculoskeletal pains.

Furthermore, reduce fever and relieve pains and aches associated with conditions such as flu, cold, sore throat, sinusitis, and other acute febrile illnesses.

4.2 Posology and mode of administration

4.2.1 Posology

- Adults: 1 to 2 tablets up to 3 times daily.
- Children 12 years and older: 1 tablet up to 3 times daily.
- Children from 6 to 12 years old: 1/2 to 1 tablet up to 3 times a day

4.2.2 Special populations

- In patients with impaired liver function, the dose will be lower (see section 4.4)
- No dose adjustment is necessary in the elderly.

4.2.2 Paediatric population

- Parol tablets are not to be used under the age of 6 years. If necessary, Parol suspension, paracetamol in an oral suspension is available for use.

4.2.3 Method of administration

- Swallow the tablets with a glass of water
- As for any analgesic, the treatment will be as short as possible and its duration strictly adapted to that of the symptomatology.
- In case of swallowing problems the tablet can be broken in half to make it easier to swallow.
- Always respect a minimum interval of 4 hours between two intakes.
- Do not use concomitantly with other medicines containing paracetamol.
- Do not exceed the prescribed dose.

4.3 Contraindications

Parol tablets are contraindicated in case of hypersensitivity or allergy to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warning and precautions for use

4.4.1 General information

Prolonged, frequent or simultaneous use of other products containing paracetamol is not recommended.

In case of **overdose** (several daily doses at one time) severe liver failure can occur, with loss of consciousness. In this case, it is imperative to perform an intravenous infusion with acetylcysteine in an intensive care unit. See also section 4.9.

After long-term treatment (> 3 months) reactive headaches can develop. These headaches caused by the abuse of analgesics (MOH or medicine-overuse headache) should not be treated by increasing the dose. In these cases, the use of analgesics should be stopped on the advice of a doctor. Sudden discontinuation after prolonged treatment with high of doses analgesics may lead to headaches, fatigue, muscle aches,

nervousness and reflex symptoms. These withdrawal symptoms disappear within a few days

Renal and hepatic insufficiency

- Administration of paracetamol to patients with moderate to severe renal impairment may result in accumulation of conjugated derivatives.
- The risk of liver toxicity is significantly increased in chronic alcohol abuse. Dosage reduction is therefore required in these patients.
- In elderly patients, liver and kidney tests should be performed to detect early liver or kidney failure.
- Caution is recommended in patients with proven hepatic impairment. It is the same in patients consuming substances inducing liver enzymes (alcohol, barbiturates, anti-epileptics). In these cases, accumulation of the toxic metabolites of paracetamol may aggravate or lead to liver injury. The risk of hepatic toxicity is considerably increased in chronic alcohol abuse. Dosage reduction is therefore required in these patients.
- Special caution and adherence to the recommended dosage are essential in epileptic children treated with barbiturates, phenytoin, carbamazepine or lamotrigine.

4.4.2 Paediatric population

No other special precautions required

4.5 Interactions with other medicinal products and other forms of interactions

4.5.1 General information

- In case of overdose of paracetamol, alcohol, barbiturates, phenytoin, carbamazepine and isoniazid may increase the risk of liver damage.
- Because of its lack of action on the gastric mucosa, paracetamol can be given to ulcer patients, or be associated, for a limited time, with nonsteroidal anti-inflammatory drugs.
- Its low plasma protein binding allows its association with anticoagulants. However, taking paracetamol for a prolonged period may increase the risk of bleeding. In this case, regular monitoring of the International Normalised Ratio (INR) is recommended.
- Paracetamol absorption may be increased if combined with metoclopramide, and decreased if combined with cholestyramine or activated charcoal.

- Due to the risk of decreased leukocyte (leukopenia) levels when concomitant administration of paracetamol and AZT (zidovudine), simultaneous administration will only be with medical advice. Simultaneous administration of diflunisal and paracetamol increases plasma levels of paracetamol by approximately 50%.

4.5.2 Additional information on special populations

No additional information

4.5.3 Paediatric population

Special caution and adherence to the recommended dosage are essential in epileptic children treated with barbiturates, phenytoin, carbamazepine or lamotrigine.

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

The results of well conducted epidemiological studies seem to exclude the deleterious effects of paracetamol on pregnancy or on the foetus or new-born. Paracetamol can be used in pregnant women.

4.6.2 Lactation

After oral administration, paracetamol is excreted in breast milk in small amounts. There were no reports of adverse effects on infants at recommended therapeutic doses in lactating women.

4.6.3 Fertility

The available clinical information on the effect of paracetamol on fertility is insufficient.

4.7 Effects on the ability to drive and use machines

Paracetamol has no or negligible effect on the ability to conduct vehicles or to use machines.

4.8 Undesirable effects

In therapeutic doses, paracetamol has only few undesirable effects

The frequencies of adverse reactions reported with paracetamol are defined as:

- 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:	Thrombocytopenia, leukopenia, pancytopenia, neutropenia, haemolytic anaemia, agranulocytosis
	Not known	Anaemia
Immune system disorders	Rare	Allergic reactions
	Very rare	Allergic reactions requiring treatment stop
	Not known	Anaphylactic choc
Metabolism and nutrition disorders	Very rare	Hypoglycaemia
Psychiatric disorders	Rare	Depression*, confusion, hallucinations
Nervous system disorders	Rare	Tremor *, headache *
Eye disorders	Rare	Abnormal vision
Cardiac disorders	Rare	Oedema
Respiratory, thoracic and mediastinal disorders	Not reported	Not reported
Gastrointestinal disorders	Rare	Haemorrhage *, abdominal pain *, diarrhoea *, nausea, vomiting, constipation
Hepatobiliary disorders	Rare	Decreased hepatic function, liver failure, hepatic necrosis, jaundice
	Very rare:	Hepatotoxicity

System organ class	Frequency	Undesirable effects
	Not known	Hepatitis
Skin and subcutaneous tissue disorders	Rare	Pruritus, rash, sweating, purpura, angioedema, urticaria
	Very rare	Severe skin reactions
Renal and urinary disorders	Very rare	Sterile pyuria (cloudy urine) and renal adverse events
	Not Known	Neuropathies (interstitial nephritis, tubular necrosis) with long-term use of high doses
General disorders and administration site conditions	Rare	Dizziness (except vertigo), malaise, pyrexia, sedation, drug interaction*
Injury, poisoning and procedural complications	Rare	Overdose and intoxication

*Without specifications

4.9 Overdose

An overdose with paracetamol may be fatal.

- Symptoms of paracetamol intoxication include nausea, vomiting, anorexia, pallor, and abdominal pain. These symptoms usually appear within 24 hours of taking the overdose.
- A paracetamol overdose of 10 g or more in a single dose in adults or 150 mg / kg body weight in a single dose in children results in hepatic cytolysis that may result in complete and irreversible necrosis resulting in hepatocellular insufficiency, metabolic acidosis, and encephalopathy may lead to coma and death.

- At the same time, hepatic transaminases (ASAT, ALT), lactic dehydrogenase, and bilirubin levels were observed to increase, with prothrombin levels decreasing 12 to 48 hours after ingestion of the overdose.
- Clinical signs of liver injury usually appear after two days and peak after 4-6 days. Even in the absence of severe hepatic injury, acute renal failure with acute tubular necrosis may occur.
- Other non-hepatic symptoms of paracetamol overdose may be myocardial alterations and pancreatitis.

Emergency treatment

- Immediate hospitalization.
- After an overdose, a blood sample should be taken to determine the paracetamol level as soon as possible before starting treatment.
- Rapid evacuation of the ingested product by gastric lavage, then administration of active charcoal (adsorbent) and sodium sulphate (laxative).
- Dialysis may reduce the plasma concentration of paracetamol.
- The treatment consists of the administration of the antidote N-acetylcysteine (NAC), intravenously or orally, if possible before the tenth hour after ingestion of the overdose. NAC treatment may result a protective effect even after 10 hours when given as a prolonged treatment.
- Symptomatic treatment.
- Liver tests should be performed at the beginning of treatment and repeated every 24 hours. In most cases, hepatic transaminases will return to normal levels within one to two weeks, and liver function will be fully restored. However, in very rare cases, liver transplantation may be indicated.

5- PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : other analgesics and antipyretics, anilides
ATC code: N02BE01

Paracetamol has both analgesic and antipyretic effect. However, it has no anti-inflammatory effect. The mechanism of analgesic action has not been fully determined. The main action of paracetamol is the inhibition of cyclo-oxygenase, an important enzyme in the synthesis of prostaglandin. Cyclo-oxygenase in the central nervous system is more

sensitive to paracetamol than peripheral cyclo-oxygenase, which is why paracetamol has antipyretic and analgesic efficacy. Paracetamol probably produces antipyretics by acting centrally on the hypothalamic centre of thermoregulation.

5.2 Pharmacokinetic properties

Absorption

Paracetamol is rapidly and completely absorbed after oral administration. Peak plasma concentration is reached within two hours.

Distribution

Paracetamol is poorly bound to plasma proteins (20 to 50%) and its diffusion is rapid.

Metabolism and elimination

Paracetamol is metabolized in the liver and is then eliminated in the urine, mainly in two forms: glucuronoconjugate (60 to 80%) and sulfoconjugate (20 to 40%). A small fraction (less than 4%) is transformed in the liver by cytochrome P 450 into a metabolite that is involved in the paracetamol hepatotoxicity. At therapeutic doses, this toxic metabolite is eliminated by conjugation with glutathione. The conjugation capacity is not modified in the elderly and the kinetics is linear for doses up to 7 g. In case of massive overdose, the conjugation capacity is exceeded, and the fraction of the hepatotoxic metabolite increases.

5.3 Preclinical safety data

- In toxicity studies in rats and mice, gastrointestinal lesions, changes in blood counts, degeneration of hepatic and renal parenchyma, and necrosis have been observed. These changes are attributed to both the mechanism of action and the metabolism of paracetamol.
- Extensive research has not shown any relevant genotoxic risk of paracetamol at therapeutic dose.
- Long-term studies in rats and mice showed no relevant carcinogenic effects at non-hepatotoxic doses of paracetamol.
- Paracetamol passes the placental barrier.
- Studies in animals have shown no reproductive toxicity.

6- PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Povidone
- Microcrystalline cellulose
- Maize starch
- Stearic acid

6.2 Incompatibilities

None known

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C, in original pack to protect from humidity.

6.5 Nature and contents of container

Each cardboard box contains 30 tablets, packed in PVC/Aluminium blister, with an instruction leaflet.

6.6 Special precautions for disposal and other handlings

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

7- MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1 Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2 Manufacturer

ATABAY İLAÇ FABRİKASI A.Ş., Acıbadem, Köftüncü Sokak No:1, 34718 Kadıköy, Istanbul, Turkey.

8- MARKETING AUHORISATION NUMBER

See list of MAs per country

9- DATE OF FIRST REGISTRATION

See list of MAs per country

10- DATE OF REVISION OF TEXT

February 2019