SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Farmalider 1000 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1000 mg of paracetamol.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.
The tablets are white, oblong, biconvex and scored on both sides.
The dimensions of the tablet are 21.4 mm (length) x 10.2 mm (width) x 8.4 mm (thickness).
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol Farmalider is indicated for symptomatic treatment of mild to moderate pain (e.g. headache, toothache, dysmenorrhea) and fever.

4.2 Posology and method of administration

Posology
Tablets are for oral administration.
Adults (including the elderly) and children aged 16 years and over: one tablet up to 4 times daily as required.
Not to be given to children under 16 years.
The minimum dosing interval is 4 hours and the maximum daily dose is 4000 mg (4 tablets)
Method of administration
Oral administration only.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

The stated dose should not be exceeded.

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

Patients should be advised to consult their doctor if:

- Symptoms persist
- Their headaches become persistent
- They suffer from non-serious arthritis and need to take painkillers every day

Paracetamol should be administered with caution under the following circumstances:

- Moderate & severe renal impairment
- Mild to moderate hepatic impairment (including Gilbert´s Syndrome)
- Non-cirrhotic alcoholic liver disease
- Severe hepatic impairment (child-pugh > 9)
- Acute hepatitis
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Alcohol abuse dehydration
- Chronic malnutrtition

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 malnutrition and 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.

This product should only be used by the person for whom it is prescribed when clearly necessary.

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 regular daily dose use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
- Concurrent use of paracetamol and chloramphenicol may result in chloramphenicol toxicity due to a decreased elimination of the latter.
- Some opioids (diamorphine, morphine, oxycodone, pentazocine and pethidine) delay gastric emptying so that the rate of absorption of oral paracetamol is reduced.

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)

<u>Effects on laboratory tests</u>

Intake of paracetamol can affect tests for uric acid by the phosphotungstic acid method and blood glucose tests by the glucose-oxidase-peroxidase method.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no malformative nor feto/neonatal toxicity of paracetamol. 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 administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, Paracetamol Farmalider may be used in breast-feeding women.

Fertility

There are insufficient fertility data available to indicate if paracetamol has any effect on fertility.

4.7 Effects on ability to drive and use machines

The influence of paracetamol on the ability to drive and use machines is null or insignificant. No effects have been described.

4.8 Undesirable effects

The most commonly reported adverse reactions during the period of use of paracetamol are: hepatotoxicity, renal toxicity, blood disorders, hypoglycaemia and allergic dermatitis.
The following frequencies are taken as a basis when evaluating undesirable effects:

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:

Very rare: Thrombocytopenia, agranulocytosis, leukopenia, neutropenia, haemolytic anaemia

Immune system disorders
Very rare: Angioedema

Metabolism and nutrition disorders:
Very rare: Hypoglycaemia
Not known: 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.

Vascular disorders:
Rare: Hypotension

Respiratory, thoracic and mediastinal disorders:
Rare: Bronchospasm* (analgesic asthma) in predisposed patients

Hepatobiliary disorders:
Rare: Increased hepatic transaminase levels
Very rare: Hepatotoxicity (jaundice)

Skin and subcutaneous tissue disorders:
Very rare cases of serious skin reactions such as Stevens Johnson syndrome and Toxic Epidermal Necrolysis have been reported.

Renal and urinary disorders:
Very rare: Sterile pyuria (cloudy urine), renal side effects (see section 4.4). Anuria, hematuria, interstitial nephritis

General disorders and administration site conditions:
Rare: Discomfort
Very rare: Hypersensitivity reactions that can vary between a simple skin rash or hives and anaphylactic shock

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

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 Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors

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 deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage 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, see the national drug database overdose section.

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 24h from ingestion should be discussed with the national poison control center or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesics and antipyretics: Anilides
ATC Code: N02BE 01

Paracetamol is an analgesic that also has antipyretic properties.

The exact mechanism of the action of paracetamol has not been fully elucidated, although it is known that it acts at Central Nervous System level and to a lesser extent by blocking the generation of painful impulse at peripheral level.

It is believed that paracetamol increases the pain threshold, inhibiting prostaglandin synthesis, by blocking of cyclooxygenases in the Central Nervous System (specifically the COX-3). However, paracetamol does not inhibit significantly the cyclooxygenases in peripheral tissues.

Paracetamol stimulates the activity of descending serotoninergic pathways that block the transmission routes of nociceptive signals to the spinal cord from peripheral tissues. Therefore, some experimental data indicate that the intraspinal administration of antagonists of different serotonin receptor subtypes can annul the antinociceptive effect of paracetamol.

The antipyretic action is related with the PGE_1 synthesis inhibition in the hypothalamus, physiological coordinating organ of the thermoregulation process.

5.2 Pharmacokinetic properties

Absorption

By oral administration its bioavailability is 75-85%.

It is absorbed widely and rapidly; maximum plasma concentration is reached according to the pharmaceutical form in 0.5-2 hours. The degree of binding to plasma proteins is 10%.

Distribution

The time that it takes to achieve maximum effect is 1 to 3 hours, and the action lasts for between 3 to 4 hours.

Biotransformation

The metabolism of paracetamol undergoes a hepatic first-pass effect, following linear kinetics. This linearity, however, disappears when doses over 2 g are administered.

Paracetamol is metabolised fundamentally in the liver (90-95%).

Elimination

Paracetamol is eliminated mainly in urine as a conjugate with glucuronic acid and to a lesser extent with sulphuric acid and cysteine; less than 5% is excreted unaltered. Its elimination half-life is 1.5-3 hours (increases in the case of overdose and in patients with hepatic insufficiency, geriatrics and children). High doses can saturate regular mechanisms of hepatic metabolism, which means that alternative metabolic pathways are used that give rise to hepatotoxic and possibly nephrotoxic metabolites by glutathione depletion.

Physiopathological variations:
Kidney failure: in case of severe kidney failure (creatinine clearance under 10 ml/min) the elimination of paracetamol and of its metabolites is delayed.
Elderly patients: the conjugation capacity is not modified. An increase in elimination half-life of paracetamol has been observed.

5.3 Preclinical safety data

Extensive studies revealed no evidence of a relevant genotoxic risk for paracetamol within the therapeutic, i.e. non-toxic, dose range.

Long-term studies on rats and mice do not indicate any relevant tumorigenic effects at non-hepatotoxic doses of paracetamol.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Besides that, 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

Pregelatinised starch (maize), stearic acid, povidone, crospovidone, microcrystalline cellulose and magnesium stearate (vegetable source)

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 storage conditions

6.5 Nature and contents of container

Containers with 1, 6, 8, 10, 12, 18, 20, 30, 32 and 100 tablets in an aluminium-PVC_PVDC blister pack.
Not all packs sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

FARMALIDER S.A.
C/ La Granja, 1,
28108 Alcobendas, Madrid
SPAIN

8 MARKETING AUTHORISATION NUMBER(S)

PL 35667/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/09/2017

10 DATE OF REVISION OF THE TEXT

03/04/2025