SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Arfen 500 mg, suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Arfen 500 mg suppositories: Each suppository contains 500mg paracetamol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppository
Arfen 500 mg suppositories: Arfen suppositories are creamy, smooth homogenous, torpedo shaped.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Arfen is indicated for the symptomatic treatment of clinical conditions that require an analgesic and/or an antipyretic, such as: headache, migraine with prior medical diagnosis, toothache, otalgia, fever, symptoms associated with flu-like conditions, menstrual pains (dysmenorrhea), traumatic, muscular, joint and osteoarthritis pains, as an analgesic before and after surgical interventions, hyperergic reaction after vaccination.

Arfen 500 mg suppositories are intended for rectal administration in adults (including the elderly) and children aged 12 years and over.

4.2. Posology and method of administration

Posology

Adults

The recommended dose depends on age and body weight.

Administration can be repeated at intervals of 6 to 8 hours. If necessary, the interval can be at least 4 hours, not exceeding 6 daily suppositories of Arfen 500 mg.

Arfen 500 mg suppositories: 1-2 suppositories 2 to 4 times per day.

The maximum daily dose of paracetamol should not exceed 4 g/day. Paracetamol is a frequent component of several drugs in combination. This should be taken into account so as not to exceed the maximum daily dose.

Paediatric population

Age	*Approx. body weight*	*Dose*	*Maximum daily dose (24 hours)*
12 – 16 years	40 – 50 kg	1 suppository of 500 mg	4 suppositories (equivalent to 2000 mg paracetamol)
16 – 18 years	>50 kg	1 – 2 suppositories of 500 mg	6 suppositories (equivalent to 3000 mg paracetamol)

For children under the age of 12 and body weight less than 40 kg, other forms of presentation are available that contain more adequate amounts of paracetamol.

The maximum daily dose of paracetamol should not exceed 3 g/day. Paracetamol is a frequent component of several drugs in combination. This should be taken into account so as not to exceed the maximum daily dose.

Hepatic impairment

In patients with hepatic impairment or Gilbert's disease, the dose should be reduces or the administration intervals extended.

Renal impairment

In the case of renal failure, the dose should be decreased.

Glomerular filtration	*Dose*
10-50 ml/min	500 mg every 6 hours
< 10 ml/min	500 mg every 8 hours

Method of administration

Intrarectal use.

Arfen suppositories should not be taken for more than 10 days or high doses.

If they softened, they shall be flushed with cold water before removing from the foil package. Do not break suppository before administration.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Severe liver disease.
Disorders of haematopoiesis.

4.4. Special warnings and precautions for use

At therapeutic doses, paracetamol is relatively non-toxic. However, it is possible for allergic skin reactions to appear, even anaphylactic situations.

Arfen should be administered with caution to patients with asthma who are allergic to acetylsalicylic acid, as mild bronchospasm reactions have been reported with paracetamol use (cross-reaction).

Arfen should not be combined with other analgesic medications that contain paracetamol (eg. combination drugs).

Taking multiple daily doses in a single administration can severely injure the liver. Cases of hepatic necrosis have been reported in patients who received high doses of paracetamol.
Caution is advised when administering paracetamol to patients with moderate to severe renal impairment, mild to moderate hepatic impairment (including Gilbert's syndrome), severe hepatic impairment (Child-Pugh >9), acute hepatitis, concomitant treatment with drugs that affect liver function, glucose-6-dehydrogenase deficiency, haemolytic anaemia, alcoholism, dehydration and chronic malnutrition.
The risk of overdose is greater in those with liver disease of non-cirrhotic alcoholic origin. Precautions should be taken in cases of chronic alcoholism. In this case, the daily dose should not exceed 2 grams. Alcohol should not be used during treatment with paracetamol.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

The maximum daily dose of suppositories should not be exceeded. Prolonged or frequent administration of this medicine is not recommended. Prolonged use of this medication can cause renal impairment. Prolonged use of painkillers, or inappropriate use of high doses, can cause headache, which should not be treated with increased doses of the drug.

In situations of high fever (over 39ºC), fever lasting more than 3 days or recurrent fever, paracetamol should not be used, as these situations may indicate a serious illness that needs additional medical assessment.

4.5. Interactions with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Studies have shown that paracetamol use may enhance the effect of warfarin. The effect appears to increase with paracetamol dose, but can occur at doses of 1.5 to 2.0 g of paracetamol per day, used for at least 5-7 days. Single doses of paracetamol in normal doses are not considered to have any effect.

The long-term use of this medicine in patients receiving treatment with oral anticoagulants should only be carried out under medical supervision. The potentiation of the effects of warfarin was observed with the continued use of high doses of paracetamol.

Concomitant administration of paracetamol and zidovudine enhances the tendency to develop neutropenia. Caution is advised if paracetamol is taken simultaneously with zidovudine.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).

Pharmacokinetic interactions

Effects of other drugs on the pharmacokinetics of paracetamol

Enzyme-inducing drugs, such as certain sedatives and anticonvulsants (phenytoin, phenobarbital, carbamazepine) has been shown in pharmacokinetic studies to reduce the plasma AUC of paracetamol to approx. 60%

Other substances with enzyme-inducing properties, eg. rifampicin and St John's wort (*hypericum*) are also suspected of causing lowered concentrations of paracetamol.

There is a higher risk of liver damage in patients treated with maximum recommended dose of paracetamol and enzyme-inducing drugs.

When administered concomitantly with medicinal products that cause an induction of the cytochrom P450 enzyme system in the liver, such as certain hypnotics/sedatives and antiepileptics

(phenobarbital, phenytoin, carbamazepine) and rifampicin, a potential toxic metabolite is formed and liver impairment may occur under the application of otherwise harmless doses of the active substance paracetamol.

Probenecid almost halves the clearance of paracetamol by inhibiting its conjugation with glucuronic acid. This means that the dose of paracetamol can be halved by concomitant treatment with probenecid.

The rate of absorption of paracetamol may be increased by metoclopramide, but the substances may be administered in combination.

The absorption of paracetamol reduced by cholestyramine. Cholestyramine should not be given within an hour of maximum analgesic effect is achieved.

Effects of paracetamol on the pharmacokinetics of other drugs
Paracetamol may delay the excretion of chloramphenicol, increasing its plasma concentrations and causing an increased risk of toxicity. Therefore, analysis of chloramphenicol in plasma is recommended in case of combination therapy with chloramphenicol for injection.

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
Paracetamol is excreted in human milk, but the risk of affecting the child appears unlikely at therapeutic doses.
After a single dose of 650 mg, an average concentration of 11 µg/ml was measured in breast milk. Since no adverse effects have been demonstrated in infants, as a rule during treatment with paracetamol, it is not necessary to interrupt breastfeeding.

4.7. Effects on ability to drive and use machines

Paracetamol does not interfere with the ability to drive or use machines.
However, it must be taken into account that during treatment with paracetamol may be observed as undesirable effects, mild drowsiness and dizziness.

4.8. Undesirable effects

Paracetamol is generally very well tolerated when administered at the recommended therapeutic doses.

The frequencies are as follows: very common (≥1/10); common ≥1/100, <1/10); uncommon (≥ 1/1 000 <1/100); rare (≥ 1/10 000, <1/1000); very rare (<1/10 000).

Blood and lymphatic system disorders
Very rare: Thrombocytopenia, neutropenia, leukopenia and hemolytic anemia, isolated cases of agranulocytosis, pancytopenia.

Immune system disorders
Very rare: Anaphylaxis, allergic reactions, exacerbated hypersensitivity reactions to paracetamol (Quincke's oedema, dyspnoea, sweating accesses, nausea, drop in blood pressure, even shock).

Nervous system disorders
Common: Slight drowsiness.
Uncommon: Dizziness, drowsiness, nervousness.

Respiratory, thoracic and mediastinal disorders
Uncommon: Pharyngeal burning sensation.
Very rare: Bronchospasm (analgesic asthma).

Gastrointestinal system disorders
Common: Nausea, vomiting.
Uncommon: Diarrhoea, abdominal pain (including cramps and burning), constipation.

Hepatobiliary disorders
Rare: Elevated liver transaminase.
Very rare: Liver damage. Liver damage occurred with alcohol abuse.

Skin and subcutaneous tissue disorders

Rare: Rash, urticaria, angioedema.

Very rare: Allergic dermatitis.

Very rare cases of serious skin reactions have been reported.

Renal and urinary disorders

Very rare: Renal effects

Despite methodological failures, clinical/epidemiological data seem to indicate that long-term administration of analgesics can cause nephropathy, including papillary necrosis.

General disorders and administration site conditions

Common: Redness (erythema) of the rectal mucosa.

Uncommon: Headache, perspiration/sweating, hypothermia.

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 the national reporting system.

4.9. Overdose

Symptoms

In case of a paracetamol overdosage, the conjugation in the liver becomes saturated and a larger proportion of paracetamol dose is metabolized oxidatively. If glutathione deposits are emptied, the reactive intermediate metabolite will bind irreversibly to liver macromolecules. Therefore, it is very important to administer the antidote as soon as possible after toxic doses, in order to prevent or stop the liver injury.

Excessive high doses of paracetamol can lead to signs of intoxication with a latency of 24 to 48 hours. Patients may develop liver function dysfunction, hepatocellular necrosis and liver coma (which can be fatal). Acute renal failure can occur as a result of liver failure or, rarely, in the absence of it.

The following symptoms of paracetamol overdose may occur:

- During phase I, which lasts between 12 to 14 hours after overdose, patients can often experience nausea, vomiting, sweating, drowsiness and malaise.
- During phase II, after 24 to 48 hours, there is a subjective improvement in symptoms, but the first signs of liver damage begin to appear: slight abdominal pain, hepatomegaly, increased levels of transaminases and bilirubin, prolonged prothrombin time and oliguria.

- During phase III, after 48 hours, the levels of transaminases reach their maximum, jaundice, coagulopathy, hypoglycemia, progression to hepatic coma.

Kidney damage may occur. Pancreatitis and toxic myocardial injury with arrhythmias and heart failure have been reported.

Toxicity

The toxic dose for children and adults is generally >140 mg/kg.

5 g during 24 hours in a child aged 3 1/2 years, 15-20 g in adults caused fatal intoxication. Malnutrition, dehydration, medication with enzyme-inducing drugs such as some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine), rifampicin and St. John's wort (hypericum), and chronic excessive alcohol consumption are risk factors and even slight overdosage can then cause marked liver damage. Even sub-acute "therapeutic" overdose has resulted in severe intoxication with doses varying from 6 g/24 hours for a week, 20 g for 2-3 days etc.

Management

Adequate control of paracetamol overdose requires immediate treatment. Despite the absence of early symptoms, patients should be referred to the emergency room for immediate treatment.

Emergency treatment in cases of overdose with paracetamol consists of gastric emptying by aspiration or gastric lavage and administration of activated charcoal (only if the antidote is administered via IV, because orally the activated charcoal prevents the absorption of the antidote), when intoxication occurred less than 4 hours ago and in a dosage equal to or greater than 10 g.

Since the amount of paracetamol ingested is generally uncertain and unreliable for the therapeutic approach, the plasma concentration of paracetamol should be determined as soon as possible, but never before 4 hours after ingestion (to ensure that the concentration maximum occurred). Specific treatment with the antidote, acetylcysteine, should be administered immediately (should not wait for laboratory results to start intoxication therapy) if it has occurred less than 24 h since ingestion. The results are optimal if acetylcysteine is administered in the first 16 h, particularly in the first 8 h. However, there are reports of therapeutic success even when acetylcysteine administration was started 36 hours after ingestion of paracetamol.

The loading dose of acetylcysteine administered orally is 140 mg/kg, followed by an oral maintenance dose of 70 mg/kg every 4 hours for 17 doses.

If the patient is unable to retain acetylcysteine due to vomiting, the placement of a duodenal tube allows the administration of acetylcysteine. If intravenous acetylcysteine is chosen, the starting dose is

150 mg/kg body weight for 15 minutes, followed by 50 mg/kg for 4 hours and then 100 mg/kg for the next 16 hours. Another alternative is the administration of 2.5 g of methionine p.o., every 4 hours for a total of 4 doses, if the patient does not vomit and is conscious.
Patients with liver failure should be given an IV glucose solution to prevent hypoglycaemia.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Other analgesics and antipyretics, ATC code: N02BE01

Paracetamol is an aniline derivative with analgesic and antipyretic properties equivalent to acetylsalicylic acid. In contrast to aspirin it is less irritant to the stomach and it and is well tolerated by patients with ulcers. Paracetamol does not affect thrombocyte aggregations or bleeding time and is generally well tolerated by patients with hypersensitivity to aspirin.

The analgesic effect is probably related to the fact that paracetamol molecule can capture and neutralize free OH- and O - radicals, which result in tissue injury.

Paracetamol does not inhibit the enzyme prostaglandin synthetase (which NSAIDs do). It is however possible that the analgesic effect may partly be explained by different impact on the synthesis of prostaglandins and leukotrienes.

The antipyretic effect may be explained by the influence of temperature regulating centers of the CNS, thereby increasing heat dissipation.

Analgesic effect is achieved after about ½ hour, the maximum effect is achieved within 1-2 hours and the duration is 4-5 hours. The antipyretic effect is slower. Therefore the maximum effect is achieved within ½ -1 hours, the maximum temperature reduction is obtained after 2-3 hours and the duration is approximately 8 hours (for tablets, effervescent tablets, oral solution, oral powder).

5.2. Pharmacokinetic properties

Paracetamol is well absorbed after oral or rectal administration. Within 2-3 hours after rectal administration peak serum concentrations can be achieved. The bioavailability (AUC) is basically the same as for the corresponding tablet intake. Plasma half-life is approximately 2 hours.

Paracetamol is primarily metabolized in the liver by conjugations with glucuronic acid (approx.. 60%), sulfuric acid (35%), cysteine (3%) and mercapturic acid. A small amount (about 3-10% of a therapeutic dose) is metabolized by oxidation and the reactive intermediate metabolite thus formed is bound preferentially to the liver glutathione and excreted as cysteine and mercapturic acid conjugates.

Excretion occurs via the kidneys. 2-3 % of a therapeutic dose is excreted unchanged; 80-90% as glucuronide and sulphate and a smaller amount as cysteine and mercapturic acid derivatives.

5.3. Preclinical safety data

In animal experiments on the acute, sub-chronic and chronic toxicity of paracetamol, in rats and mice, lesions in the gastrointestinal tract, changes in blood count and lesions of the hepatic and renal parenchyma appeared. These changes are attributable to the mechanism of action of paracetamol and its metabolism. The metabolites to which the toxic effects and changes in the corresponding organs are attributable have also been demonstrated in humans.
Consequently, paracetamol should not be administered in high doses over long periods of time.

Paracetamol in high concentrations is genotoxic, *in vivo* and *in vitro*. The genotoxic activity of paracetamol depends on several mechanisms, but non-toxic or therapeutic doses do not reach the threshold for its triggering.

Prolonged dietary studies have shown that paracetamol is not carcinogenic in non-hepatotoxic doses in rats and mice. Considering the knowledge about hepatotoxicity, metabolism and the threshold of mechanisms associated with paracetamol genotoxicity, animal studies do not suggest carcinogenic potential in humans at non-hepatotoxic doses.

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

Studies in mice and rats did not reveal a teratogenic or fetotoxic effect of paracetamol. The drug showed adverse effects on mouse spermatogenesis, when administered in high doses over two generations.

Paracetamol crosses the placenta.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Soya lecithin
Hard fat (witepsol)

6.2. Incompatibilities

None known.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

Store below 25ºC, in the original package, in order to protect from light and moisture.

6.5. Nature and contents of container

Cream smooth homogenous suppositories of uniform texture
PVC – Aluminum blisters.

Packs of 10 suppositories.

6.6. Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

05101/07219/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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8/04/2022