PACKAGE INSERT – ARFEN

1. NAME OF THE MEDICINAL PRODUCT

Arfen 125 mg, suppositories
Arfen 250 mg, suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Arfen 125mg: Each suppository contains 125mg paracetamol.
Arfen 250mg: Each suppository contains 250mg paracetamol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppository
Arfen 125mg and 250mg suppositories are creamy, smooth homogenous and torpedo shaped.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the treatment of mild to moderate pain and pyrexia in children:
Arfen 125 mg is indicated in children aged 1 to 5 years.
Arfen 250 mg is indicated in children aged 6 to 12 years.
Arfen suppositories may be especially useful in patients unable to take oral forms of paracetamol, e.g. post-operatively or with nausea and vomiting.

4.2. Posology and method of administration

Posology
Paediatric population

Children 1 to 5 years (125 mg suppositories)

The dosage should be based on age and weight i.e.	
1 year (10 Kg)	125mg (1 suppository)
5 years (20 Kg)	250mg (2 suppositories)

Children 6 to 12 years (250 mg suppositories)

The dosage should be based on age and weight i.e.	
6 years (20 Kg)	250mg (1 suppository)
12 years (40 Kg)	500mg (2 suppositories)

Method of administration
Intrarectal use.
These doses may be repeated up to a maximum of 4 times in 24 hours. The dose should not be repeated more frequently than every 4 hours. The recommended dose should not be exceeded. Higher doses do not produce any increase in analgesic effect. Only whole suppositories should be administered – 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.

4.4. Special warnings and precautions for use

- Arfen should not be combined with other analgesic medications that contain paracetamol (e.g. combination drugs).
- Paracetamol should be given with care to patients with impaired kidney or liver function. Doses higher than those recommended involve a risk of very severe liver damage. Liver damage is also associated with certain risk factors (see also section 4.5, and section 4.9). If liver damage is suspected then liver function tests should be performed.

- Allergy alert: Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash. This could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away.

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.

Pharmacokinetic interactions

Effects of other drugs on the pharmacokinetics of paracetamol

- Enzyme-inducing drugs, such as certain 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.
- In addition there is a higher risk of liver damage in patients treated with maximum recommended dose of paracetamol and enzyme-inducing drugs.
- 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 Arfen on the pharmacokinetics of other drugs*
- Acetaminophen may affect chloramphenicol pharmacokinetics. Therefore, analysis of chloramphenicol in plasma is recommended in case of combination therapy with chloramphenicol for injection.

4.6. Fertility, pregnancy and lactation

Pregnancy

No known risks when used during pregnancy.

Breast-feeding

Paracetamol is excreted in human milk, but the risk of affecting the child appears unlikely at therapeutic doses.

4.7. Effects on ability to drive and use machines

Arfen treatment has no effect on alertness.

4.8. Undesirable effects

Side-effects at therapeutic doses are rare.

Frequency	System Organ Class (SOC)	Event
Common (≥1/100 to <1/10)	Gastrointestinal disorders	Redness of the rectal mucous membranes
Rare (≥1/10,000 to <1/1,000)	Immune system disorders	Allergic reaction
	Hepatobiliary disorders	Liver damage
	Skin and subcutaneous tissue disorders	Exanthema, urticaria, angioedema
	Investigations	Increase in creatinine (mostly secondary to hepatorenal syndrome)

Very rare cases of serious skin reactions have been reported.

Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported.

There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Hepatic necrosis may occur after overdosage (see below).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions is an important way to gather more information to continuously monitor the benefit / risk balance of the medicinal product. Any suspected adverse reactions should be reported via the national reporting system.

4.9. Overdose
Toxicity
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.

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
- is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

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.
Initially after the intake and during the first days, symptoms like abdominal pain, nausea and vomiting may occur. Clinical symptoms of liver damage manifests itself usually only after a couple of days and culminates usually after 4-6 days.
Kidney damage may occur. Pancreatitis and toxic myocardial injury with arrhythmias and heart failure have been reported.

Management
Careful monitor liver and kidney function, coagulation, fluids and electrolytes status.

Acetylcysteine is the antidote for paracetamol overdosage and acetylcysteine administration started within 8-10 hours after paracetamol use gives full protection against liver damage, then the effect disappears.
Acetylcysteine may provide some protection even after 10 hours but on prolonged administration. Acetylcysteine reduces the mortality at manifested paracetamol induced liver failure. Liver and kidney failure therapy is often required in cases where the time for effective antidote administration is exceeded and paracetamol toxic concentrations are present. Hemoperfusion may under certain circumstances be indicated. In extreme cases, liver transplantation may also be considered.

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
Absorption
Paracetamol is well absorbed by both oral and rectal routes. Peak plasma concentrations occur about 2 to 3 hours after rectal administration. The plasma half life is about 2 hours.
Biotransformation
Paracetamol is primarily metabolised in the liver by conjugation to glucuronide and sulphate. A small amount (about 3-10% of a therapeutic dose) is metabolised by oxidation and the reactive intermediate metabolite thus formed is bound preferentially to the liver glutathione and excreted as cysteine and mercapturic acid conjugates.
Elimination
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
There are no preclinical data of relevance to safety beyond those already included in the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Arfen 125mg and 250mg suppositories:
Hard fat and Soya lecithin

6.2. Incompatibilities
None known.

6.3. Shelf life
5 years

6.4. Special precautions for storage
Store below 30°C, in the original package, in order to protect from light and moisture.

6.5. Nature and contents of container
Arfen 125mg and 250mg suppositories are packed using aluminium – aluminium strips.
Boxes of 20 and 100 suppositories are available.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling
None.

7. PRODUCT REGISTRATION HOLDER

Komedic Sdn Bhd, 4 Jalan PJS 11/14, Bandar Sunway, 46150 Petaling Jaya

8. MANUFACTURER

Medochemie Ltd (Cogols Facility), 1-10 Constantinoupoleos Street, 3011 Limassol, Cyprus

9. PRODUCT REGISTRATION NUMBER

Arfen 125mg: MAL19921171XZ
Arfen 250mg: MAL19921172XZ

10. DATE OF REVISION OF THE TEXT

February 2022