SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alvedon Suppositories 125 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alvedon Suppositories 125 mg: Each suppository contains Paracetamol 125 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppositories

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of mild to moderate pain and pyrexia in children:

Alvedon 125 mg is indicated in children aged 1 to 5 years.

Alvedon 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

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)

Method of administration
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 paracetamol or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Alvedon Suppositories should not be combined with other analgesic medications that contain paracetamol. 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 Interaction with other medicinal products and other forms of interaction, and Section 4.9 Overdose). If liver damage is suspected then liver function tests should be performed.

Do not exceed the recommended dose. If symptoms persist consult your doctor. Keep out of the sight and reach of children.

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 in patients with malnutrition or 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.

Label and Leaflet will state the following warnings:

Label:
“Immediate medical advice should be sought in the event of an overdose, even if the child seems well”.

“Do not give with any other paracetamol-containing products.”

Leaflet:

"Immediate medical advice should be sought in the event of an overdose, even if the child seems well, because of the risk of delayed, serious liver damage."

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which induce hepatic microsomal enzymes such as alcohol, barbiturates and other anticonvulsants, may increase the hepatotoxicity of paracetamol, particularly after overdosage.

The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding. The effect appears to increase as the dose of paracetamol is increased, but can occur with doses as low as 1.5–2 g paracetamol per day for at least 5–7 days. Occasional doses have no significant effect.

Probenicid inhibits the glucuronidation of paracetamol which can affect the clearance of paracetamol. This should be considered when these medicines are administered concomitantly.

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)

Paracetamol may affect the pharmacokinetics of chloramphenicol. This interaction should be considered when these medications are administered concomitantly, especially in malnourished patients.

Enzyme-inducing medicines, such as some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine, primidone) have been shown in pharmacokinetic studies to reduce the plasma AUC of paracetamol to approx. 60 %. Other substances with enzyme-inducing properties, e.g. rifampicin and St. John's wort (hypericum) are also suspected of causing lowered concentrations of paracetamol. In addition, the risk of liver damage during treatment with maximum recommended doses of paracetamol will be higher in patients being treated with enzyme-inducing agents.

4.6 Fertility, pregnancy and lactation

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.

Paracetamol is excreted in breast milk but not in clinically significant amounts.

Available published data do not contraindicate breast-feeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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)
Not known (cannot be estimated from the available data)	Metabolism and nutrition disorders	High anion gap metabolic acidosis

Side-effects at therapeutic doses are rare.

Description of selected adverse reactions

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.

Very rare cases of serious skin reactions 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 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 Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Toxicity
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).

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
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 administration and clinical symptoms generally culminate after 4 to 6 days. 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 clinically significant early symptoms, patients should be referred urgently to hospital for immediate medical attention. This is because early 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 BNF overdose section.

As concentrations soon after paracetamol ingestion are unreliable, plasma paracetamol concentration should be measured at 4 hours or later after the initial administration. Treatment with N-acetylcysteine may be used for up to 24 hours after administration of paracetamol; however, the maximum protective effect is only obtained up to 8 hours post-administration. The effectiveness of this antidote declines sharply after this 8 hour time period. If required, the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If

vomiting is not a problem, then oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of those patients presenting with serious hepatic dysfunction 24 hours after paracetamol administration should be discussed with the National Poisons Information Centre (NPIS) or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides

ATC code: N02BE01

Paracetamol is an aniline derivative with analgesic and antipyretic actions similar to those of aspirin but with no demonstrable anti-inflammatory activity. Paracetamol is less irritant to the stomach than aspirin. It does not affect thrombocyte aggregation or bleeding time. Paracetamol is generally well tolerated by patients hypersensitive to acetylsalicylic acid.

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 cystein 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 cystein and mercapturic acid derivatives.

5.3 Preclinical safety data

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

Hard fat (Witepsol H12)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/polyethylene blister strips each containing 5 suppositories. Packs of 5 or 10 suppositories.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Peel the wrapper apart to remove the suppository, gently push into the rectum pointed end first.

7. Marketing Authorisation holder

Esteve Pharmaceuticals Ltd
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Maidenhead
Berkshire

SL6 6PT

8 MARKETING AUTHORISATION NUMBER(S)

PL 17509/0071

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28/28/2002

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