Product Summary

1. Trade Name of the Medicinal Product

Calpol Six Plus Fastmelts (250 mg Orodispersible Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paracetamol 250 mg
Excipients: also contains mannitol (E421), aspartame ((E951) contains 8mg aspartame per tablet), benzyl alcohol and glucose.
For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Orodispersible tablet

Round, white, bi-convex tablets with central concave depression.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Calpol Six Plus Fastmelts is indicated for the treatment of mild to moderate pain and as an antipyretic. It can be used in many conditions including headache, toothache, earache, sore throat, colds and influenza, aches and pains and post-immunisation fever.

4.2 Posology and method of administration

Oral:
Tablets should be placed in the mouth where they melt on the tongue. The tablet will rapidly disperse to a pleasant tasting paste that can be easily ingested. Alternatively the tablet can be dispersed in a teaspoonful of water or milk.

Adults and children

Child's Age	How Much	How often (in 24

		hours)
Under 6 years	Not recommended	N/A
6 - 9 years	1 tablet	4 times
9 - 12 years	2 tablets	4 times
12 – 16 years	2 to 3 tablets	4 times
Adults and children over 16 years	2 to 4 tablets	4 times
• Do not give more than 4 doses in any 24 hour period • Leave at least 4 hours between doses • Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist		

Use in the Elderly
Normal adult dosage is appropriate. However, a reduction in dosing may be necessary in frail, elderly subjects (see Section 5.2).

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

Do not exceed the recommended dose. Taking more than the recommended dose (overdose) may cause liver damage. In case of overdose, get medical help straight away. Quick medical attention is critical for adults as well as children even if signs or symptoms are not noticed.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Chronic alcohol users should consult a doctor before use.

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.

Calpol Six Plus Fastmelts contains 8 mg aspartame, which is a source of phenylalanine equivalent to 0.04 mg/250 mg tablet. The phenylalanine in the tablets may be harmful to people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Calpol Six Plus Fastmelts contain mannitol, which may have a mild laxative effect.

This medicine contains 0.0011 g of glucose in each tablet. Patients with rare glucose-galactose malabsorption should not take this medicine.

This medicine contains 0.00064 mg benzyl alcohol in each tablet. Benzyl alcohol may cause allergic reactions. Ask your doctor or pharmacist for advice if you are pregnant or breastfeeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis")."

Patients should be informed about the signs of serious skin reactions and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Taking this product with other paracetamol-containing medicines could lead to overdose and should therefore be avoided.

<u>The label contains the following statements:</u>
Contains paracetamol.
Do not give anything else containing paracetamol while giving this medicine.
Do not give more medicine than the label tells you to. If your child does not get better, talk to your doctor.
For oral use only
Do not give more than 4 doses in any 24 hour period.
Leave at least 4 hours between doses.
Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist
As with all medicines, if your child is currently taking any other medicine consult your doctor or pharmacist before using this product.
Keep out of the sight and reach of children.
Talk to a doctor at once if your child takes too much of this medicine, even if they seem well.

<u>The leaflet contains the following statements:</u>
Talk to a doctor at once if your child takes too much of this medicine, even if they seem well. This is because too much paracetamol can cause delayed, serious liver damage.

Very rare cases of serious skin reactions have been reported. Symptoms may include:
- Skin reddening
- Blisters

- Rash

If skin reactions occur or existing skin symptoms worsen, stop use and seek medical help right away.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which induce hepatic microsomal enzymes
Metabolism of paracetamol possibly accelerated by carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone (also isolated reports of hepatotoxicity).

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

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).

Chronic alcohol intake can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol. Acute alcohol intake may diminish an individual's ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged.

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.

When given to the mother in therapeutic doses (1 g single dose), paracetamol crosses the placenta into foetal circulation as early as 30 minutes after ingestion and is metabolised in the foetus by conjugation with sulfate and increasingly with glutathione.

Breast-feeding
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast-feeding.

Fertility
There is no information relating to the effects of this medicine on fertility.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with paracetamol are listed below by System Organ Class (SOC). The frequencies are defined according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available, or 2) when incidence is unavailable, frequency category is listed as 'Not known'.

System Organ Class (SOC)	**Frequency**	**Adverse Drug Reaction (Preferred Term)**
Blood and lymphatic system disorders	Not known	Blood disorder (including thrombocytopenia and agranulocytosis)[1]
Immune system disorders	Very rare	Anaphylactic reactions
	Very rare	Hypersensitivity
Hepatobiliary disorders	Not known	Liver injury[2]
Skin and subcutaneous tissue disorders	Very rare	Rash
	Not known	Fixed eruption
	Not known	Rash pruritic
	Not known	Urticaria
Renal and urinary disorders	Uncommon	Nephropathy toxic
	Not known	Renal papillary necrosis[3]
Investigations	Not known	Transaminases increased[4]
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis

1. Reported following paracetamol use, but not necessarily causally related to the drug.
2. Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year.
3. Reported after prolonged administration.

4.Low level transaminase elevations may occur in some patients taking therapeutic doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.

Very rare cases of serious skin reactions have been reported.

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of their disease improved after paracetamol withdrawal.

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.

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 at: *www.mhra.gov.uk/yellowcard* or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Liver damage is possible in adults and adolescents (≥12 years of age) who have taken 7.5g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. 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 carbamezepine, Phenobarbital, 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 overdose in the first 24 hours are pallor, nausea, hyperhidrosis, malaise, vomiting, anorexia and abdominal pain. Liver damage may

become apparent 12 to 48 hours after ingestion. This may include hepatomegaly, liver tenderness, jaundice, acute hepatic failure and hepatic necrosis. Abnormalities of glucose metabolism and metabolic acidosis may occur. Blood bilirubin, hepatic enzymes, INR, prothrombin time, blood phosphate and blood lactate may be increased. 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.

Haemolytic anaemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Haemolysis has been reported in patients with G6PD deficiency, with use of paracetamol in overdose.

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 the overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF 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 NPIS or a liver unit.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other Analgesics and Antipyretics (Anilides)
ATC Code: N02 BE01

Paracetamol has analgesic and antipyretic effects similar to those of aspirin and is useful in the treatment of mild to moderate pain.

5.2 Pharmacokinetic Properties

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract. Peak plasma concentrations are reached 30-90 minutes post dose.

Paracetamol is distributed rapidly throughout all tissues. Protein binding is low.

The plasma half-life is in the range of 1 to 4 hours after therapeutic doses.

Following therapeutic doses 90-100% of the drug is recovered in the urine within 24 hours almost entirely following hepatic conjugation with glucuronic acid (about 60%), sulphuric acid (about 35%) or cysteine (about 3%). Small amounts of hydroxylated and deacetylated metabolites have also been detected. Children have less capacity for glucuronidation of the drug than do adults. In overdose there is increased N-hydroxylation followed by glutathione conjugation. When the latter is exhausted reaction with hepatic proteins is increased leading to necrosis.

In the elderly, the rate and extent of paracetamol absorption is normal but plasma half-life is longer and paracetamol clearance is lower than in young adults.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, and carcinogenicity.

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

Mannitol (E421)
Crospovidone
Aspartame (E951)
Strawberry flavouring E. 9620941 (containing benzyl alcohol and glucose)
Magnesium stearate
Basic butylated methacrylate copolymer
Polyacrylate dispersion 30%
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Strip containing 24 tablets.

The blister consists of a blister complex (Polyamide/PVC/Aluminium) and either: an aluminium sealing sheet
or
a paper/aluminium child resistant sealing sheet.

6.6. Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

McNeil Products Limited
50 – 100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
UK

8. MARKETING AUTHORISATION NUMBER

PL 15513/0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/03/2009

10 DATE OF REVISION OF THE TEXT

20/03/2025