DRAFT REGULATORY - for text and graphics regulatory submission

Panadol®

Panadol Caplet 500mg Optizorb Formulation

Each caplet contains 500mg paracetamol, pregelatinised starch, magnesium stearate, carnauba wax, calcium carbonate, alginic acid, blend of sodium parabens, crospovidone, povidone (K-25), colloidal anhydrous silica and opadry white.

Product Description
White to off-white film-coated capsule-shaped caplet. Circled P embossed on one side, breakline on the other.

Indication
Paracetamol is an analgesic and an antipyretic.
Relief of fever.
Relief of headache, migraine, sore throat, fever and toothache.

Recommended Dose
• Do not exceed the stated dose.
• The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.
• Minimum dosing interval: 4 hours
• Maximum daily dose: 4000mg (8 tablets)

Adults (including the elderly) and children aged 12 years and over:
1 to 2 caplets (500mg to 1000mg paracetamol), taken every 4 to 6 hours as required.

Children 6 to 11 years:
No more than 4 doses in any 24-hour period.
Maximum duration of continued use without medical advice: 3 days.
Maximum daily dose: 60mg/kg to be administered in divided doses of 10-15 mg/kg throughout the 24-hour period.
Children 6 to 8 years: ½ caplet (250mg)
Children 9 to 11 years: 1 caplet (500mg)

Children under 6 years:
Not recommended for children under the age of 6 years.

Renal Impairment:
Patients who have been diagnosed with renal impairment must seek medical advice before taking this medication. The restrictions related to the use of paracetamol products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug (see Warnings and Precautions).

Hepatic Impairment:
Patients who have been diagnosed with liver impairment must seek medical advice before taking this medication. The restrictions related to the use of paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (see Warnings and Precautions).

Route of Administration
Oral administration only

Contraindication
Do not use if you are allergic to paracetamol or any of the other ingredients in the product.

Warning and Precautions
Do not take more than the recommended dose as it may cause serious harm to your liver.

Check with your doctor before use if you:
- Have liver or kidney problems
- Are underweight or malnourished.
- Regularly drink alcohol.

You may need to avoid using this product altogether or limit the amount of paracetamol that you take.

Check with your doctor before use if you:
- Have a severe infection, are severely malnourished, severely underweight or are a chronic heavy alcohol user as this may increase the risk of metabolic acidosis. Signs of metabolic acidosis include:
- Deep, rapid, difficult breathing
- Feeling sick (nausea), being sick (vomiting)
- Loss of appetite

Contact a doctor immediately if you get a combination of these symptoms.

Please see your doctor if your symptoms do not improve.

Keep out of sight and reach of children / Jauhkan daripada kanak-kanak.

Always read and follow the label.

This preparation contains PARACETAMOL. Do not take any other paracetamol containing medicines at the same time.

ALLERGY ALERT: Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters and rash. These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away.
Each caplet contains Paracetamol 500mg, 0.2% w/w sodium parabens (preservative).
Sodium methyl-, sodium ethyl- and sodium propyl-parahydroxybenzoates (E219, E215, E217) may cause allergic reactions (possible delayed).

Interactions With Other Medicaments
Before taking this medicine, make sure you consult your doctor if you are taking warfarin or similar medicines used to thin the blood. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Pregnancy and Lactation
Pregnancy
As with the use of any medicine during pregnancy, pregnant women should seek medical advice before taking paracetamol. The lowest effective dose and shortest duration of treatment should be considered.

Lactation
Paracetamol is excreted in breast milk but not in a clinically significant amount at recommended dosages. Available published data do not contraindicate breastfeeding.

Side Effects
Stop taking this medicine and tell your doctor immediately if:
• you experience allergic reactions such as skin rash or itching, sometimes with breathing problems or swelling of the lips, tongue, throat or face.

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PHARMA CODE REF. IS:

Version: 1	gsk
Harmony AMS Artwork Information Panel	
AMS Document Number: DFT-00360-2487109	
Manufacturing Site(s): GSK_Kuala Lumpur_MALAYSIA	
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Sub Brand: OPTIZORB	
Variant: N/A	
Approving Market(s): MALAYSIA	
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Smallest Text Size: 7pt	
Leading: 7.5pt	
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175 mm Measuring Bar

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Design 1:

Total Colours & Varnishes: 1

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Total Special Finishes: 0

Colour Standard Reference:
For colour, please match to Industry Standard Pantone values

Material Type: White Paper	SUBSTRATE

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NOTE TO MARKET

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IMPORTANT

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• you experience a skin rash or peeling, or mouth ulcers.
• you have previously experienced breathing problems with aspirin or non-steroidal anti-inflammatories, and experience a similar reaction with this product.
• you experience unexplained bruising or bleeding.
These reactions are rare.

From post marketing data, the reactions below are very rare: Thrombocytopaenia, Anaphylaxis, cutaneous hypersensitivity reactions including, among others, skin rashes, angioedema, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis, Bronchospasm in patients sensitive to aspirin and other NSAIDs, Hepatic dysfunction.

Symptoms and Treatment of Overdose
If you take more of the medicine than you should, seek medical advice immediately even if you do not have any symptoms because of the risk of liver failure.

Symptoms and Signs
Paracetamol overdose may cause liver failure which can lead to liver transplant or death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity.

Treatment
Immediate medical management is required in the event of overdose, even if symptoms of overdose are not present.

If overdose is confirmed or suspected, seek immediate advice from National Poison Centre and refer patient to nearest Emergency Medical Centre for management and expert treatment. This should happen even in patients without symptoms or signs of overdose due to the risk of delayed liver damage.

Administration of N-acetylcysteine or methionine may be required.

National Poison Centre (Phone: +604-657 0099, Website: www.prn.usm.my, Email: prnnet@usm.my).

Effects on Ability to Drive and Use Machine
Unlikely to cause an effect on ability to drive and use machines.

Pharmacodynamics
Mechanism of Action
Paracetamol is an analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system.

Pharmacodynamic Effects
The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract. Paracetamol is, therefore, particularly suitable for: patients with a history of disease or patients taking concomitant medication, where peripheral prostaglandin inhibition would be undesirable (such as, for example, those with a history of gastrointestinal bleeding or the elderly).
In two dental pain studies conducted in patients following surgical removal of third molars, pain relief was observed at a median time of 15 minutes following administration of the 1000mg dose of Panadol Tablets with Optizorb.
Panadol Tablets with Optizorb demonstrated superior pain relief at 1000 mg dose compared to placebo and to Panadol Tablets with Optizorb at 500mg dose. Panadol Tablets with Optizorb at the 500 mg dose also demonstrated superior efficacy compared to placebo.

Pharmacokinetics
Absorption
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract.

Distribution
Binding to the plasma proteins is minimal at therapeutic concentrations.

Metabolism
Paracetamol is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate conjugates.

Elimination
Less than 5% is excreted as unmodified paracetamol.
Paracetamol is rapidly absorbed from the gastrointestinal tract and is distributed into most body tissues. Binding to plasma proteins is minimal at therapeutic concentrations. Paracetamol is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate metabolites - less than 5% is excreted as unmodified paracetamol. The mean plasma half life is about 2.3 hours.
Paracetamol Tablets with Optizorb contain a disintegrant system which optimises tablet dissolution compared to standard paracetamol tablets.
Human scintigraphy data demonstrate that Paracetamol Tablets with Optizorb generally start to disintegrate by 5 minutes post dose. Human pharmacokinetic data demonstrate that paracetamol can generally be detected in plasma by 10 minutes.
Human pharmacokinetic data demonstrate that early absorption of paracetamol (fraction of dose over the first 60 minutes) is 32% greater from Paracetamol Tablets with Optizorb compared to standard paracetamol tablets ($p<0.0001$). There is also less between-subject and less within- subject variability ($p<0.0001$) in early absorption of paracetamol from Paracetamol Tablets with Optizorb compared to standard paracetamol tablets.
Human pharmacokinetic data demonstrate that maximum plasma concentration of paracetamol is reached at least 25% faster for Paracetamol Tablets with Optizorb compared to standard paracetamol tablets in fasted and fed states ($p < 0.01$).
Total extent of absorption of paracetamol from Paracetamol Tablets with Optizorb is equivalent to that from standard paracetamol tablets.

Storage
Store below 30°C

Pack Sizes
30's, 36's 144's and 150's caplets.
Not all pack sizes may be marketed.

Date of revision
November 2019

For PRH: GlaxoSmithKline Consumer Healthcare Sdn Bhd (3467-X)
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