Centamol Plus
Suspension

1. **Generic Name**

Paracetamol, Mefenamic acid

2. **Qualitative and Quantitative composition**

Paracetamol	125mg
Mefenamic acid	50mg

3. **Dosage form and strength**

Oral suspension of Paracetamol 125mg, Mefenamic acid 50mg

4. **Clinical particulars**

4.1 Therapeutic indication

Centamol Plus suspension is licensed for treatment of pain and fever in children.

4.2 Posology and method of administration

The usual recommended oral dose of Centamol Plus in children is as under:

- 6 months-2 years age: 1 table spoonful three times a day.
- 2-5 years age: 1- 2 table spoonful three times a day.

4.3 Contraindication

The use of Centamol Plus suspension is contraindicated in patients with:

- Hypersensitivity to any of the ingredients of the formulation.
- Patients with severe hepatic dysfunction

4.4 Special warnings and precautions for use

- In case a hypersensitivity reaction occurs which is rare, Centamol Plus suspension should be discontinued.
- Centamol Plus suspension should be used with caution in patients with renal or hepatic dysfunction, diabetes mellitus, hyperthyroidism, cardiovascular problems, epilepsy and closed angle glaucoma.
- Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive Paracetamol use, although reports of this event are rare. These reports usually involve cases of severe chronic alcoholics and dosages of Paracetamol that most often exceed recommended doses. Chronic alcoholics should not exceed 2 g/day of Paracetamol.
- To be sold by retail on the prescription of R.M.P only.
- Risk of medication errors and hepatotoxicity: Take care when prescribing and administering Centamol Plus to avoid dosing errors which could result in accidental overdose and death.
- Centamol Plus contains Paracetamol. Paracetamol has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of paracetamol at doses that exceed the maximum daily limits, and often involve more than one paracetamol-containing product

4.5 Drug interactions

<u>Paracetamol</u>

- Anticoagulant drugs (warfarin) - dosage may require reduction if Paracetamol and anticoagulants are taken for a prolonged period of time
- Paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide
- Paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics
- Paracetamol may increase chloramphenicol concentrations

- The risk of Paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents
- Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid
- Cholestyramine reduces the absorption of Paracetamol if given within 1 hour.
- Antivirals: Regular use of Paracetamol possibly reduces metabolism of Zidovudine (increased risk of neutropenia).

Mefenamic acid

- Mefenamic Acid enhances activity of oral anticoagulants but rarely significant.
- Increased cyclosporine, lithium toxicity and convulsions reported with ciprofloxacin.
- Absorption is increased by Magnesium Hydroxide antacids.

4.6 Use in special population

- Paediatric: Centamol Plus suspension is safe in children.
- Geriatric: Elderly population may be at greater risk for the side-effects.
- Liver impairment: Use with caution.
- Renal failure: Use with caution.
- Pregnancy and lactation: Pregnancy: Category A: Paracetamol has been used for over 40 years and available data indicate that Paracetamol in therapeutic doses does not adversely affect the pregnant mother or the fetus. Maternal ingestion of Paracetamol in recommended analgesic doses does not present a risk to the nursing infant. Amounts in milk range from 0.1% to 1.85% of the ingested maternal dose. Accordingly, breast feeding need not be interrupted.

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Centamol Plus suspension is known.

4.8 Undesirable effects

The most commonly reported adverse effects are Thrombocytopenia, Coagulopathy ,Agranulocytosis, Anaemia, Neutropenia, Leukopenia, Tachycardia, Palpitations, Cardiac arrest, Cardio-respiratory arrest , Vertigo, Tinnitus, Hypothyroidism, Periorbital oedema, Eyelid oedema, Eye swelling, Periorbital swelling, Ocular hyperaemia, Vision blurred, Visual impairment, Orbital oedema, Vomiting, Nausea, Diarrhoea, dry mouth, Abdominal pain, Dyspepsia, Abdominal pain upper, Abdominal discomfort, Constipation, Lip swelling, Dysphagia, Gastrointestinal haemorrhage, Gastritis, Fatigue, Acute hepatic failure , Liver injury, Hepatotoxicity, Rash, Urticaria, Pruritus

4.9 Overdose

There is limited experience of overdose with Centamol Plus suspension. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 Mechanism of action

<u>Paracetamol</u>

Paracetamol act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis. The antipyretic properties of acetaminophen are likely due to direct effects on the heat-regulating centres of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation.

<u>Mefenamic acid</u>

Mefenamic acid is non-steroidal anti-inflammatory drug (NSAID) and has anti-inflammatory, analgesic and antipyretic properties. Its anti-inflammatory effect was first established in the UV erythema model of inflammation. Prostaglandins are implicated in a number of disease processes including inflammation, modulation of the pain response, dysmenorrhoea, menorrhagia and pyrexia.

In common with most NSAIDs mefenamic acid inhibits the action of prostaglandin synthetase (cyclo-oxygenase). This results in a reduction in the rate of prostaglandin synthesis and reduced prostaglandin levels.

5.2 Pharmacodynamic properties

Paracetamol is a widely used analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. It is a major ingredient in numerous cold and flu medications and many prescription analgesics. It is extremely safe in standard doses, but because of its wide availability, deliberate or accidental overdoses are not uncommon. Paracetamol, unlike other common analgesics such as aspirin and ibuprofen, has no anti-inflammatory properties or effects on platelet function, and it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs or NSAIDs. At therapeutic doses Paracetamol does not irritate the lining of the stomach nor affect blood coagulation, kidney function, or the fetal ductus arteriosus (as NSAIDs can). Like NSAIDs and unlike opioid analgesics, Paracetamol does not cause euphoria or alter mood in any way. Paracetamol and NSAIDs have the benefit of being completely free of problems with addiction, dependence, tolerance and withdrawal. Paracetamol is used on its own or in combination with pseudoephedrine, dextromethorphan, Chlorpheniramine, diphenhydramine, doxylamine, codeine, hydrocodone, or oxycodone.

Mefenamic acid: Pharmacotherapeutic group: Anti-inflammatory and anti- rheumatic products, non-steroids, fenamates.

5.3 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The elimination half-life of Paracetamol varies from about 1 to 3 hours. Paracetamol is metabolised mainly in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged Paracetamol. A minor hydroxylated metabolite (Nacetyl-p-benzoquinoneimine), is usually produced in very

small amounts by cytochrome P450 isoenzymes (mainly CYP2E1 and CYP3A4) in the liver and kidney. It is usually detoxified by conjugation with glutathione but may accumulate after Paracetamol over dosage and cause tissue damage.

Mefenamic acid

Absorption and Distribution: Mefenamic acid is absorbed from the gastro intestinal tract. Peak levels of 10 mg/l occur two hours after the administration of a 1g oral dose to adults.

Biotransformation: Mefenamic acid is predominantly metabolised by cytochrome P450 enzyme CYP2C9 in the liver, first to a 3 hydroxymethyl derivative (metabolite I) and then a 3-carboxyl derivative (metabolite II). Both metabolites undergo secondary conjugation to form glucuronides.

Therefore, in patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates, mefenamic acid should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Elimination: Fifty two percent of a dose is recovered from the urine, 6% as mefenamic acid, 25% as metabolite I and 21% as metabolite II. Assay of stools over a 3-day period accounted for 10-20 % of the dose chiefly as unconjugated metabolite II.

The plasma levels of unconjugated mefenamic acid decline with a half-life of approximately two hours.

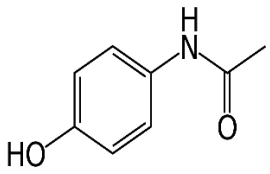
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

NA.

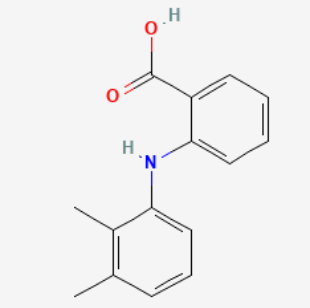
7. Description

Paracetamol belongs to Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Its chemical name is N-acetyl-para-aminophenol (APAP) and its structural formula is:



Its empirical formula is $C_8H_9NO_2$ and its molecular weight is 155.19 g/mol.

Mefenamic acid is an anthranilic acid and non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities. Its chemical name is N-(2,3-dimethylphenyl)-2-aminobenzoic acid and its structural formula is:



Its empirical formula is $C_{15}H_{15}NO_2$and its molecular weight is 241.28 g/mol.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Centamol Plus suspension is available bottle of 60ml.

8.4 Storage and handling instructions

Store below 25°C. Protect from light

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. **Manufactured by**

CENTAUR PHARMACEUTICALS PVT. LTD.

11. Details of permission or license number with date

158(450)/MFG/DFDA/2012/3360 dated. 15.10.2012 for domestic.

12. Date of revision:

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