1. NAME OF THE MEDICINAL PRODUCT

Drugamol® (Paracetamol 500mg) Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Drugamol tablet contains Paracetamol 500mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solid- (Tablet)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Fast relief of pains, headaches, toothaches, cold symptoms, muscular aches and feverishconditions
- Pyrexia of unknownorigin
- Symptomatic relief of fever and pain associated with common childhood disorders. Tonsillitis, Urinary Tract Infections and post immunization reactions e.t.c.
- For prevention of febrile convulsion

4.2 Posology and method of administration

Posology

Adult	-	0.5g – 1g every 4 - 6hours, maximum 4gdaily
6 to12 years	-	250mg – 500mg may be repeated every 4 - 6hours if necessary (maximum 4 doses in24hours)

Method of Administration

For oral administration.

4.3 Contraindications

Patient with alcoholic hepatic disease, viral hepatitis or alcoholism are risk for Paracetamol induced hepatotoxicity since glucuronide conjugation of the drug may be decreased. Depletion of hepatic glutathione reserves limits the ability of the liver to conjugation Paracetamol which predisposes the patient to further hepatic injury. Although it is always prudent to use the smallest dose of paracetamol for the shortest duration necessary, short courses (<5 days) of normal adult doses have been administered safely to patients with stable chronic liver disease. Paracetamol should not be used for self-medication in patients who consume 3 or more alcoholic patients with aminotransferase levels > 1,000 U/L and Paracetamol blood levels should be checked in thesepatients.

Chronic paracetamol administration should be avoided in patients with underlying renal disease; however it is the analgesic of choice for episodic pain in these patients. Case control studies have found an increased risk of developing papillary necrosis, chronic renal failure or end-stage renal disease with chronic Paracetamol use. There are many confounding factors in these studies which limit the ability to determine the actual role of chronic Paracetamol use as a single risk factor for renal disease. Repeated overdoses of paracetamol in **children** in combination with decreased nutrition may lead to change in the metabolism of Paracetamol leading to hepatotoxicity. This combination leads to decreases in sulfation, glucuronidation and glutathione production. Factors, which may lead to inadvertent overdose in children, include finishing pediatric formulation and substituting adult Paracetamol formulations for convenience, misreading or interpreting instructions or administering more Paracetamol due to persistent fever.

Paracetamol should be used cautiously in patients with **anemia** since this condition can be aggravated. Cyanosis may not be apparent in patients with preexisting anemia, in spite of dangerously high blood concentrations of methemoglobin. Paracetamol should be used cautiously in patients with **asthma** who also have salicylate hypersensitivity. A single-blind prospective study of 50 aspirin-sensitive asthmatic subjects and 20 other asthmatics that were not aspirin-sensitive revealed that 27 of 50 aspirin-sensitive subject reacted to Paracetamol while no subject in the other groupreacted.

Paracetamol was administered in doses of 1,000mg and 1,500mg. The majorities of the reactions were mild bronchospasm and were easily reversed. The authors concluded that high doses of Paracetamol) e.g., > 1,000mg) should be avoided in patients with aspirin-sensitivity who are also asthmatic. Symptoms of acute **infection** (e.g. fever, pain) can be masked during treatment with Paracetamol in patients with **bone marrow suppression,** especially **neutropenia,** or **immunosuppression.** Certain Paracetamol products containing aspartame (Nutria sweet) should be avoided in patients who have **phenylketonuria** or who must restrict intake of phenylalaninine. Paracetamol may interfere with some home blood glucose monitoring systems resulting in decreases of > 20% in mean glucose values. This effect seems to be drug, concentration and systemdependent.

Patients should not self-medicate with Paracetamol for the treatment of pain >5 days in children or >10days in adult. Fever should not be treated longer than 3 days in children or adults without consulting a physician or other health care professional.

4.4 Special warnings and precautions for use

Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

Care is advised in the administration of Paracetamol to patients with alcohol dependency (see section 4.9), severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Leaflet Precaution:

Necessary precaution should be taken in cases of hepatic and renal impairment.

Paracetamol should be used with extreme caution in both cases.

Patient should not exceed maximum recommended dose of 4g (8 tablets) daily or use for more than 72 hours without medical advice.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids or food can delay and decrease the oral absorption of Paracetamol. **Chenothiazines**can interfere with thermoregulation. Conconmintant use of Paracetamol with **chenothiazines**can produce hypothermia if Paracetamol is given in large doses and the patient is exposes to cold ambient temperatures. The risk of developing hepatotoxicity from Paracetamol appears to be increased in patients who regularly consume **ethanol**. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of Paracetamol. Chronic ethanol use increase Paracetamol-induced hepatotoxicity by depleting liver glutathione stores. Administration of Paracetamol should be limited or avoided altogether in alcoholics or patients who consume ethanolregularly.

However, acute ethanol ingestion may reduce Paracetamol-induced hepatotoxicity by substrate competition for CYP2E1. Other agents which may induce or inhibit CYP 2E1 or 1A2 may increase or decrease the hepatotoxicity of Paracetamol. Agent that inhibit CYP 2E or 1A2 and may decrease Paracetamol-induced hepatotoxicity include **cimetidine,** ciprofloxacin, clarithromycin, erythromycin, grapefruit juice, **isoniazid, INH**ketoconazole, levoflxacin, omeprazole and paroxetine. Agent which may induce CYP 2E1 and 1A2, potentially increasing the risk for Paracetamol-induced hepatotoxicity, include **carbamazepine**, **barbiturates, phenytoin, rifampin**, and **ritonavir.** At least one case has been reported of Phenobarbital enhancing Paracetamol hepatotoxicity. Despite the use of only moderate doses of Paracetamol, the patient has been consuming Paracetamol regularly for 3 months. While chronic Paracetamol use should be discouraged during Phenobarbital therapy, intermittent use of Paracetamol is probably safe. The clinical significance of the other interaction is notknown.

Sulfinpyrazonecan induce hepatic microsomal enzymes that metabolize Paracetamol and this in turn increases the risk of Paracetamol hepatotoxicity due to the formation of increased amounts of toxic paracetamol metabolites. The risks of Paracetamol hepatotoxicity in patients taking **sulfinpyrazone**can increases with larger Paracetamol doses, particularly overdoses. Although Paracetamol is necessary for a patient receiving therapy with **warfarin**, Paracetamol has also been shown to augment the hypoprothrombinemic response to warfarin. Concomitant Paracetamol ingestion can increases PT (or INR) in adose-related fashion. Both INR prolongation and clinical bleeding have been reported.

Single doses or short (i.e. several days) courses of treatment with Paracetamol are probably safe in most patients taking warfarin. Clinicians should be alert for an increased INR if Paracetamol is administered daily in large doses for longer than 10 days. Use of Paracetamol prior to <72 hours) or concurrently with busulfan may result in decreased clearance of busulfan due to Paracetamol-induced decreases in glutathionelevels.

4.6 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.

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

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Paracetamol can be hepatotoxic. In most cases, Paracetamol hepatotoxicity occurs as a result of an acute overdose, however, moderately excessive doses, if taken chronically, can also produce hepatotoxicity. Paracetamol-induced hepatotoxicity is manifested as **hepatic necrosis, jaundice,** bleeding and **encephalopathy.** After acute overdose, 2 or 3 days pass before maximum liver damage becomes apparent. **Nausea/Vomiting, anorexia**, and **abdominal pain** usually occur within 2-3 hours after ingestion of toxic doses. Elevated hepatic enzymes and **hypoprothrombinemia**are seen. G1 bleeding can occur secondary to low prothrombin levels. Recovery may occur within 5-10 days. Regular use of Paracetamol for period of 5-39 months produced hepatotoxicity in 11 patients. If plasma Paracetamol half-life exceeds 4 hours, hepatic necrosis can occur, and if the half-life exceeds 12 hours, hepatic encephalopathy and coma is likely to develop. Young children appear to be at less risk of developing hepatotoxicity, possibly because of an age-related difference in the metabolism of the drug. Agents, which affect cytochrome P450 function and ethanol, may affect the severity of Paracetamol-induced hepatotoxicity. It has also been suggested that recent fasting is associated with hepatotoxicity in patients taking higher than recommended doses. Treatment of Paracetamol overdose is with prompt oral administration of N-acetylcysteine, which serves as a substitute sulfhydryl donorm forglutathione.

Paracetamol can cause acute **renal tubular** necrosis and chronic analgesic nephropathy, which is characterized by interstitial nephritis and **renal papillary necrosis,** in patients receiving high doses (e.g. 2.5 – 10g/day) chronically or after acute overdose. Acute renal failure may occur 25-30% of patients secondary to liver dysfunction. Rarely, acute renal failure may occur without severe hepatic toxicity. The risk of renal complication appears to be higher in alcoholicpatients.

Chronic paracetamol use has been implicated as a contributing factor in the decline of renal function in patients with underlying renal disease, including diabetic nephropathy.

Methemoglobinemiacan occur after acute overdoses of Paracetamol and can lead to hemolysis thereby causing hemolytic**anemia.** This can result in cyanosis of the fingernails, skin and mucosa. Children develop **Methemoglobinemia**more readily than do adults. Other hematologic reactions reported with Paracetamol include **neutropenia, leucopenia, thrombocytopema,** and **pancytopenia.** Hypersensitivity reactions to Paracetamol may be manifested by **urticaria, erythema, rash** (unspecified), and**fever.**

4.9 Overdose

Symptoms of overdose may include nausea, vomiting, abdominal pain, diaphoresis, generalized weakness and lethargy. If am over dosage of Paracetamol is suspected, blood should be withdrawn immediately for Paracetamol plasma assay, without regard to the presence or absence ofsymptomology.

TREATMENT: The acute hepatotoxicity and nephrotoxicity of Paracetamol can be overcome by the administration of sylphahydryl donors e.g. N-acetylcysteine which should be given as soon aspossible.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, Anilides

ATC code N02B E01

Paracetamol has analgesic and antipyretic properties but it has no useful anti-inflammatory properties.

Paracetamol's effects are thought to be related to inhibition of prostaglandin synthesis.

5.2 Pharmacokinetic properties

Absorption

Paracetamol is readily absorbed from the gastrointestinal tract.

Distribution

Peak plasma concentrations occur 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.

Biotransformation

It is metabolised in the liver. A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following Paracetamoloverdosage and cause tissue damage.

Elimination

It is excreted in the urine, mainly as the glucuronide and sulfate conjugates. The elimination half-life varies from about 1 to 4 hours.

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

Microcrystalline Cellulose
Polyvinyl Pyrrolidone K-30
Aerosil 200
Corn Starch for Paste
Magnesium Stearate
Methyl Paraben
Propyl Paraben

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 30^{o}C in tight container protected from light and moisture.

6.5 Nature and contents of container

Drugamol® Tablet is a white oblong shape tablet presented in a blister pack of 12 tablets, each pack containing 8 blisters of 12 tablets arranged in a hardboard carton and in a Jar of 1000 tablets.

6.6 Special precautions for disposal and other handling

No special precautions for disposal and other handling

7. APPLICANT/MANUFACTURER

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04 – 3649

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09/2022