

SUMMARY OF PRODUCT CHARACTERISTICS

GACET - 500

1. NAME OF THE MEDICINAL PRODUCT

GACET - 500 (Paracetamol Effervescent Tablets BP 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains

Paracetamol BP..... 500mg

Excipients q.s.

For a full list of excipient see section 6.1

3. PHARMACEUTICAL FORM

Effervescent Tablet

White to off white colour, round flat faced beveled edged tablets with orange odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild to moderate pain and/or fever.

4.2 Posology and method of administration

Dosage in adults and children from 27 kg (or from 8 years)

The usual dosage is: For children weighing 27 to 40 kg (approximately 8 to 13 years), the dosage is 1 tablet of 500 mg per dose, to be repeated if necessary after 6 hours, not exceeding 4 tablets per day.

For children weighing 41 to 50 kg (approximately 12 to 15 years), the dosage is 1 tablet of 500 mg per dose, to be repeated if necessary after 4 hours, not exceeding 6 tablets per day.

For adults and children weighing more than 50 kg (from about 15 years old):

The usual dosage is 1 or 2 tablets of 500 mg per dose (depending on the intensity of the pain), to be repeated if necessary after at least 4 hours.

It is generally not recommended to exceed 3 g of paracetamol per day, or 6 tablets per day.

However, in case of more severe pain, and on the advice of your doctor or pharmacist, the

total dose can be increased up to 4 g per day, or 8 tablets per day.

GACET - 500 Effervescent Tablets are for oral administration. The tablets should be placed in a full tumbler of water immediately before use and allowed to dissolve completely before swallowing.

Frequency of administration:

Regular intakes prevent pain or fever from returning: see section "Dosage".

In children, the catch should be kept at regular intervals, including at night, preferably 6 hours and at least 4 hours.

In adults, catches should be spaced at least 4 hours apart.

In case of severe kidney disease (severe kidney failure), you should wait at least 8 hours between each dose.

If you feel that the effect of GACET - 500 is too strong or too weak, consult your doctor or pharmacist.

4.3 Contraindications

Hypersensitivity to Paracetamol, or any of the excipients.

4.4 Special warnings and precautions for use

Prolonged or frequent use is discouraged. Patients should be advised not to take other Paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In children treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness. Caution is advised in the administration of Paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatocellular insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (Child-Pugh >9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic anaemia, dehydration, alcohol abuse and chronic malnutrition (see section 4.2).

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2000mg in such case.

Alcohol should not be used during the treatment with Paracetamol.

“Caution is advised in asthmatic patients sensitive to aspirin, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5% of the patients tested.”

Abrupt discontinuation of long term use of high-dosed analgesics, taken not as directed, may cause headache, tiredness, muscular pain, nervousness and vegetative symptoms. The withdrawal symptoms subside within a few days. Patients should be advised to consult their doctor if headaches become persistent.

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.

This medicinal product contains 438mg of sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

Do not exceed the stated dose.

If symptoms persist consult a doctor.

Treatment with an antidote is advised if an overdose is suspected.

Paracetamol Effervescent 500mg Tablets is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

Hepatotoxic substances may increase the possibility of paracetamol accumulation and overdose. The metabolism of paracetamol is increased in patients taking enzyme-inducing drugs such as rifampicin and some antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). Isolated reports describe unexpected hepatotoxicity in patients taking enzyme-inducing drugs and alcohol.

Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.

- ✓ Salicylamide may prolong the elimination $t_{1/2}$ of Paracetamol.
- ✓ Metoclopramide and domperidone accelerate absorption of Paracetamol.
- ✓ Cholestyramine reduces absorption of Paracetamol and therefore should not be administered within an hour following Paracetamol administration.
- ✓ Concomitant use of Paracetamol (4000mg per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation.
- ✓ Isoniazid: Reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver.
- ✓ Lamotrigine: decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of liver metabolism.

Interference with laboratory tests:

Paracetamol may affect uric acid tests and blood sugar tests by glucose-oxidase-peroxidase.

4.6 Fertility, pregnancy and lactation

Pregnancy:

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of paracetamol. Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of GACET - 500 Effervescent Tablets may be considered during pregnancy, if necessary.

Lactation:

Paracetamol/ metabolites are excreted in human milk, but at therapeutic doses of GACET - 500 Effervescent Tablets no effects on the breastfed newborns/infants are anticipated. GACET - 500 Effervescent Tablets can be used during breast-feeding.

Fertility:

There are no or limited amount of date from the influence of GACET - 500 effervescent tablets on fertility.

4.7 Effects on ability to drive and use machines:

Paracetamol has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The frequency using the following convention should be: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency	System	Symptoms
Rare ($\geq 1/10000$ - $< 1/1000$)	Blood and lymphatic system disorders	Platelet disorders, stem cell disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic, anaemia, pancytopenia
	Immune system disorders	Allergies (excluding angioedema).
	Psychiatric disorders	Depression NOS, confusion, hallucinations.
	Nervous system disorders	Tremor NOS, headache NOS.
	Eye disorders	Abnormal vision
	Cardiac disorders	Oedema
	Gastrointestinal disorders	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting
	Hepato-biliary disorder	Abnormal Hepatic function, hepatic failure, hepatic necrosis jaundice.
	Skin and subcutaneous	Pruritus, rash, sweating, purpura, angioedema, urticaria

	General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
	Injury, poisoning and procedural complications	Overdose and poisoning
Very Rare (<10,000)	Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Hepato-biliary disorders	Hepatotoxicity
	General disorders and administration site conditions	Hypersensitivity reaction (requiring discontinuation of treatment)
	Metabolism and nutrition disorders	Hypoglycaemia
	Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects

Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of epidermal necrolysis, Stevens Johnson syndrome, erythema multiform, oedema of the larynx, anaphylactic shock, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastro intestinal effects and vertigo have been reported.

4.9

Overdose

There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism and in patients with chronic malnutrition. Overdose of Paracetamol is potentially fatal in all populations.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, and abdominal pain. Immediate emergency measures are necessary in case of paracetamol overdose, even when no symptoms are present.

- ✓ Overdose, 10g or more of Paracetamol in adults or 150mg/kg of body weight, causes liver cell necrosis likely to induce complete and irreversible necrosis,

resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death.

- ✓ Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Emergency Procedure:

- ✓ Immediate transfer to hospital.
- ✓ Blood sampling to determine initial paracetamol plasma concentration.
- ✓ IV (or oral if possible) administration of the antidote N-acetylcysteine as soon as possible or within 8 hours of the overdose.
- ✓ Activated charcoal may be used if the dose of Paracetamol ingested exceeds 12g or 150mg/kg and should be undertaken if within 1 hour of the overdose.
- ✓ Oral methionine is also effective provided that it is given within 10 to 12 hours of the overdose.
- ✓ Symptomatic treatment should be implemented.
- ✓ Haemodialysis or haemoperfusion is possible in cases of severe poisoning.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: *other analgesics and antipyretics; anilides*

ATC code: N02BE01

5.2 Pharmacokinetic properties

Absorption:

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution:

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low.

Metabolism:

Paracetamol is metabolised mainly in the liver following two major metabolic pathways: glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalysed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination:

Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form. Elimination half-life is about 2 hours.

Special patient groups:

Renal Insufficiency: in cases of severe renal insufficiency (creatinine clearance lower than 10ml/min) the elimination of paracetamol and its metabolites is delayed. Elderly Subjects: the capacity for conjugation is not modified.

5.3 Preclinical safety data:

In animal studies investigating the acute sub-chronic and chronic toxicity of paracetamol in the rat and mouse, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma and necrosis were observed. These changes are, on the one hand, attributed to the mechanism of action and, on the other, to the metabolism of paracetamol. The metabolites that is probably responsible for the toxic effects and the corresponding organic changes have also been found in humans. Moreover, during long term use (i.e.

1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. At sub-toxic doses, symptoms of intoxication can occur following a 3-week intake period.

Paracetamol should therefore not be administered over a long period of time or at high doses. Extensive investigations showed no evidence of any relevant genotoxic risk of

paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice yielded no evidence on relevant carcinogenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol crosses the placental barrier. Animal studies and clinical experience to date have not indicated any teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Citric acid

Sodium Bicarbonate

Sodium Saccharin

Sodium Benzoate

Povidone (PVP K30)

Simethicone

Tween 80

Iso Propyl alcohol

Sodium Carbonate

Aspartame

Flavour Orange

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life:

36 months

6.4 Special precautions for storage

Store below 25°C. Protect from moisture and light.

6.5 Nature and contents of container

4 Strips (Aluminium foil) of 4 tablets in mono carton along with product insert.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

BLISS GVS PHARMA LIMITED

102, Hyde Park, Saki-Vihar road,

Andheri (East) Mumbai 400 072

INDIA.

Manufacturing Site and Address:

FP MANUFACTURER

Company name: BLISS GVS Pharma Ltd

at Vovantis Laboratories Pvt. Ltd.

Address: Survey No. 546/1/1, Opposite Ranoli Railway Station,

Near GACL Plant,

City: Ranoli-391 350,

Dist.: Vadodara, Gujrat State.

Country: India