SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol / Caffeine 500 mg/65 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg and Caffeine 65 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule shaped tablets

White to off white, capsule shaped, biconvex tablets plain on both sides approximately 17.46 mm X 7.14 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderate pain and/or fever in adults and children aged 16 years or over.

4.2 Posology and method of administration

Oral use.

Adults (16 years and over):

Two tablets up to four times daily. The dose should not be repeated more frequently than every 4 hours. Do not exceed 8 tablets in 24 hours.

Elderly:

As for adults.

Not recommended for children under 16 years.

Impaired Renal Function:

In case of renal insufficiency dose adjustment is necessary:

Impaired Hepatic Function:

In patients with impaired hepatic function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

The daily effective dose of paracetamol should not exceed 60 mg/kg/day (up to maximum 2 g paracetamol /day) in the following situations:

_ Adults or adolescents weighing less than 50 kg

_ Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-heamolytic jaundice)

_ Dehydration

_ Chronic malnutrition

_ Chronic alcoholism

Method of administration

Route of administration: Oral

4.3 Contraindications

Hypersensitivity to paracetamol, caffeine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Caution is advised in the administration of Paracetamol to patients with mild 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).

Do not exceed stated dose.

Contains paracetamol. Do not use with any other paracetamol containing products. The concomitant use with other products containing paracetamol may lead to an overdose.

Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

Care is advised in the administration of paracetamol to patients with renal or hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol may increase the risk of metabolic acidosis (see section 4.9).

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.

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 2 grams in such cases.

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.
Paracetamol / Caffeine 500 mg/65 mg Tablets should be given with care to patients with gout, hyperthyroidism and arrhythmia.

Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product as excess caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heart beat.
Glomerular filtration Dose
10-50 ml/min 1 tablet every 6 hours
< 10 ml/min 1 tablet every 8 hours

As caffeine is found naturally in tea, coffee and chocolate, and in some carbonated drinks there is the potential for users to take more than the recommended 390 mg/day of caffeine (6 tablets) per day. Patients should take account of dietary and other medicinal sources of caffeine and ensure that they do not exceed the stated dose.
Typical amounts of caffeine available from dietary sources are
Brewed coffee; 50-100mg/100ml*
Instant coffee and tea: 20-73mg/100ml*
Carbonated drinks (cola) 9-19mg/100ml*
Chocolate 5-20mg/100ml
(*100ml is equivalent to about 1 small cup of fluid)

If symptoms persist, medical advice must be sought.
Keep out of the sight and reach of children.

Important information regarding the excipients in this medicine
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol
Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The risk of hepatotoxicity of paracetamol may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, and alcohol.
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. 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.

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)

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

- Salicylamide may prolong the elimination half-life of Paracetamol.
- Metoclopramide accelerate absorption of Paracetamol.
- Cholestyramine reduces absorption of Paracetamol.
- Concomitant use of Paracetamol (4 g 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 reduces paracetamol clearance by 20%, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver. The clinical relevance is unknown
- Paracetamol decreases the bioavailability of lamotrigine with possible reduction of its effect due to possible induction of its metabolism in the liver
- Co-administration of paracetamol with zidovudine may result in neutopenia or hepatotoxicity. However, these effects have not been consistently reported. The chronic / multiple dose paracetamol use in patients on zidovudine therapy should be avoided, however, if chronic

paracetamol and zidovudine are to be given concurrently white blood count and liver function tests should be monitored particularly in malnourished patients

- Paracetamol may affect the pharmacokinetics of chloramphenicol. Monitoring of chloramphenicol plasma levels is recommended if combining paracetamol with chloramphenicol injection treatment.
- Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxidase-peroxidase.

Caffeine
Caffeine may increase clearance of lithium. Concomitant use is therefore not recommended.

Phenylpropanolamine increases caffeine plasma concentrations four-fold. There is a risk of additive CNS adverse events. Isolated reports describe the development of acute psychosis when caffeine was given with phenylpropanolamine.

Fluvoxamine, a potent inhibitor of CYP 1 A2, markedly reduces the clearance of caffeine. Concomitant administration may lead to caffeine intoxication.

Ciprofloxacin reduces caffeine metabolism, leading to two-fold increases in caffeine plasma concentrations.

Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers. Caffeine may enhance the tachycardic effect of phenylpropanolamine and other sympathomimetic drugs.

Caffeine can increase blood pressure and counters the hypotensive action of Beta blockers such as atenolol, metoprolol, oxprenolol and propranolol. This medicine should not be used at the same time as beta blockers.

Disulfiram decreases caffeine clearance by up to 50%. Concomitant use of disulfiram and Paracetamol / Caffeine 500 mg/65 mg Tablets should be avoided.

Dipyridamole: injectable dipyramidole: decrease of the vasodilating effect of dipyramidole.

Treatment with caffeine should be discontinued at least 5 days before myocardial imaging. Coffee, tea and chocolate consumption should be avoided in the 24 hours preceding the test. Use with caution.

Enoxacin: increase of caffeine plasmatic concentrations due to a decrease of its hepatic metabolism, which can lead to excitement or hallucinations. Concomitant use is therefore not recommended.

Mexiletine: increase of caffeine plasmatic concentration due to inhibition of its hepatic metabolism with mexiletine. To be taken into account.

Norfloxacin: increase of caffeine plasmatic concentration due to inhibition of its hepatic metabolism with norfloxacin. To be taken into account.

Stiripentol: possible increase of caffeine plasmatic concentration with risk of overdose, due to its hepatic metabolism inhibition. Use with caution.

Caffeine exerts a competitive inhibition of the metabolism of clozapine. Therefore clozapine and caffeine must not be used concurrently.

Use of lithium carbonate and caffeine may cause a small decrease in serum lithium levels. Therefore concomitant ingestion of caffeine should be avoided. In case of concomitant use, the risk of an increase in serum lithium on abrupt cessation of caffeine should be taken into account.

Monoamine oxidase inhibitors may increase the stimulant effects of caffeine.
Methoxsalen reduces clearance of caffeine and may increase the effects of caffeine.
Phenytoin doubles caffeine clearance, although caffeine does not affect the metabolism of phenytoin.

Pipemidic acid reduces caffeine clearance, enhancing the effects of caffeine.

Theophylline and caffeine share the same metabolic pathway, leading to decreased clearance times for theophylline when used concurrently with caffeine. Concomitant use should be avoided.

Levothyroxine, like caffeine can increase blood pressure, and therefore these two active ingredients should not be used concurrently.

Ephedrine and caffeine interact to produce significant cardiovascular effects. Therefore caffeine should be avoided when ephedrine is being taken.

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. Paracetamol-caffeine is not recommended for use during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption during pregnancy.

Breast-feeding

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

Caffeine in breast milk may have a stimulating effect on breast-fed infants. Irritability and poor sleeping pattern in the infant have been reported. Due to the caffeine content of this product it should not be used if you are pregnant or breast feeding.

Fertility
There is insufficient information available on the effects of Paracetamol and Caffeine on human fertility.

4.7 Effects on ability to drive and use machines

Paracetamol / Caffeine 500 mg/65 mg Tablets has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, considered attributable are tabulated below by MedDRA System Organ Class. Adverse reactions identified during postmarketing use are reported voluntarily from a population of uncertain size, the frequency of these reactions is unknown but likely to be listed below by system organ class and frequency.

Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000 including isolated reports) and not known (cannot be estimated from available data).

Paracetamol

System Organ Class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Rare	Platelet disorders, stem cell disorders.
	Very Rare	Thrombocytopenia, Leukopenia, Neutropenia, hemolytic anemia, agranulocytosis,
Immune system disorders	Rare	Anaphylaxis Cutaneous hypersensitivity reactions including (amongst others) skin rashes and angioedema, allergic dermatitis
Metabolism and nutrition disorders	Very Rare	Hypoglycaemia
	Not known	High anion gap metabolic acidosis
Psychiatric disorders:	Common	Insomnia, restlessness, anxiety
	Rare	Depression NOS, confusion, hallucinations.
Gastrointestinal	Common	Gastrointestinal disorder

disorders	Rare	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting
Nervous system disorders	Common	Dizziness, Nervousness
	Rare	Tremor NOS, headache NOS
Eye disorders	Rare	Abnormal vision.
Cardiac disorders	Rare	Oedema.
Respiratory, thorasic and mediastinal disorder	Very Rare	Bronchospasm- more likely in patients sensitive to aspirin and other NSAIDs
Hepato-biliary disorders	Rare	hepatic failure, Hepatic dysfunction, hepatic necrosis, jaundice.
	Very Rare	Hepatotoxicity, increased transaminases
Skin and subcutaneous tissue disorders	Rare	Pruritus, rash, sweating, purpura, angioedema, urticaria
	Very Rare	Serious skin reactions have been reported.
Renal and urinary disorders	Very Rare	Sterile pyuria (cloudy urine) and renal side effects
General disorders and administration site conditions	Rare	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
	Very Rare	hypersensitivity reaction (requiring discontinuation of treatment)
Injury, poisoning and procedural complications	Rare	Overdose and poisoning

Not known: Irritability, Palpitations, tachycardia, Edema of the larynx, anaphylactic shock, anaemia, bronchospasm*, liver alteration and hepatitis, renal alteration (severe renal impairment, nephrite interstitial, haematuria, anuresis), gastrointestinal effects and vertigo have been reported.
* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Description of selected adverse reactions

<u>High anion gap metabolic acidosis</u>

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.

When the recommended dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as nervousness, dizziness, insomnia, restlessness, anxiety, irritability, headache, gastrointestinal disorder and palpitations.

CAFFEINE

When the recommended paracetamol-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects.

Body System	Undesirable effect
Central nervous system	Dizziness Headache
Cardiac disorders	Palpitation
Psychiatric disorders	Insomnia Restlessness Anxiety and irritability
Gastrointestinal disorders	Gastrointestinal disturbances

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; website: 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 who have taken 10 g or more of paracetamol. Ingestion of 5 g 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 carbamazepine, phenobarbitone, 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 overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain.

Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. 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.

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 overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

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 National Poisons Information Unit or a liver unit.

Caffeine

Symptoms

Overdose of caffeine may result in epigastric pain, vomitting, diuresis, tachycardia or cardia arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

Cardiovascular features commonly include hypertension and sinus tachycardia. Less commonly hypertension-induced reflex bradycardia has been reported. In severe cases a hypertensive crisis, supraventricular and ventricular arrhythmias, myocardial ischaemia and infarction may occur. Ultimately hypotension may supersede with haemodynamic compromise.

Central nervous system features may include agitation, confusion, ataxia, delirium and hallucinations. Less common features include tremors, hyperreflexia, convulsions and cerebral haemorrhage.

Biochemical abnormalities include hypokalaemia, hyponatraemia, hyperglycaemia, and lactic acidosis.

Other features include diaphoresis, headache, hyperthermia, leukocytosis, mydriasis, tachypnoea, vomiting, and rhabdomyolysis.

There have been also been reports of pulmonary oedema and disseminated intravascular coagulation (DIC).

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related toxicity.

Management

Patients should receive general supportive care (e.g. hydration and maintenance of vital signs). The administration of activated charcoal may be beneficial when performed within one hour of the overdose, but can be considered for up to four hours after the overdose. The CNS effects of overdose may be treated with intravenous sedatives.

Summary
Treatment of overdose requires assessment of plasma paracetamol levels for antidote treatment, with signs and symptoms of caffeine toxicity being managed symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Analgesics; Other Analgesics and Antipyretics; Analides: Paracetamol, combinations excl.

ATC code: N02B E51

The combination of paracetamol and caffeine is a well-established analgesic combination.

Paracetamol

ANALGESIC:

The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting a prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

ANTIPYRETIC:

Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating, and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

Caffeine

Central nervous system stimulant – Caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amfetamines.

ANALGESIA ADJUNCT:

Caffeine constricts cerebral vasculature with an accompanying decrease in cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing a more rapid onset of action and/or enhanced pain relief with lower doses of analgesic.

5.2 Pharmacokinetic properties

PARACETAMOL

Absorption and Fate

Paracetamol is readily absorbed from the gastro-intestinal tract.with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate

conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

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 paracetamol overdosage and cause liver damage.

Physiopathological Variations: Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed

CAFFEINE

Absorption and Fate

Caffeine is absorbed readily after oral administration and is widely distributed throughout the body. Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged.

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

Povidone K-30 (E1201)

Povidone K-90 (E1201)

Potato starch

Pregelatinised starch

Purified Talc

Croscarmellose sodium

Stearic acid (E570)

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Paracetamol and Caffeine 500 mg/65 mg Tablets are packaged in blister packs comprising of white opaque PVC/PVdC (20 micron/40gsm) and with backing of foil, which are placed in an outer carton along with leaflet. These are available in the pack sizes of 4, 6, 12, 16, 24, 30, 32, 48, 60 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited

Unit 3, Canalside, Northbridge Road,

Berkhmastead, Hertfordshire,

HP4 1EG, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0583

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2022

10 DATE OF REVISION OF THE TEXT

28/01/2025