SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol / Caffeine 500mg/65mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500mg and Caffeine 65mg
For 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 17.46mm X 7.14mm.

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

Posology

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

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).

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.

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.

Paracetamol & Caffeine 500mg/65mg 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)

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

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).

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

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.

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 potentially 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 mg/65mg 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, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attribute are tabulated below by MedDRA System Organ Class, Adverse reactions identified during post-marketing 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

Body system	**Undesirable effect**
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis
Immune system disorders	Very rare cases of serious skin

	reactions have been reported. Anaphylaxis Cutaneous hypersensitivity reactions including (amongst others) skin rashes and angioedema.
Respiratory, thoracic and mediastinal disorders	Bronchospasm – more likely in patients sensitive to aspirin and other NSAIDs
Hepatobiliary disorders	Hepatic dysfunction
Metabolism and Nutrition disorders	Not known - High anion gap metabolic acidosis

Description of selected adverse reactions

High anion gap metabolic acidosis

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.

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, see BNF overdose section.

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, vomiting, diuresis, tachycardia or cardia arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).

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 is rapidly and almost completely absorbed from the gastro-intestinal tract. It is relatively uniformly distributed throughout most body fluids and exhibits variable protein binding. Excretion is almost exclusively renal, in the form of conjugated metabolites. Caffeine is absorbed readily after oral administration. Maximal plasma concentrations are achieved within one hour and the plasma half-life is about 3.5 hours. 65 - 80% of administered caffeine is excreted in the urine as 1-methyluric acid and 1-methylxanthine.

Paracetamol/ caffeine Tablets contain a disintegrant system which accelerates tablet dissolution compared to standard paracetamol and caffeine tablets.

Human pharmacokinetic data demonstrate that the time taken to reach plasma paracetamol threshold (4-7 mcg/ml) is at least 44% faster with Paracetamol/ caffeine Tablets compared with standard paracetamol and caffeine tablets.

Total extent of absorption of paracetamol and caffeine from Paracetamol/ caffeine Tablets is equivalent to that from standard paracetamol and caffeine tablets.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC..

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

No special storage conditions.

6.5 Nature and contents of container

Paracetamol & Caffeine 500mg/65mg 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 and 16 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,

Berkhamsted, Hertfordshire,

HP4 1EG, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0305

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/04/2022

10 DATE OF REVISION OF THE TEXT

29/01/2025