SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Plus Tablets
Boots Paracetamol Extra 500mg/65mg Tablets
Paracetamol Plus Caplets
Paracetamol Extra Tablets
Co-op Paracetamol Extra Pain Relief Tablets
Health Essentials Pain Relief Plus Tablets
Best-In Paracetamol Extra Pain Relief Tablets
Spar Paracetamol Extra Pain Relief Tablets
Happy Shopper Paracetamol Extra Pain Relief Tablets
The Local Independent Trading Company Ltd Extra Pain Relief500mg/65mg Tablets
Today's Select Paracetamol Extra Pain Relief 500mg/65mg Tablets
Numark Paracetamol Plus 500mg/65mg Tablets
Essential Waitrose & Partners Paracetamol Plus 500mg/65mg Tablets
OptiPharma Paracetamol Plus 500mg/65mg Tablets
Paracetamol and Caffeine 500mg/65mg Tablets
Sainsburys Healthcare Paracetamol Plus 500mg/65mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

INGREDIENT	QTY	UNIT	DOSE
Paracetamol	500	mg	tablet
Caffeine	65	mg	tablet

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet
White capsule shaped tablets with no marks and plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, symptomatic relief of sprains, strains, rheumatic pains, sciatica, lumbago,

fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, feverishness and feverish colds.

4.2 Posology and method of administration

Posology

For all indications:

Adults, the elderly and children over 16 years of age:
Two tablets every 4-6 hours when necessary to a maximum of 4 doses (8 tablets) in 24 hours.

Children aged 12 to 15 years:
One tablet every 4-6 hours when necessary to a maximum of 4 doses (4 tablets) in 24 hours.

Not recommended for children under 12 years of age.

Special populations

Elderly patients:

Elderly patients, especially those who are frail or immobile, may require a reduced dose or frequency of dosing.

Renal impairment:

Patients who have been diagnosed with kidney impairment must seek medical advice before taking this medication. It is recommended, when giving paracetamol to patients with renal failure, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours. The restrictions related to the use of paracetamol products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

Hepatic impairment:

Patients who have been diagnosed with hepatic impairment or Gilbert's Syndrome must seek medical advice before taking this medication. The restrictions related to the use of paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (see section 4.4).

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 520 mg/day of caffeine (8 tablets) per day. Therefore users 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/ml*
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)

Method of administration

Route of administration: Oral.
Do not exceed the recommended daily dosage or the specified number of doses because of the risk of liver damage (see sections 4.4 and 4.9).

Minimum dosing interval: 4 hours.

If pain or fever persist for more than 3 days or gets worse, or if any other symptoms occur, treatment should be discontinued and a physician consulted.

4.3 Contraindications

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

This medicine should not be used by people who have been diagnosed with hypertension or who are receiving antihypertensive medication, or who have a history of cardiac arrhythmia.

This medicine should not be used by patients recovering from chronic alcoholism who are taking disulfiram.

This medicine should not be used if antidepressants (including lithium carbonate), anxiolytics (including clozapine) and sedatives are being used , or by persons with anxiety disorders.

This medicine should not be used by any persons who are also taking ephedrine (see also section 4.5).

Caffeine shares the same metabolic pathway as theophylline and therefore this medicine should not be used concurrently with theophylline.

4.4. Special Warnings and Special Precautions for Use

- Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.
- Patients should be advised not to take other paracetamol containing products concurrently. Immediate medical advice should be sought in the event of overdosage even if the patient feels well because the risk of irreversible liver damage (see section 4.9).
- Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.
- Paracetamol should be administered only with particular caution under the following circumstances:
    - Hepatocellular insufficiency
    - Renal failure (GFR≤50ml/min)
    - Gilbert’s Syndrome (familial non-haemolytic jaundice)

- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- The elderly, adults and children weighing less than 50kg.

– Precaution should be observed in patients with asthma who are sensitive to acetylsalicylic acid, since mild bronchospasms are reported in association with paracetamol (cross reaction).

– Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product (see section 4.9: Overdose, caffeine).

– 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.

4.5. Interaction with other Medicinal Products and other forms of Interaction

Paracetamol

Paracetamol is metabolized in the liver and can therefore interact with other medicines that follow the same pathway or may inhibit or induce this route; causing hepatotoxicity, particularly in overdose (see Section 4.9).

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption may be reduced by cholestyramine. Cholestyramine should not be administered within one hour of taking paracetamol.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged 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)

In case of concomitant treatment with probenecid, the dose of paracetamol should be reduced since probenecid reduces the clearance of paracetamol by 50% since it prevents the conjugation of paracetamol with glucuronic acid.

There is limited evidence suggesting that paracetamol may affect chloramphenicol pharmacokinetics but its validity has been criticised and evidence of a clinically relevant interaction appears to lack. Although no routine monitoring is needed, it is important to bear in mind this potential interaction when these two medications are concomitantly administered, especially in malnourished patients

Caffeine

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 520 mg/day of caffeine (8 tablets) per day. Therefore users should take account of dietary and other medicinal sources of caffeine and ensure that they do not exceed the stated dose (See section 4.2).

Xanthine derivatives such as caffeine can weaken the vasodilating effect of substances used for myocardial imaging such as adenosine and dipyridamole. Therefore, caffeine should be avoided for 24 hours before myocardial imaging.

Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers.

Caffeine may enhance the tachycardia effect of some decongestants.

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

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 increases caffeine clearance by up to 50%. Concomitant use of disulfiram and caffeine should be avoided (see contraindications).

Use of lithium carbonate and caffeine may cause a small to moderate rise in serum lithium levels. Concomitant use should be avoided (see contraindications).

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 increased clearance times for theophylline when used concurrently with caffeine. Concomitant use should be avoided (see contraindications).

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.

44.6 Fertility, pregnancy and lactation

Pregnancy

This medicinal product is not recommended during pregnancy unless advised by a physician.

Paracetamol: 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.

Caffeine: In pregnancy a total daily consumption above 200 mg caffeine per day could possibly increase the risk of spontaneous abortion and low birth weight.

Lactation

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

Caffeine appears in breast milk. Irritability and poor sleeping pattern in the infant have been reported. Caffeine in breast milk may potentially have a stimulating effect on breast fed infants.

Therefore, due to caffeine content of this product it should not be used if you are breast feeding.

Fertility

There are no data available regarding the influence of paracetamol this medicinal product on fertility.

4.7 Effects on ability to drive and use machines

None stated.

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 attributable are listed below by system class. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare and serious reactions are very rare.

Adverse reactions reported from extensive post-marketing experience are tabulated below by System Organ Class and frequency. The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Post marketing data

Paracetamol

System Organ Class (SOC)	**Frequency**	**Adverse Reaction**
Blood and lymphatic	Very rare	Thrombocytopenia,

system disorders		agranulocytosis
Immune system disorders	Rare	Anaphylaxis
	Very rare	Allergies (not including angioedema)
Respiratory, thoracic and mediastinal disorders	Very rare	Bronchospasm*
Hepatobiliary disorders	Very rare	Hepatic dysfunction
Skin and subcutaneous tissue disorders	Very rare	Cutaneous hypersensitivity reactions including skin rashes, pruritus, sweating, purpura, urticaria and angioedema.
	Very rare	Very rare cases of serious skin reactions have been reported. Toxic epidermal necrolysis (TEN), drug-induced dermatitis, Stevens-Johnson syndrome (SJS), Acute generalized exanthematous. pustulosis (AGEP).
Renal and urinary disorders	Very rare	Sterile pyuria (cloudy urine)
Metabolism and nutrition disorders	Frequency not known (cannot be estimated from the available data)	High anion gap metabolic acidosis**

* 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
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

System Organ Class (SOC)	**Frequency**	**Adverse reaction**
Central nervous system disorders	Not known	Nervousness, Dizziness

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 such as restlessness and palpitations.
Undesirable effects are not normally observed in healthy individuals taking caffeine at doses up to 520 mg per day. However some users who are caffeine naïve, have abstained from caffeine for a period or who are more sensitive to caffeine may experience effects more commonly seen at higher doses. These include tremor, insomnia, nervousness, irritability, anxiety, headache, tinnitus, arrhythmia, and tachycardia, diuresis, gastrointestinal disturbances and elevated respiration. Individuals who experience these effects must stop taking this medicine (and any others containing caffeine) and any other dietary caffeine.
Following regular use of caffeine, cessation of intake may lead to withdrawal symptoms which may last for up to a week and which include headache, tiredness and decreased alertness.

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 at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

PARACETAMOL

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of

5g 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 NPIS or a liver unit.

CAFFEINE

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time, may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.

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.

Symptoms

An overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, stimulation of the nervous system (insomnia, restlessness, excitement, agitation, nervousness, tremors, and convulsions).

Management

Patients should receive general supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Anilides, combinations excluding psycholeptics.

ATC code: N02B E51

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 prostagalandin synthesis in the hypothalamus.

The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract.

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. Caffeine possesses a weak diuretic action.

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. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.

Caffeine enhances and prolongs the analgesic activity of paracetamol up to 3 hours.

5. PHARMACOLOGICAL PROPERTIES

5.2 Pharmacokinetic properties

PARACETAMOL

Absorption

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 10 minutes to 60 minutes after ingestion depending on pharmaceutical form.

Distribution

Paracetamol is relatively uniformly distributed throughout most bodily fluids and exhibits variable protein binding.

Biotransformation

It is metabolised in the liver mainly as the glucuronide and sulphate conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalysed by the Cytochrome P 450 (mostly CYP2E1), 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 mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination

Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60-80%) and sulfate conjugates (20-30%). In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects.

CAFFEINE

Absorption

Caffeine is rapidly absorbed from the gastrointestinal tract after oral administration. Maximum plasma concentrations are achieved within one hour and the plasma half-life is about 4.9 hours, but there are large inter-individual and intraindividual differences ranging between 1.9-12.2 hours.

Distribution

Caffeine administered orally is practically fully bioavailable and distributes into all body fluids. The mean plasma protein binding of caffeine is 35%. Maximum plasma concentrations are reached after 30-40 minutes.

Biotransformation

Caffeine is almost completely metabolised in the liver by oxidation, demethylation and acetylation, and is excreted in the urine. The major metabolites are 1-methylxantine, 7-methylxantine, 1,7-dimethylxantine (paraxantine). Minor metabolites include 1- methyluric acid and 5-acetylamino-6formylamino 3-methyluracil (AMFU) and other metabolites with only about 1% unchanged.

Elimination

Caffeine and its metabolites are primarily eliminated by the kidneys.

5. PHARMACOLOGICAL PROPERTIES

5.3 Preclinical safety data

Paracetamol and caffeine, individually and in combination, have a well-established Safety profile. 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

Maize Starch
Methylcellulose
Povidone
Talc
Calcium Stearate

6.2 Incompatibilities

None stated

6.3 Shelf life

3 years

6.4 Special precautions for storage

None required.

6.5 Nature and Contents of Container

UPVC/aluminium foil blisters in cartons of 8, 12, 16, 24, 32 tablets.

35gsm Glassine (Pergamin) paper/9 micron soft temper Aluminium foil/250 micron PVC blister

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Wrafton Laboratories Limited

Wrafton

Braunton

North Devon EX33 2DL

8 MARKETING AUTHORISATION NUMBER(S)

PL 12063/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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01/05/2025