Public Assessment Report

UKPAR

Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets

(Paracetamol and Caffeine)

Procedure No: UK/H/6500/001/DC

UK Licence Number: PL 31980/0005

IDL INTERNATIONAL DRUG LICENSING
This is a summary of the Public Assessment Report (PAR) for Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets (UK/H/6500/001/DC; PL 31980/0005). It explains how Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets.

The product will be referred to as Paracetamol and Caffeine Tablets throughout the remainder of this lay summary.

For practical information about using Paracetamol and Caffeine Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Paracetamol and Caffeine Tablets and what are they used for?
Paracetamol and Caffeine Tablets are a medicine with ‘well established use’. This means that the medicinal use of the active ingredients of Paracetamol and Caffeine Tablets are well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Paracetamol and Caffeine Tablets are used for the symptomatic treatment of mild to moderate pain and/or fever in adults and children aged 15 years or over.

How do Paracetamol and Caffeine Tablets work?
Paracetamol and Caffeine Tablets contain two active ingredients, paracetamol and caffeine. Paracetamol is a pain releiver (analgesic) which brings down high temperatures (reduces fever) and caffeine helps to increase the pain relief from paracetamol and makes the patient more alert.

How are Paracetamol and Caffeine Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure. The patient must not take more than the recommended dose.

This medicine should be swallowed whole, with a drink of water. Paracetamol and Caffeine Tablets are for short term use only.

The recommended dose in adults, the elderly and adolescents (aged 15-18 years) weighing more than 60 kg is:
- Take 1-2 tablets every 4-6 hours as required (up to 3 times daily)
- Do not take more than 6 tablets in any 24-hour period
- Do not take more often than every 4 hours.

Use in adults, the elderly and adolescents (aged 15-18 years) weighing between 50 kg and 60 kg:
- Take 1 tablet every 4-6 hours as required (up to 3 times daily)
- Do not take more than 4 tablets in any 24-hour period
Do not take more often than every 4 hours

Use in children and adolescents:
- Paracetamol and Caffeine Tablets should not be given to children under 15 years or to adults or adolescents weighing less than 50 kg.

If the fever persists for more than 3 days or pain for more than 5 days or gets worse or other symptoms appear, the patient should stop taking this medicine and consult their doctor.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Paracetamol and Caffeine Tablets are available as a general sales list (GSL) medicine.

For further information on how Paracetamol and Caffeine Tablets are used, refer to the package leaflet or Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Paracetamol and Caffeine Tablets have been shown in studies?
As paracetamol and caffeine are well known substances, and their use in the symptomatic treatment of mild to moderate pain and or fever in adults and children aged 15 years or over is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of paracetamol and caffeine in the symptomatic treatment of mild to moderate pain and or fever in adults and children aged 15 years.

What are the possible side effects from Paracetamol and Caffeine Tablets?
For the full list of all side effects reported with Paracetamol and Caffeine Tablets, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.

Why were Paracetamol and Caffeine Tablets approved?
The MHRA decided that the benefits of Paracetamol and Caffeine Tablets are greater than the risks and recommended that the product is approved for use.

What measures are being taken to ensure the safe and effective use of Paracetamol and Caffeine Tablets?
A Risk Management Plan has been developed to ensure that Paracetamol and Caffeine Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Paracetamol and Caffeine Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Paracetamol and Caffeine Tablets
Belgium, France and the UK agreed to a grant marketing authorisation for Paracetamol and Caffeine Tablets on 04 May 2018

Following a subsequent national phase, a marketing authorisation was granted in the UK on 01 June 2018.

The full PAR for Paracetamol follows this summary.
For more information about treatment with Paracetamol and Caffeine Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2018.
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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted IDL INTERNATIONAL DRUG LICENSING a Marketing Authorisation for the medicinal product Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets (UK/H/6500/001/DC; PL 31980/0005) on 01 June 2018. Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets are available as a general sales list (GSL) medicinal product. Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets are recommended for the symptomatic treatment of mild to moderate pain and/or fever in adults and children aged 15 years or over.

This application was submitted as an abridged national application according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

The mechanism of analgesic action of paracetamol 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.

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 is a central nervous system stimulant. Caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines. 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.

No new non-clinical studies were submitted, which is acceptable given that this is a bibliographic application for a product containing active substances of well-established use.

No new clinical data have been submitted and none are required for an application of this type, since the scientific evidence found in the published literature was sufficient to discuss all pharmacological, pharmacokinetic and toxicological profiles of the proposed medication and similar medicinal products containing the same active ingredients have been on the market in the EEA for several decades.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

No new or unexpected safety concerns arose during the review of information provided by the MAH and it was, therefore, judged that the benefits of taking Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets outweigh the risks and the RMS considered that this application could be approved at the end of the procedure on 04 May 2018. After a subsequent national phase, a licence was granted in the UK on 01 June 2018.
II QUALITY ASPECTS

II.1 Introduction
The finished product is formulated as a film-coated tablet containing 500 mg of paracetamol and 65 mg of caffeine. Other pharmaceutical ingredients consist of pregelatinized starch, povidone, crospovidone, stearic acid, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate. The tablet film coating Opadry II 85F18422 consists of polyvinyl alcohol, macrogols, talc and titanium dioxide.

Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets are packaged into opaque polyvinyl chloride (PVC) 250 µm / polyvinylidene chloride (PVdC) 80 g/m² - Alu 20 µm blister packs in an outer cardboard carton, containing 4, 6, 8, 10, 12, 14 and 16 tablets. Not all pack sizes may be marketed.

II.2 Drug Substance
1. Paracetamol

INN: Paracetamol
Chemical name: N-(4-Hydroxyphenyl)acetamide

Molecular formula: C₈H₉NO₂
Molecular weight: 151.16 g/mol
Appearance: White or almost white, crystalline powder
Solubility: Sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride

Paracetamol is the subject a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, paracetamol, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

2. Caffeine

INN: Caffeine
Chemical name: 1,3,7-trimethyl-1,3-dihydro-1H-purine-2,5-dione, or 1,3,7-trimethylxanthine.

Structure:
Molecular formula: \( \text{C}_8\text{H}_{10}\text{N}_4\text{O}_2 \)
Molecular weight: 194.2 g/mol
Appearance: white or almost white, crystalline powder or silky white or almost white, crystals
Solubility: It is sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol (96%). It dissolves in concentrated solutions of alkali benzoates or salicylates.

Caffeine is the subject a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, caffeine, are covered by an EDQM Certificate of Suitability.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, tablets containing 500 mg of paracetamol and 65 mg of caffeine.

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for each excipient. Suitable batch analysis data have been provided for each excipient.

With the exception of stearic acid, none of the excipients contain materials of animal or human origin. The suppliers of stearic acid have provided Certificates of Suitability from the EDQM to show that stearic acid is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE). Confirmation has been provided that magnesium stearate is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on production scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.
Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years with no special storage conditions.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The data submitted with this application are acceptable. There are no objections to the approval of this application from a pharmaceutical viewpoint. The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol and caffeine are well known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

The non-clinical overview is acceptable. The overview refers to references dated up to 2018, and is composed of a mixture of journal references, online database searches, reference books, and reference product information.

The SmPC includes an appropriate statement to describe the effects (or lack of effect/data) of the components in the product during pregnancy as agreed by CMDh.

There are no major concerns raised with respect to impurities or excipients in the drug substance and product.

III.2 Pharmacology

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets are intended for generic substitution, this will not lead to an increased exposure of the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

Discussion on the non-clinical aspects

The grant of a Marketing Authorisation is recommended.
IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical pharmacology data, efficacy data or safety data have been submitted and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of paracetamol and caffeine.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

Absorption
Paracetamol
Paracetamol is rapidly absorbed from the gastrointestinal tract, reaching peak plasma levels within 40 to 60 min. The oral administration shows an absolute bioavailability of 60-70%. The area under the concentration versus time curve increases proportionally with dose, indicating linearity of pharmacokinetics.

Caffeine
Caffeine is readily absorbed after oral administration. Maximal plasma concentrations of caffeine are achieved within 1 h. With increasing doses, AUC increases disproportionately indicating non-linear kinetics. Caffeine exhibits dose-dependent pharmacokinetics.

Distribution and Protein binding
Paracetamol
Paracetamol is rapidly and uniformly distributed into most body tissues. About 25% of paracetamol in blood is bound to plasma proteins. Volume of distribution is in the order of 1 l/kg in various species. Paracetamol is transferred across the placenta with an extraction ratio of 0.12. Paracetamol passes rapidly into milk of nursing mothers.

Caffeine
Caffeine methylxanthines are distributed into all body compartments; they cross the placenta and pass into breast milk. The apparent volume of distribution is 0.4 -0.6 l/kg. At therapeutic concentrations, the protein binding of theophylline averages about 60%.

Metabolism and Elimination
Paracetamol
Paracetamol is almost completely cleared from the body by biotransformation. Paracetamol is metabolised by microsomal enzyme systems in the liver. About 80-85% of the paracetamol in the body undergoes conjugation principally with glucuronic acid and to a lesser extent with sulphuric acid. A small amount of paracetamol is also conjugated with cysteine. A small amount of paracetamol is also deacetylated. When there is a deficiency in glutathione, the hepatotoxic metabolite N-acetyl-p-benzoquinoneimine is generated. Paracetamol is excreted in urine principally as paracetamol glucuronide with small amounts of paracetamol sulphate and mercaptate and unchanged drug. Approximately 85% of a dose of paracetamol is excreted in urine as free and conjugated paracetamol. Paracetamol has a plasma half-life of 1.25-3 h.

Caffeine
Caffeine methylxanthines are eliminated primarily by metabolism in the liver. Only 5% of administered caffeine are recovered unchanged in the urine. Caffeine is metabolised in man by demethylation to 1-and 7-methylxanthine, 1,7-dimethylxanthine and 1,3-dimethyluric acid and by oxidation at position 8. The major pathway in man proceeds through the formation of paraxanthine (1,7-dimethylxanthine), leading
to the principal urinary metabolite, 1-methylxanthine, 1-methyluric acid, and an acetylated uracil derivative. At least four human CYP isoforms are involved in caffeine metabolism. The percentage of caffeine excreted unchanged in the urine is low, 1.2 - 3.0%. Elimination half-life is in the range of 1 to 4 h in various species.

**Kinetics in patients with impaired renal/hepatic function**

**Paracetamol**

Impaired elimination of paracetamol was found in hepatitis patients, while peak plasma concentrations were unaffected. The sulphate and glucuronide metabolites of paracetamol accumulated substantially in patients with renal failure.

**Caffeine**

Caffeine disposition is not significantly altered by liver cirrhosis.

**Kinetics in elderly people**

**Paracetamol**

Plasma paracetamol concentration was unaffected by age. The sulphate and glucuronide metabolites of paracetamol accumulated to a low degree in elderly controls. Elimination half-life averaged 2.7 h and was not related to age or sex. Volume of distribution declined with age in both sexes. Paracetamol clearance tended to decline with age in both sexes, but differences were of borderline significance.

**Caffeine**

Comparing the pharmacokinetics of caffeine in healthy young and elderly men time to peak concentration, peak concentration, and the percentage of the peroral dose systemically available were essentially identical in both age groups. Elimination half-lives ranged from 2.27 - 9.87 h. The average volume of distribution was significantly lower in the elderly subjects.

The pharmacokinetics of paracetamol and caffeine are well known and adequately presented in the applicant’s dossier. No new pharmacokinetic data were submitted, and none were required for an application of this type.

### IV.2 Pharmacodynamics

**Paracetamol**

The exact mechanism of action of paracetamol remains to be determined. There is evidence for a number of central mechanisms, including effects on prostaglandin production, and on serotonergic, opioid, nitric oxide (NO), and cannabinoid pathways, and it is likely that a combination of interrelated pathways are in fact involved.

Paracetamol is termed a simple analgesic and an antipyretic. Despite enduring assertions that it acts by inhibition of cyclooxygenase (COX)7-mediated production of prostaglandins, unlike non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol has been demonstrated not to reduce tissue inflammation.

**Caffeine**

Caffeine, a naturally occurring xanthine derivative like theobromine and the bronchodilator theophylline, is used as a CNS stimulant, mild diuretic, and respiratory stimulant (in neonates with apnoea of prematurity). Often combined with analgesics or with ergot alkaloids, caffeine is used to treat migraine and other headache types. Over the counter, caffeine is available to treat drowsiness or mild water-weight gain.

Caffeine stimulates medullary, vagal, vasomotor, and respiratory centres, promoting bradycardia, vasoconstriction, and increased respiratory rate. This action was previously believed to be due primarily to increased intracellular cyclic 3’,5’-adenosine monophosphate (cyclic AMP) following inhibition of phosphodiesterase, the enzyme that degrades cyclic AMP.
The combination treatment of paracetamol and caffeine is supported by both the comparable pharmacokinetic features of the drugs and by the increased pharmacodynamic efficacy of the combination which complement each other. The interaction potential of the combination appears to be low. There is no evidence available that would support an increased toxicological hazard of the combination in addition to the effects of the single drugs except an increased pharmacodynamic response.

The pharmacodynamics of paracetamol and caffeine are well known and adequately presented in the applicant’s dossier. No new pharmacokinetic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data are presented for this application and none are required. However, the applicant has provided a review of study reports published in the literature confirming the efficacy and safety regarding the effectiveness of paracetamol and caffeine in the treatment of mild to moderate pain and is summarised below.

The efficacy and role in the therapeutic strategy of paracetamol at the dose of 500 mg in fixed combination with caffeine at the dose of 65 mg are well established and no longer need to be demonstrated in the indications, dosages, and age groups claimed by the proprietary medicine Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets.

The usual dosage is 1 to 2 tablets, repeated if necessary after a minimum of 4 hours. It is usually unnecessary to exceed 3 grams of paracetamol per day, or 6 tablets. However, in case of more intense pain, the maximum dosage can be increased up to 4 grams of paracetamol per day, or 8 tablets per day. A 4-hour interval between intakes must always be observed.

The use is restricted to adults over 50 kg (15 years old and over) due to the presence of caffeine. The choice of an analgesic depends on the intensity and the origin of the pain. Paracetamol is effective in mild to moderate pain of various origins and types (musculoskeletal, post-traumatic, dental, headache). For symptomatic treatment of mild to moderate pain conditions and/or febrile conditions, paracetamol is the first-line systemic analgesic.

In the meta-analysis performed by in a literature review, the efficacy and safety of paracetamol/caffeine was compared with paracetamol alone in the short-term relief of acute pain. A total of 8 randomised, double-blind studies comparing the combination of Paracetamol 1g/caffeine 130mg to 1 g of paracetamol alone in various acute pain settings (dysmenorrhoea, headache, postpartum pain and dental pain) were included. The percentage of patients who achieved at least 50% pain relief between 0 and 4 hours post-dose was 65% in the paracetamol/caffeine group and 57% in the paracetamol alone group (relative risk = 1.12; 95% CI: 1.05-1.19). Analysis of the data pertaining to the effects of the combination of paracetamol and caffeine on the liver shows no increase in the hepatotoxicity of paracetamol.

The main analgesics studied were paracetamol (7 studies) and ibuprofen (5 studies) with doses of caffeine between 50 and 260 mg. The percentage of patients with at least 50% pain relief was 67% (1,803 / 2,678, 27% to 93%) in the analgesic/caffeine group, and 61% (1,617 / 2,656; 6 % to 80%) in the analgesic alone group. There was a small benefit from the addition of caffeine to analgesic with a relative risk of 1.1 (1.08 to 1.2) compared to analgesic alone.

A Cochrane meta-analysis compared in 2012 the efficacy of the analgesic/caffeine combination to analgesic alone in alleviating acute pain. A total of 19 randomised, double-blind studies in various acute pain types (headache, postpartum pain, dental pain and dysmenorrhoea) were included.
Clinical efficacy conclusion
The clinical efficacy of paracetamol and caffeine are well known and adequately presented in the applicant’s dossier. No new pharmacokinetic data were submitted and none were required for an application of this type.

IV.5 Clinical safety
The applicant has mostly supplied information on the toxicology and overdose of paracetamol and to a lesser extent of caffeine. These are summarised below.

Paracetamol
The safety of the paracetamol/caffeine fixed association (500mg/65mg) in the indications and dosages claimed by the proprietary medicine is well validated. It should be understood in light of pharmacokinetics and toxicology data.

Potential fatal kidney, brain, and liver damage may be caused by acute overdose of paracetamol, and in rare individuals, even after a therapeutic dose, attributable perhaps to the presence of subclinical risk factors such as ‘fast-metaboliser’ status, glutathione deficiency or both. However, usage within the therapeutic range, particularly frequent regular use, can also impact on other organ systems, with effects that are less widely acknowledged.

In the case of paracetamol overdose, hepatic stores of glutathione become depleted, leaving the toxic metabolite free to damage liver tissue. Such damage is unlikely to occur unless the plasma concentration of paracetamol peaks above 150 μg/mL.

With therapeutic doses the plasma concentrations are between 5 and 20 μg/mL. Moreover, there is evidence for the formation of paracetamol free radical metabolite, by mammalian peroxidases, as has been proposed previously. Long term therapeutic use of paracetamol does not appear to be associated with liver damage, although some case reports suggest the possibility. Paracetamol poisoning follows an acute overdose. Treatment with specific antidotes like N-acetylcysteine is effective when initiated within 10-24 hours of the time of overdose.

Caffeine
Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, and 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.

Regarding treatment, 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.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Paracetamol and Caffeine IDL 500 mg/65 mg film-coated tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
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<th>What is Known</th>
<th>Preventability</th>
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<td>Allergic reactions to paracetamol, caffeine, or to any other ingredients of this medicine (hypersensitivity to paracetamol, caffeine, or to any of the excipients)</td>
<td>The use of paracetamol and caffeine is contraindicated for patients allergic to paracetamol, caffeine, or to any of the other inactive substances of this medicinal product. Severe allergic reactions (anaphylactic reaction), allergic dermatitis, rash, swelling of the deep layers of skin (angioedema), life-threatening dermatologic reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) are rare (affecting up to 10,000 users) side effects reported with use of this medicinal product.</td>
<td>Yes. Patients should not use this medicinal product if they are allergic to paracetamol, caffeine, or to any of the other inactive substances that it contains. If patients experience any of these side effects, they should contact their doctor immediately.</td>
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<td>Liver problems (hepatic impairment)</td>
<td>The use of paracetamol and caffeine is contraindicated for patients suffering from liver problems. Caution is advised in the administration of paracetamol to patients suffering from mild to severe liver problems (including a pathology called the Gilbert’s syndrome, a type of jaundice), acute hepatitis (inflammation of liver), a pathology called glucose-6-phosphatedehydrogenase deficiency, or if under concomitant treatment with medicinal products affecting hepatic functions.</td>
<td>Yes. Patients should not use this medicinal product if they are suffering from liver problems. In case of mild to severe liver problems, the daily dose should not exceed 2 g.</td>
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<td>'Overdose (accidental and intentional) and risk to exposure to multiple products containing paracetamol</td>
<td>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 is on long term treatment with medicines used to treat epilepsy (carbamazepine, phenobarbitone, phenytoin), depression (St John's Wort), anticonvulsants (primidone), some antibiotics (rifampicin), or other drugs that induce liver enzymes, or regularly consumes ethanol in excess, or if he suffers from eating disorders, cystic fibrosis, HIV infection,</td>
<td>Yes. Patients should always take this medicine exactly as described in the leaflet or as it has been told by their doctor or the pharmacist. Patients must not take anything else containing paracetamol while taking this medicine. Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of</td>
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The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

I. At the request of the RMS;

II. Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

The RMP will need to be updated according to GVP V rev 2 at the next RMP update.

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<th>Risk</th>
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<th>Preventability</th>
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<td>dehydration or chronic malnutrition. Symptoms of paracetamol over-dosage 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/sugar breakdown and metabolic acidosis may occur. In severe poisoning, liver failure may progress to brain disorders (encephalopathy), bleeding (haemorrhage), low blood sugar levels (hypoglycaemia), accumulation of fluid in the brain (cerebral oedema), and death. Acute renal problems (acute tubular necrosis), strongly suggested by loin pain and blood and proteins in urines (haematuria and proteinuria), may develop even in the absence of severe liver damage. Cardiac arrhythmias (abnormal heart beats) and pancreatitis (swelling of the pancreas) have been reported.</td>
<td>significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Management should be in accordance with established treatment guidelines.</td>
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If the dates for submission of a Periodic Safety Update Report and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

**IV.7 Discussion of the clinical aspects**
There are no objections to the approval of this application from a clinical point of view. The grant of a Marketing Authorisation is recommended.

**V User consultation**
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

**VI Overall conclusion, benefit/risk assessment and recommendation**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Paracetamol and caffeine are widely used and well-known active substances which have a long history of established favourable risk-benefit profile. Their use is well established with recognised efficacy and acceptable safety. The benefit-risk is, therefore, considered to be positive.
The approved labelling text for Paracetamol and Caffeine Tablets is presented below:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Carton – OTC

1. **NAME OF THE MEDICINAL PRODUCT**

   Paracetamol/Caffeine IDL International Drug Licensing 500 mg/65 mg film-coated tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each tablet contains 500 mg Paracetamol and 65 mg Caffeine.

3. **LIST OF EXCIPIENTS**

   See package leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

   - Box of 4 film-coated tablets
   - Box of 6 film-coated tablets
   - Box of 8 film-coated tablets
   - Box of 10 film-coated tablets
   - Box of 12 film-coated tablets
   - Box of 14 film-coated tablets
   - Box of 16 film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

   Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.
Do not take anything else containing paracetamol while taking this medicine.
Talk to a doctor at once if you take too much of this medicine, even if you feel well.

8. **EXPIRY DATE**

   EXP

9. **SPECIAL STORAGE CONDITIONS**

   This medicinal product does not require any special storage conditions.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

    **IDL INTERNATIONAL DRUG LICENSING**
    DELRIV
    Face an n°9 quai du Quatre Septembre
    92100 Boulogne-Billancourt
    FRANCE

12. **MARKETING AUTHORISATION NUMBER(S)**

    PL 31980/0005

13. **BATCH NUMBER**

    Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

    Medicinal product not subject to medical prescription.

15. **INSTRUCTIONS ON USE**
Symptomatic treatment of mild to moderate pain and/or fever in adults and children aged 15 years or over.

Do not give Paracetamol and Caffeine IDL to children under 15 years or to adults or adolescents weighing less than 50kg.

Adults, elderly and adolescents (aged 15-18 years) weighing more than 60kg
Take 1-2 tablets every 4-6 hours as required (up to 3 times daily).
Do not take more than 6 tablets in any 24 hour period.

Adults, elderly and adolescents (aged 15-18 years) weighing between 50kg and 60kg
Take 1 tablet every 4-6 hours as required (up to 3 times daily).
Do not take more than 4 tablets in any 24 hour period.

Do not take more frequently than every 4 hours.
For short term use only.

16. INFORMATION IN BRAILLE

Paracetamol/Caffeine IDL International Drug Licensing 500 mg/65 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.
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<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
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1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

2. **METHOD OF ADMINISTRATION**

3. **EXPIRY DATE**

4. **BATCH NUMBER**

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

6. **OTHER**
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**Blisters**

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Annex 1 Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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