IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Solpa-Extra 500 mg/65 mg Soluble Tablets
Caffeine
PARACETAMOL
PA1186/017/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6161/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 08th August 2019 under procedure number IE/H/1038/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/017/001
Marketing Authorisation Holder: Chefaro Ireland DAC

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Paracetamol and Caffeine soluble tablets (PL 02855/0243; UK/H/6161/001/DC) could be approved.

This is a decentralised abridged application submitted under Article 10a (well-established use application) of Directive 2001/83/EC, as amended. The United Kingdom acted as RMS and Cyprus, Estonia, Greece, Ireland, Lithuania, Latvia, Poland and Romania were CMSs.

Paracetamol is an analgesic with antipyretic properties and will relieve the generalised aches, pains and fever of the conditions. Paracetamol has been widely available as an over-the counter (OTC) analgesic in many countries since the late 1950s, being sold alone and in combination in numerous proprietary preparations in both oral and rectal forms. The maximum recommended adult dose of paracetamol is 500-1000 mg every 4-6 hours up to a maximum of 4 g in 24 hours. Paracetamol at the maximum recommended adult oral dosage of 4 g daily is well-tolerated with only very occasional mild side effects.

The presence of caffeine in Paracetamol and Caffeine soluble tablets at a daily dose of up to 520 mg provides a central nervous system (CNS) stimulant effect that helps to counter the mood depressing effect of pain and is considered to act as an analgesic adjuvant in this combination.

The application is for a non-prescription medicine (General Sales List in the UK)- this is consistent with similar products on the UK market.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that this is a bibliographic application for actives of well-established use.

The RMS 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 and assembly of this product.

All Member States agreed to grant licences for the above products at the end of procedure (Day 210 - 9 November 2016). After a subsequent national phase, the UK granted a licence for this product on 30 November 2016 (PL 02855/0243).

II. QUALITY ASPECTS

II.I Introduction

This decentralised abridged application is submitted by Omega Pharma Limited under Article 10a (well-established use or bibliographic) of Directive 2001/83/EC, as amended.

Paracetamol and Caffeine soluble tablets contain 500 mg of Paracetamol and 65 mg of Caffeine per tablet. Other ingredients consist of the pharmaceutical excipients sorbitol, saccharin sodium, sodium hydrogen carbonate, sodium laurilsulfate, citric acid anhydrous, sodium carbonate anhydrous, povidone, dimeticone and purified water.

The finished product is packed in a sachet consisting of a paper outer-layer and an inner layer which is comprised of polyethylene and aluminium.

All primary product packaging complies with EU legislation and are suitable for contact with foodstuffs. Packaging components are not approved for use until a quality assurance assessment has been undertaken on samples to show that their quality meets the required specifications and acceptance criteria.

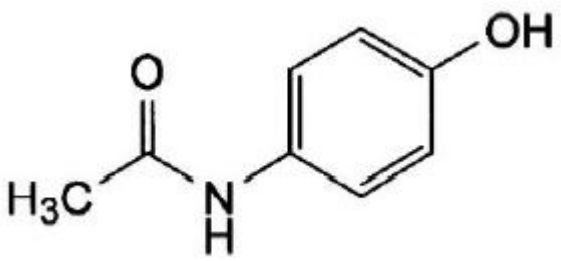
II.2 DRUG SUBSTANCES

1. Paracetamol

rINN: Paracetamol

Chemical Name: N-(4-hydroxyphenyl)acetamide

Structure:



Molecular Formula: $C_8H_9NO_2$

Molecular Weight: 151.2

Appearance: Paracetamol is a white, crystalline powder.

Solubility: It is sparingly soluble in water; but freely soluble in alcohol and very slightly soluble in dichloromethane.

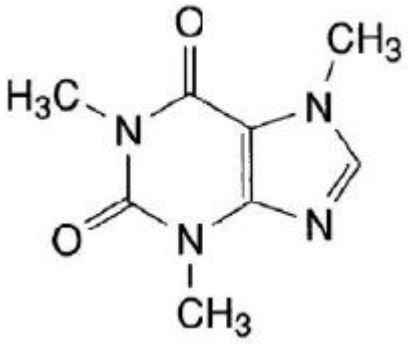
All aspects of the manufacture and control of the active substance, paracetamol, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

2. Caffeine

rINN: Caffeine

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

Structure:



Molecular formula: $C_8H_{10}N_4O_2$

Molecular Weight: 194.2

No polymorphs have been reported for caffeine.

Appearance: Caffeine is a white or almost white, crystalline powder. It is sparingly soluble in water, freely soluble in boiling water, and slightly soluble in ethanol.

The proposed drug substance specification is satisfactory.

Batch analyses have been provided for three batches, from each active substance manufacturer, indicating compliance with the Ph.Eur. specification.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed and the proposed retest period of 60 months is justified and a storage statement in line with CHMP guidelines has been proposed. All aspects of the manufacture and control of the active substance, caffeine, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to formulate safe, efficacious, soluble tablets containing 500 mg of paracetamol and 65 mg of caffeine per tablet.
A satisfactory level of detail was provided in relation to the pharmaceutical development. All the excipients comply with the appropriate monographs in the Ph. Eur. and the product manufacturer will be using pharmacopoeial methods to test the materials.

None of the excipients are of human or animal origin and furthermore, none are sourced from genetically modified organisms.

There were no novel excipients used.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. Test methods have been described and are adequately validated. Batch data have been provided that comply with the release specification.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 48 months with a storage condition 'Do not store above 25°C' is set. This is satisfactory.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.I 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.

III.2 Pharmacology

Paracetamol has both analgesic and antipyretic activity, which is believed to be mediated through inhibition of the cyclooxygenase (COX) pathway. Although this mechanism is shared with the non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol does not have significant anti-inflammatory activity nor does it inhibit production of pro-clotting thromboxanes. Additional pathways such as the serotonergic descending pain pathways may be involved in the anti-nociceptive effect of paracetamol.

Caffeine is well known to be a mild stimulant of the central nervous system (CNS) and is widely used for this purpose at oral doses of 50-200 mg.

III.3 Primary Pharmacodynamics

The pharmacology of the individual active substances is adequately discussed in the applicant's non-clinical overview and is only briefly summarised below.

Paracetamol possesses both analgesic and antipyretic properties. It is a weak anti inflammatory drug, and is effective as an antipyretic and analgesic agent at doses that partly inhibit the cyclooxygenases, but appears to have fewer gastrointestinal side effects than the other non-steroidal anti-inflammatory drugs (NSAIDs).

Paracetamol is thought to inhibit cyclo-oxygenase (COX) enzymes via inhibition of their peroxidase function. This results in inhibition of the formation of a phenoxyl radical from a tyrosine residue that is essential for the synthesis of prostaglandins. Paracetamol shows selectivity for inhibition of the synthesis of prostaglandins and related factors when low levels of arachidonic acid and peroxides are available but little activity when substantial levels of arachidonic acid and peroxides are present. As a result, paracetamol is generally ineffective in suppressing the severe inflammation of conditions such as rheumatoid arthritis or severe gout, but does inhibit lesser inflammation, for example following the extraction of teeth. This activity has been demonstrated in a variety of inflammatory tests in experimental animals.

Paracetamol probably exerts its antipyretic action by inhibition of prostaglandin synthesis in the hypothalamic heat-regulating centre, resulting in peripheral vasodilation, which in turn causes increased blood flow through the skin, sweating and heat loss.

Caffeine
Caffeine is a naturally occuring methylxanthine alkaloid which is also produced by chemical synthesis. It is routinely ingested as a component of coffee, tea, cocoa, chocolate, cola, and many medicinal products.

Caffeine is well known to be a mild stimulant of the central nervous system (CNS) and is widely used for this purpose at oral doses of 50-200 mg. In addition, it is often included in oral analgesic preparations at unit doses ranging from about 15 to 65 mg. The quantity of caffeine in a cup of coffee is about 50-100 mg.

Caffeine has been shown to have intrinsic anti-nociceptive activity in several rodent models and to augment the analgesic effects of paracetamol and non-steroidal anti-inflammatory agents. These effects may be due to antagonism of central adenosine A(2A) and A(2B) receptors as well as inhibition of synthesis of cyclo-oxygenases at some sites.

Other biochemical effects of caffeine have been observed *invitro* and these include the inhibition of phosphodiesterases, direct and indirect effects on intracellular calcium concentrations and uncoupling of intracellular calcium increases with muscle contractile elements, inhibition of glycogen phosphorylases in the liver and muscle and stimulation of cellular membrane sodium/potassium pumps. High concentrations of caffeine have been shown to inhibit secretion of parathyroid hormone in human parathyroid cells, possibly due to a reduction in intracellular levels of cAMP. This could theoretically result in a reduction in bone mineral density, urinary calcium loss and impaired bone development, although the effects are unlikely to be seen at therapeutic dose levels.

Caffeine has been shown in non-clinical studies to act as a weak inhibitor of monoamine oxidases MAO-A and MAO-B, and high doses of caffeine are also thought to cause stimulation of cardiac muscle, increases in blood pressure and cardiac output, increased gastric acid and pepsin secretion, smooth muscle relaxation (notably of the bronchial muscle), diuresis and increased free fatty acid and catecholamine release from the adrenal medulla.

Caffeine may also stimulate the respiratory centre to increase the rate and depth of respiration. In cardiovascular terms, the stimulatory effect of caffeine on the medullary vasomotor centre and its positive inotropic effect on the myocardium are compensated by a peripheral vasodilator effect on the arterioles, so that the net effect on blood pressure is generally low.

Paracetamol and caffeine in combination

The use of paracetamol-caffeine combinations in the oral treatment of painful and febrile conditions is well-established in clinical practice, particularly via self-administration.

The effect of caffeine on the anti-nociceptive effect of paracetamol in the murine formalin test was investigated. The formalin test was the pain model chosen, as it involves activation of sensory afferents and recruitment of ascending and descending circuitry involved in pain signalling and modulation. Mice were chronically administered caffeine in their drinking water for 8 days. Paracetamol at a dose of 300 mg/kg administered intra-peritoneally (i.p.) 20 minutes pre-treatment reduced the cumulative Phase II flinching behaviours by approximately 60%, whereas a 100 mg/kg dose was ineffective. A caffeine dose of 10 mg/kg had no anti-nociceptive effect, but inhibited the anti-nociception produced by paracetamol 300 mg/kg given i.p. against Phase II flinches. Caffeine appeared to inhibit the anti
nociceptive effect of paracetamol via adenosine A1 receptors specifically located in the spinal cord. This implies that dietary caffeine could potentially inhibit analgesia produced by paracetamol in humans, although this effect has not been displayed clinically.

III.4 Pharmacokinetics

Paracetamol, in man, is rapidly absorbed from the gastrointestinal tract (small intestine), and rapidly and relatively uniformly distributed throughout the body tissues. Paracetamol is extensively metabolised with only 2-5% of a therapeutic dose excreted unchanged in urine.
It has good oral bioavailability and displays low to moderate plasma protein binding at therapeutic concentrations.

Paracetamol is metabolised predominantly in the liver, undergoing extensive biotransformation to sulphate and glucuronide conjugates. The major metabolites of paracetamol are the 4-sulphate and 4-glucuronide conjugates, but a minor fraction is converted by hepatic mixed function oxidase to N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive alkylating metabolite. This metabolite is normally rapidly inactivated by conjugation with reduced glutathione and eventually excreted in the urine as cysteine and mercapturic acid conjugates. Large doses of paracetamol cause acute hepatic necrosis as a result of depletion of glutathione and of covalent binding of the excess reactive metabolite to vital cell constituents.

Urinary excretion is the predominant pathway of elimination for all paracetamol metabolites, although substantial quantities of both the 4-glucuronide and 3-glutathione conjugates are excreted initially in bile. At higher doses, there is a shift to the glucuronidation pathway, resulting in a higher biliary excretion.

There are few reports of pharmacokinetic drug interactions although drugs that increase the rate of gastric emptying, such as domperidone and metoclopramide, may accelerate the absorption of paracetamol. Colestyramine may reduce the rate of absorption of paracetamol. Pre-treatment with probenecid can decrease paracetamol clearance and increase its plasma half-life. These interactions are discussed in the clinical overview.

The first known report of an interaction of paracetamol and grapefruit juice was published following a study in mice, concomitant administration of the juice increased plasma concentrations of paracetamol one and two hours after dosing in comparison with control animals, possibly due to an increase in the elimination half-life of the paracetamol.

Caffeine in humans is well described. It is rapidly absorbed and widely distributed around the body. It crosses the placenta and appears in low concentrations in breast milk. Binding to human serum albumin has been demonstrated *invitro*. Caffeine shows about 35% protein binding in human volunteers.

Caffeine is eliminated primarily by hepatic metabolism. In humans it is metabolised in hepatic microsomes by oxidation, demethylation and acetylation before excretion in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamine-3-methyluracil (AFMU) and more than 20 other metabolites.

As caffeine undergoes extensive metabolism by cytochrome P450, it may be subject to numerous interactions with other drugs and substances that enhance or reduce its metabolic clearance as discussed in the clinical overview. Obesity, exercise, disease states and smoking may also affect the elimination of caffeine due to either stimulation or inhibition of hepatic metabolising enzymes.

Co-administration of caffeine has been reported to increase the absorption of paracetamol by increasing gastric and ileal blood flow and by lowering gastric pH, thereby enhancing diffusion. It may also prolong the duration of activity of paracetamol.

Paracetamol and caffeine in combination

Pharmacology studies in both animals and man have shown that caffeine has a beneficial effect on the analgesic properties of paracetamol. This effect partly arises from the influence that caffeine can have on the absorption of paracetamol. Caffeine can lower gastric pH and increase gastric and hepatic blood flows, hence a number of different authors have speculated that because of these properties caffeine might improve the absorption of agents whose pKa renders them non-ionised in an acid environment (for example, aspirin). Some reports have shown that caffeine co-administration results in a reduction of paracetamol and aspirin plasma concentrations. Until very recently it has been suggested that modification of the anti-nociceptive effect of analgesics by caffeine was not likely to be due to a pharmacokinetic interaction.

A study in 24 healthy subjects has shown that paracetamol-caffeine combination doses and paracetamol only doses were bioequivalent for paracetamol with respect to their bioavailability (later area under the concentration-time curves [AUCs]). However the early AUC values and the peak plasma concentration (Cmax) for paracetamol were higher with a paracetamol-caffeine combination. Hence there appears to be a pharmacokinetic element within the adjuvant analgesic effect that caffeine provides when co-administered with paracetamol.

III.5 Toxicology

A comprehensive review of the published literature has been provided by the applicant, citing the well-established toxicology properties of paracetamol. The summaries of these findings are presented below.

Paracetamol: Non-clinical data reveal no special hazard based on conventional studies of safety pharmacology, repeat dose toxicity, reproduction, teratogenicity, genotoxicity, and carcinogenic potential, except for N-acetyl-p-benzoquinoneimine (NAPQI)-induced organ toxicity (especially liver and kidney) at high doses, and reversible blockade of DNA synthesis and repair. Experience in terms of patient exposure to the active substances is considerable (i.e. widespread use for many decades) and demonstrates low general toxicity and no teratogenic, genotoxic or carcinogenic properties relevant to consumer safety at therapeutic doses.

The most common target organs reported in association with single-dose toxicity data are the liver and kidneys; primarily involving hepatocellular necrosis and changes in renal function. Human data suggest an approximately 10-fold difference between the recommended dose and a potentially fatal single dose. This represents a relatively low margin of safety but this is well known for paracetamol. The proposed product is not considered to present a greater risk of acute toxicity than other products containing paracetamol. It is proposed that the packaging will include clear instructions that it should not be taken with other products that contain paracetamol.

Paracetamol does not cause gene mutations in either bacteria or mammalian cells but it consistently produces chromosome aberrations in *invitro* studies. The clastogenicity is concentration- and incubation time- dependent with clastogenic effects generally absent until cytotoxic concentrations are reached.

Three possible mechanisms of genotoxicity have been suggested, all of which show dose thresholds:

1) inhibition of ribonucleotide reductase;
2) increase in cytosolic and intranuclear calcium levels;
3) DNA damage caused by NAPQI after glutathione depletion.

An extensive review article indicates that reliable studies on the ability of paracetamol to affect germ cell DNA are not available but concludes that, based on the amount of drug likely to reach germ cells and the evidence of thresholds, paracetamol is not expected to cause heritable damage in man.

In animal reproduction toxicity studies, paracetamol reduces male fertility due to toxicity to early spermatocytes. Such effects are not expected at therapeutic dose levels. No teratogenic effect of paracetamol was observed in humans, although paracetamol-induced fetal liver toxicity has been described after toxic maternal doses.

Caffeine: The LD50 of single subcutaneous injections of caffeine has been reported as 265 mg/kg in adult rats and 155-220 mg/kg in two-day old rats. High doses of caffeine caused convulsions, tremor, lethargy and licking of lips. Acute intraperitoneal injections of caffeine had an anxiogenic effect in male mice and following chronic administration for 21 days resulted in tolerance to the anxiogenic effect, but abrupt discontinuation produced anxiety like behaviour.

Caffeine may either lower the convulsive threshold in experimental models of epilepsy or induce seizure activity at doses greater than 400 mg/kg in rodents. The results of a series of studies of three intravenous doses of caffeine in 13 dogs showed a dose-dependent arrhythmogenic effect.

The available data suggest that caffeine is not mutagenic in higher organisms, and following detailed review of non-clinical and clinical data it was concluded that caffeine is unlikely to be genotoxic in humans, and considered not to be carcinogenic.

Using a chick embryo model for the development of the fetal nervous system, caffeine was found to cause malformations of the neural tube and other teratogenic effects on neurodevelopment. Teratogenic effects of caffeine have been demonstrated in mice at high daily doses of 50-75 mg/kg and in rats at 80 mg/kg (or 300 mg/kg when given in divided daily doses). The most frequently observed malformations in rodents were those of limbs and digits, ectrodactyl, craniofacial malformations and delays in the ossification of limbs, jaw and sternum. Maternal exposure to caffeine also had long-term effects on the sleep, locomotion, learning ability, emotivity and anxiety of rat offspring.

Recent studies have demonstrated that prenatal exposure to very high doses of caffeine (120 mg/kg/day) induced intra-uterine growth retardation leading to an increased susceptibility to metabolic syndrome with alternation of glucose and lipid metabolic programming in adult first-generation and second-generation rats.

As discussed in the clinical overview, many epidemiological studies have evaluated the effect of caffeine on fertility in humans but the results have been inconsistent. Moderate daily intake of caffeine is not generally thought to have an adverse effect on male or female
fertility.

Paracetamol and caffeine: No teratogenic effects were seen in Wistar rats following prenatal exposure to repeated doses of paracetamol (3.5, 35 or 350 mg/kg) in combination with caffeine (0.7, 7 or 70 mg/kg). Decreases in organ and maternal weight are observed, as were dose-dependent effects on fetal body weight and growth and placental weight.

The applicant has indicated that the primary data related to safety of the use of the combination is found following clinical use, this combination has been approved for over 40 years.

III.6 Impurities

A section of the non-clinical overview is dedicated to impurities.

It is stated that all active substances comply with their respective Ph. Eur. monographs. Impurity levels are therefore controlled in accordance with the requirements of the monographs.

The level of the paracetamol known and unknown related substances is controlled in the release and shelf life specifications in accordance with the limits specified in ICH Q3B (R2) ''Note for Guidance on Impurities in New Drug Products", which specify a Qualification
Threshold of 0.2% with respect to the maximum daily dose for paracetamol (>100 mg- 2 g per day).

Caffeine
There are no recognised degradants of caffeine listed in the Ph. Eur. monograph.

III.7 Environmental Risk Assessment
Since this product will be used as a substitute of other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.

III.8 Discussion on non-clinical aspects

There are no objections to the approval of Paracetamol and Caffeine soluble tablets from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.I 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:
Oral paracetamol is readily absorbed from the upper small intestine to give peak plasma concentrations (C_{max}) of 15-20 µg/mL in 30-120 minutes after oral administration of a 1 g dose in adults. The speed of gastric emptying modifies the rate of absorption.

Caffeine:
Caffeine is rapidly absorbed after oral administration with C_{max} occurring after about 20-60 minutes.

Combination:
A study incorporating caffeine 60 mg with a dose of paracetamol of 1 g showed that caffeine had no significant effect on paracetamol absorption.

Distribution

Paracetamol:
Plasma protein binding is minimal and there is distribution to all tissues. There is limited first-pass metabolism of paracetamol after oral administration and about 80% of a 1 g dose is bioavailable.

Caffeine:
The plasma protein binding is about 35%.

Combination:
No studies specifically addressing the distribution of paracetamol and caffeine have been identified. Given the lack of significant clinical effect of dynamic and kinetic interactions, it is considered unlikely that the addition of caffeine would have any clinically relevant effect on the distribution of paracetamol.

Metabolism

Paracetamol:
Paracetamol is metabolised primarily in the liver. After a 1 g oral dose in adults, 50-60% is recovered in the mine as the glucuronide conjugate, 25-35% as the sulfate conjugate, up to 5% as unchanged paracetamol, and 2-5% as the cysteine or mercapturate metabolites. The latter are formed from the combination of glutathione with the oxidation metabolite of paracetamol, N-acetyl-p-benzoquinoneimine (NAPQI).

Caffeine:
It is almost completely metabolised in the liver by oxidation and demethylation to various xanthine derivatives.

Combination:
From a pharmacokinetic standpoint, no significant clinical interaction is to be expected between paracetamol and caffeine. In particular their individual metabolism is largely different, with the oxidation pathway for caffeine being a very minor metabolic pathway for paracetamol.

Elimination
(Excretion)
Paracetamol:
Excretion via the urine is rapid and the plasma half-life (t½) after oral administration is about 2.3 hours.

Caffeine:
In the urine. The plasma t½ of caffeine is about 4 hours.

Combination:
No studies specifically addressing the elimination of paracetamol and caffeine have been identified. Given the lack of significant clinical effect of dynamic and kinetic interactions, it is considered unlikely that the addition of caffeine would have any clinically relevant effect on the elimination of paracetamol.

There was a reduction in the total body clearance of paracetamol when caffeine was co administered. The reduced clearance is unlikely to increase toxicity because production of the toxic reactive metabolite of paracetamol would be unaffected. Contrasting results were obtained in a randomised, crossover study in nine health volunteers, in which peak plasma and paracetamol levels decreased and the rate of elimination of paracetamol increased when caffeine was given concomitantly.

Special populations

Elderly
Paracetamol:
In a study the metabolism of paracetamol was compared in young adults, with a mean age of 20.8 years, and the elderly, with a mean age of 79.3 years. There were no significant differences in apparent oral clearance or partial metabolic clearances to the glucuronide or glutathione-derived derivatives of paracetamol. However, renal clearance of the unchanged drug was 42.9% lower and partial metabolic clearance to paracetamol sulfate was 23.1% lower in the elderly compared with young adults.

Caffeine:
Combination:
From a pharmacokinetic standpoint, no significant clinical interaction is to be expected. In particular, their individual metabolism is largely different, with the oxidation pathway for caffeine being a very minor metabolic pathway for paracetamol.

Children

Paracetamol:
There is no evidence or valid scientific reason to suggest that the efficacy profile in 12-18 year-olds should differ from the rest of the population.

A recent review by Martino and Chiarugil describes several clinical trials, involving hundreds of children aged between 6-17 years. There is consistent evidence to support the efficacy of paracetamol in this age group.

A review describes several studies to support the efficacy of paracetamol in pain following surgical removal of wisdom teeth. The majority of the studies involved young adults aged 18-25 years, but several studies included patients aged 15-18 years. The precise numbers of 15-18 year-olds is not provided, but the consistent evidence of efficacy in this challenging pain model in young adults, including some adolescents, provides strong support for similar efficacy in 15-18 year-old adolescents.

A further review described studies which compared ibuprofen and paracetamol after surgical removal of lower molars. The age range of the participants was slightly different across the studies but broadly similar. In Forbes 1990 and Mehlisch 1995, the age range was > 15 years, in Hersh 2000 and Mehlisch 2010a, it was > 16 years. Age ranges applied in one study (16 to 40 years), with a range of 16 to 65 years used by another study. The results suggested superior efficacy for ibuprofen, but there was sufficient evidence of paracetamol efficacy in those studies involving a placebo period.

A group reviewed studies involving migraine in children. A total of 1575 patients were included, with a mean age of 11.7 +/-2.2 years (range: 4-18). Insufficient detail was provided to specify the exact numbers of 12-18 year old patients in particular studies, but overall, the studies support the efficacy of paracetamol in migraine in young and older children, including adolescents.

A meta-analysis described several studies of pain in children. Although most of the studies involved children under 10 years, two studies had mean ages of 11 and 14 years respectively. These studies provide secondary support for efficacy in young adolescents.

Paracetamol and caffeine in combination:
There are sufficient data from clinical trials to confirm that the efficacy of a paracetamol and caffeine combination is superior to that of paracetamol alone in young adults.

There are limited data specifically related to adolescents, but data relating to paracetamol monotherapy confirms efficacy in children and adolescents. Since caffeine acts purely as an adjuvant, the efficacy profile of the combination is likely to exceed that of the monotherapy. It is considered therefore that efficacy of the combination is confirmed in adolescents.

The safety profile of caffeine 65mg is well established by the long marketing exposure of hundreds of millions of tablets. Clinical trial data, though sparse in adolescents, confirms the overall safety profile. Normal use of the tablet in line with the SmPC provides caffeine exposure similar to normal dietary intake. The main concern in adolescents is over consumption, especially the increasing popularity of"high energy" drinks. This is adequately documented in the cunent SmPC.

Overall conclusions on pharmacokinetics
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.

Bioequivalence
No bioequivalence study has been conducted to support these bibliographic applications. This is appropriate for this well-established use application.

IV.3 Pharmacodynamics

Paracetamol:
The precise mechanism for the analgesic properties of paracetamol remains to be established. Data suggest that central prostaglandin synthetase inhibition is likely to be of primary importance. Paracetamol is a weak inhibitor of cyclooxygenase-1 (COX-1) and COX-2, leading to the suggestion that there may be another form of COX that is more sensitive to inhibition by paracetamol. A third distinct COX isoenzyme has been described (COX-3), which is inhibited by paracetamol and expressed in specific tissues with highest levels in human cerebral cortex and heart. Whether this is the target for paracetamol is uncertain. Paracetamol does not exhibit a clinical anti-inflammatory effect.

The antipyretic activity of paracetamol is thought to be mediated by its ability to selectively inhibit prostaglandin synthesis in the CNS.

Paracetamol, unlike non-steroidal anti-inflammatory drugs (NSAIDs), does not appear to inhibit the peripheral generation of prostaglandins. For example, it does not alter the gastric mucosal generation of prostaglandins and these data are supported by clinical evidence demonstrating the extreme rarity of serious renal and gastro-intestinal adverse events associated with paracetamol.

The analgesic effect has been shown to be dose dependent, with 1 g being more effective than lower doses and therefore useful for more severe pain. The onset of analgesic action occurs within 30 minutes, peaks at approximately 2 hours and lasts 3-4 hours. Paracetamol and aspirin are equally effective on a mg per mg basis.

Caffeine:
Caffeine is a methylxanthine that has an action mainly on the higher centres of the CNS causing stimulation that can increase mental alertness and reduce fatigue. At high doses, well above those achieved with Paracetamol and Caffeine soluble tablets, caffeine can produce nervousness, anxiety, restlessness, insomnia, tremors and hyperaesthesia; it can cause vasodilatation and diuresis.

Combination:
The applicant conducted an extensive search of the literature from 1970 onwards which did not identify studies specifically designed to assess the pharmacodynamics of the combination compared to the individual actives alone. However, in practical clinical terms, the most valid surrogate of pharmacodynamics is clinical efficacy. There is ample published evidence that the combination provides additive and possibly synergistic dynamics (see efficacy section below). There is no evidence that the dynamics of the two actives is adversely affected by the combination.

The multiple dynamic actions of caffeine may contribute to improved analgesic efficacy of the paracetamol in the following ways, largely through competitive antagonism of adenosine A1 and A2 receptors.

- Improved drug absorption of paracetamol through lower gastric pH and increased gastric blood flow.
- Reduced metabolic clearance of drugs through reduced hepatic blood flow.
- Blockade of peripheral pro-nociceptive adenosine signalling, and activation of the central noradenosine pathway (pain-suppressing systems).

- Transcriptional down-regulation of cyclo-oxygenase-2 (COX-2), via blockade of the adenosine A2a receptor.
- Relief of inhibitor adenosine actions on central cholinergic nerve terminals.
- Changes in mood and emotional state contributing to changes in the perception of pain.
- Cerebral vascular constriction, leading to decreased cerebral blood flow and reduced oxygen tension in the brain.

IV.4 Clinical Efficacy

No new efficacy data were submitted and none were required for an application of this type. The clinical efficacy of paracetamol and caffeine is well-established. Efficacy is adequately reviewed in the clinical overview.

Paracetamol:
Paracetamol 500-1000 mg is widely used as an analgesic for relief of mild to moderate pain, such as dental pain, episiotomy, headache, migraine, neuralgia, dysmenorrhoea, muscle ache, musculoskeletal pain, osteoarthritis, sore throat and as an antipyretic. Paracetamol has been in clinical use for 40 years as an analgesic for mild to moderate pain at a usual dosage of 1 g every four hours as required up to a maximum of 4 g in 24 hours. It is described in all standard textbooks and monographs as an effective analgesic.

Two hundred and seventeen published reports of clinical studies of paracetamol involving nearly 20 000 subjects have been reviewed in published literature. The pain studied included dental pain, headache, various musculo-skeletal pains, postoperative pain and trauma pain. In 65 of the studies, the dose of paracetamol studied was 1 g, repeated up to four times a day in many. Some of the studies are difficult to evaluate, in part due to the use of combinations containing paracetamol, but the overall conclusions are that paracetamol is more effective than placebo, as effective as aspirin and other NSAIDs as an analgesic, but less effective in inflammatory rheumatic disease than full dosage NSAIDs. The review also noted that according to the time course of drug concentrations following therapeutic doses and changes in pain intensity in clinical studies generally, the level of plasma concentrations for effective analgesia in man is probably about 5 to 20 mg/L. Such a plasma concentration is provided by oral doses of 1 g.

The review analysed 69 studies concerned with the antipyretic activity of paracetamol. It was noted that in children with fever, the antipyretic activity of paracetamol was found to depend on the initial temperature and a highly significant correlation was shown between efficacy and the plasma concentration of paracetamol.

Caffeine:
The CNS stimulant activity of caffeine is well recognised but published clinical studies to investigate it are limited. Two studies in young and middle-aged adults in whom the effect of caffeine on sleep variables have been reviewed in published literature. It was found that a dose of 2.3 mg/kg was required to show an effect on sleep. The older subjects were found to be more sensitive. However, it is considered that doses of 85-250 mg will produce significant CNS stimulation. The dosage of caffeine when administered as Paracetamol and Caffeine soluble tablets is 130 mg repeated to a maximum of 520 mg in 24 hours. This is considered sufficient to provide a significant pharmacological effect.

Combination:
The efficacy of a combination of paracetamol 1000 mg and caffeine 130 mg was assessed in a phase IV, randomised, double-blind, double-dummy, cross-over, multi-centre trial involving 264 subjects who suffered an acute migraine attack. The effectiveness of this
paracetamol-caffeine combination was compared with sumatriptan 50 mg, which is considered the gold standard for treating acute migraine attacks. Efficacy was determined as the sum of pain intensity differences (SPID), the curve of mean pain intensity, the number of subjects who were pain free at 2 hours, and total pain relief (TOTPAR). Subjects received rescue medication 3 hours after administration of trial medication if pain lasted more than 2 hours. There was a highly significant ($p<0.0001$) decrease in pain intensity after 1 hour versus baseline in both treatment groups. There were no significant differences between treatments in mean (standard deviation) SPID at baseline or during the 4-hours obsetvation period: paracetamol-caffeine 2.1 (0.7) and 3.2 (3.8), respectively, and sumatriptan 2.1 (0.8) and 3.2 (3.7), respectively ($p=0.88$). The TOTPAR scores did not differ significantly between paracetamol-caffeine and sumatriptan: 7.0 (3.6) and 7.4 (3.6), respectively ($p=0.48$). Rescue medication was taken by 38% of subjects receiving paracetamol-caffeine and 45% of subjects receiving sumatriptan: the difference was not statistically significant (Fisher exact test: $p=0.3308$). This study confirms the efficacy of the paracetamol-caffeine combination in treating acute migraine attacks.

Another study examined the analgesic effect of paracetamol-caffeine with paracetamol alone. Study medications were paracetamol **1**g, or paracetamol 1 g plus caffeine 100 mg or aspirin 1 g or glafenine 400 mg or placebo. Three hundred and fifty patients each received medication in a parallel group, double-blind design after surgical extraction of an impacted wisdom tooth from the lower jaw. Pain relief was assessed on a four point verbal scale. Treatments were assessed by the percentage of

patients reporting pain relief. Unlike other test medications, the analgesic effect of the paracetamol-caffeine combination was not influenced by the degree of pain at the time of administration and was associated with a higher response rate (81%) than paracetamol alone (60%), but the difference was not statistically significant. All the active treatments were more effective than placebo ($p<0.05$).

A group reported on a cross-over study which again showed trends in favour of the combination for the relief of pain in patients suffering from headache or postoperative pain of moderate intensity.

An updated review assessed the relative efficacy of a single dose analgesic in combination with caffeine compared with analgesic alone. Database searched were the Cochrane Central Register of Controlled Trials (CENTRAL) to 28 August 2014, MEDLINE from 1946 to 28
August 2014, EMBASE from 1974 to 28 August 2014, and Oxford Pain Relief Database for the original review. The review included randomised, double-blind trials that compared a single dose of analgesic plus caffeine with the same dose of the analgesic used alone for the treatment of acute pain. No new studies were identified, and the analysis included 4262 subjects for the analysis of the effects of caffeine, which was lower than the previous review due to the use of different outcomes for headache in some studies. The methodological quality of the studies was generally good and standard scales for measuring pain were mostly used. However, many studies of post-operative pain were small-scale. Most of the studies involved paracetamol or ibuprofen, with 100-130 mg caffeine, and the most common pain conditions studies were post-operative dental pain, postpartum pain, and headache.

A small but statistically significant benefit was observed with caffeine at dose of 100 mg, which did not depend on the type of pain. It was reported that 5-10% more subjects achieved a good level of pain relief of at least 50% of maximum over 4-6 hours with the addition of caffeine, which gave a munber needed to treat (NNT) of about 14, with high quality evidence. Most of the comparison reported numerical superiority for the combination of analgesic plus caffeine over analgesic alone.

The relative efficacy of a single dose of any analgesic plus caffeine compared with the same dose of analgesic alone was assessed in acute pain. Multiple databases were searched to, as well as internet searches and direct contact made with pharmaceutical companies known to have performed unpublished studies. The analysis included randomised, double-blind trials. Validated measures of efficacy were sought, especially the number of subjects who experienced at least 50% of maximum possible pain relief over 4-6 hours, and who reported a global evaluation of treatment as very good or excellent, or relief of headache after 2 hours. Comparable data were pooled in order to detect a statistically significant difference, and the numbers needed to treat (NNT) to benefit with caffeine were calculated. Numerical
superiority with addition of caffeine was also sought. A total of 19 studies involving 7238 participants were identified, with most studies using the combination of paracetamol or ibuprofen with 100 mg to 130 mg of caffeine. The most common types of pain were postoperative dental pain, postpartum pain and headache. A small but statistically significant benefit was detected with caffeine dose of 100 mg, which did not depend on the type of pain or type of analgesic.

Good pain relief (at least 50% of maximum) was achieved by 5-10% more subjects who received caffeine, giving an NNT of about 15. Most of the comparisons showed numerical superiority of adding caffeine, though not statistical superiority. This demonstrated that addition of caffeine (100 mg) to standard doses of commonly used analgesic resulted in a small but clinically impmtant increased in the number of subjects achieving a good level of pain relief.

Systematic literature searches were performed using online libaries for active ingredients already considered in therapy recommendations and for newly added active ingredients for the treatment of migraine and tension-type headaches. This led to the formulation of guidelines by four scientific societies in Germany. The fixed combination of paracetamol caffeine was recommended as one of the first-line therapies for self-medication of tension type headache.

The benefit analysis of paracetamol combined with caffeine for the short-term management of pain was determined following database searches for double-blind randomised controlled trials (RCT) that compared paracetamol-caffeine (1000 mg/130 mg) with paracetamol alone (1000 mg). The studies included used a verbal rating scale or a visual analogue scale (VAS) for assessing pain intensity, pain relief or both at 4 hours post-dose.

The percentage of subjects in each treatment group who achieved at least 50% of the maximum possible TOTPAR was calculated using validated equations and then converted into the total number of patients in each group who achieved at least 50% of the maximmum TOTPAR. This data was then used to compute the NNT for paracetamol-caffeine versus caffeine alone. Seven papers were identified, of which 4 included RCTs, for a total of 8 separate studies. Pain states assessed were post-partum pain (n = 3), headache (n = 2), post-

surgical dental pain (n = 2), and dysmenonhoea (n = 1). The analysis showed that 65% of subjects treated with paracetamol-caffeine achieved at least 50% maximum TOTPAR over 0-4 hours compared with 50% of subjects given paracetamol alone ($p<0.05$).
The NNT was calculated to be 14. The relative benefits compared with placebo were 1.42 (95% CI: 1.29-1.56) and NNT 5 for paracetamol-caffeine, and 1.27 (95% CI: 1.15-1.40) and NT 8 for paracetamol. This demonstrated that paracetamol-caffeine was an effective treatment options in subjects who experienced inadequate pain relief with paracetamol alone or who were unable to use NSAIDs because of contraindications or precautions.

A group reported on four studies which compared paracetamol plus caffeine with paracetamol alone. All four studies used a similar double-blind, single dose, parallel group, protocol. All studies estimated pain intensity on a four-point scale (none to severe) at baseline, after 30 minutes, 60 minutes and then hourly until 4 hours after the dose. Pain relief was assessed using a five-point scale and onset time to analgesia was also recorded. The first three studies involved 1345 patients with post-episiotomy pain or uterine cramping. There were seven treatment groups, patients either receiving one, two or three tablets of paracetamol (500 mg), or paracetamol (500 mg) plus caffeine (65 mg), or placebo). For all study variables, the mean response score was statistically significantly higher or the response faster for the combination than for the corresponding number of paracetamol tablets. Based on the summary variables, almost twice as much paracetamol alone would be required to produce the same response as the dose given in combination with caffeine. The authors concluded that their results provide substantial evidence in support of the proposition that caffeine contributes to the effectiveness of oral analgesics'. The fourth study was conducted in patients after dental extraction. The same tablets were compared as in the first three studies but the dosage was changed to two or four tablets with no placebo group (four groups in total). Two hundred patients were entered of whom 173 were analysed. Increasing the dose from two to four tablets had no significant effect on any of the parameters and indeed, there was a slight trend towards four tablets being less effective.

The group also analysed the data from 30 clinical trials involving more than 10 000 patients. Twenty-seven of these trials were conducted in post-partum pain, two in headache and one in dental extraction pain. Most of the studies reviewed were previously unpublished but
included the four studies described above. Seven of the studies involved comparisons between tablets containing 500 mg paracetamol and tablets containing 500 mg paracetamol plus caffeine 65 mg. All of these studies assessed pain intensity, pain relief and time to onset of analgesia and used more than one dosage level of both paracetamol and the combination. This allowed the construction of dosage/effect curves and the estimation of relative potency (i.e. the factor by which paracetamol dosage would have to be increased in order to obtain the same analgesic effect as the combination). The authors constructed various pools or subsets of the original data. Each of the pools demonstrated a significant effect of caffeine as an analgesic adjuvant. From their analysis, it was estimated that it required approximately 1.4 times as much of the analgesic to achieve the same analgesia as combinations with caffeine. The authors concluded that 'based on these studies and a review of the literature, it seems reasonable to conclude that the addition of 65 mg caffeine to an analgesic tablet taken in a two tablet dose results in a more effective analgesic.

Mood enhancement may also result. For many patients, this could of course be of considerable importance.' Beaver, commenting on this analysis observed that given the small repertoire of OTC constituents then available as analgesics, the addition of caffeine seemed to be a safe and useful way to extend the efficacy of over-the-counter analgesics.

A report by another group included two studies involving 838 patients and compared paracetamol (1 g) plus caffeine (130 mg) with paracetamol (1 g) and placebo (Migliardi et al., 1994). Each patient received two of the three medications in a randomised, double-blind, two period cross-over study design. Patients used the first medication for the first two episodes of headache at least 48 hours apart and then crossed to their second medication which they used to treat a further two episodes after a 7-day washout. Pain intensity and pain
relief were recorded. In all studies the caffeine-containing combinations were significantly superior to paracetamol or placebo. These studies have been criticised because in some instances, headache may be precipitated by withdrawal of normal caffeine consumption. However, the significant effect seen in these studies was assessed and found to be independent of the patients' normal caffeine use or consumption of caffeine in the 4 hours before medication. These well-controlled studies provide excellent and direct evidence of a clinically useful adjuvant action for caffeine at a dose level of 130 mg.

The safety profile of paracetamol and caffeine is well-known. No new safety data are provided or required for this application.

IV.5 Clinical Safety

No new safety data were submitted and none were required for this bibliographic application. Safety is adequately reviewed in the clinical overview. The safety profile of paracetamol and caffeine is well-known.

Chronic Liver Disease

The liver is an important site of paracetamol metabolism. Approximately 80% of the drug is removed from the circulation by microsomal liver enzymes, via conjugation with glucmonic and sulfuric acids. While studies have shown that the plasma t ½ of paracetamol is prolonged in patients with chronic liver disease, there is no evidence that paracetamol is harmful when taken at the recommended dosage. Thus it is appropriate to exercise caution in administering Paracetamol and Caffeine soluble tablets to patients with severe hepatic irnpairment.

Chronic Renal Failure

Oral paracetamol is metabolised extensively by conjugation with glucuronic and sulfuric acids. A small fraction of the dose is converted to a reactive intermediate metabolite, which is then conjugated with glutathione and excreted as cysteine and mercapturate conjugates. Over 90% of a therapeutic dose is normally excreted in the urine as metabolites within 24 hours. In patients with renal failure the ability of the kidney to eliminate polar metabolites is limited and accumulation of paracetamol conjugates would be predicted. Thus it is appropriate to exercise caution in administering Paracetamol and Caffeine soluble tablets to patients with severe renal impairment.

Risk of Cancer

The risk of cancer in association with paracetamol has been investigated. One study looked specifically at ovarian, breast or colon cancer, and the other at cancer in general. Previous studies have had conflicting results, and the International Agency for Research on Cancer (IARC) concluded in 1999 that there is inadequate evidence in both humans and experimental animals for the carcinogenicity of paracetamol. Using a UK Research Database, a retrospective case-control study on 483 women with ovarian cancer (1877 controls), 3706 women with breast cancer (14155 controls) and 635 women with colon cancer (2434 controls) found no evidence of a decreased ovarian or colon cancer risk for women with regular paracetamol exposure, but they did have a slightly decreased risk of developing breast cancer (odds ratio 0.8, 95% confidence interval 0.7-1.0). The other Danish cohort study compared the cancer incidence among 39 946 people receiving prescriptions for paracetamol with the expected incidence based on the population who did not receive paracetamol prescriptions over a 9-year period. Their results do not support a major role for paracetamol in the development of cancers of the urinary tracts, and found little evidence of any protection against ovarian cancer. The elevated risks for oesophageal, lung and liver cancers may warrant further investigation, although they are most likely a result of confounding variables that were not accounted for in this study.

Use in Patients with Asthma

The association between analgesic use and severity of asthmatic attacks has been evaluated.
The study concluded, "Frequent use of paracetamol may contribute to asthma morbidity and rhinitis in adults". The authors however acknowledged that "Paracetamol should remain the preferred analgesic and antipyretic because of the potential risks associated with aspirin and NSAIDs - namely severe sensitivity reactions in those with asthma, gastrointestinal bleeding in adults, and Reye's syndrome in children". At the time of the study, the UK Government's independent scientific advisory body, the Committee on Safety of Medicines, considered the study and concluded, "There is no reason for advising any change in use of paracetamol. Paracetamol is a safe and effective pain killer for many patients including asthmatics, children, the elderly and pregnant women" (Paracetamol Information Centre).
A second paper consisted of a follow-up, ecological study comparing paracetamol sales and atopic disease in children and adults. The study indicated that paracetamol sales were high in English-speaking countries, and were positively associated with atopy in both children and adults. The authors themselves accepted that their findings require cautious interpretation and acknowledge the possibility that some unknown confounding factor, strongly associated with Anglophone culture and paracetamol sales, was responsible for the findings.

Alcohol

Acute Ingestion of Alcohol

When taken together, alcohol competes with paracetamol for the enzyme CYP2El. CYP2E1 accepts alcohol more readily than paracetamol. Studies in animals have shown that when alcohol and paracetamol are administered at approximately the same time, oxidation of paracetamol by hepatic microsomal enzymes declines and toxicity of paracetamol is reduced.

Many patients who take an overdose of paracetamol also consume alcohol at the same time. In this situation, acute alcohol ingestion may help to prevent liver damage, which could partly account for the wide variability noted between patients in susceptibility to paracetamol toxicity. The CNS effects of an oral dose of alcohol (2.2 mL/kg body weight) were not antagonised by caffeine 150 mg given per os (PO); instead, a synergistic interaction was noted resulting in a further increase in reaction time (Obome and Rogers, 1983). Thus, consumption of caffeine after drinking alcohol does not appear to lead to sobering up.

Chronic Ingestion of Alcohol

In contrast to the findings with acute alcohol administration, chronic administration of alcohol in animals induces microsomal enzymes leading to an increase in the metabolic activation and hepatotoxicity of paracetamol. One would therefore predict

that chronic alcoholics would be more susceptible to paracetamol toxicity than other people. Clinical evidence does not support this assertion.

Clinical studies have shown that chronic alcohol ingestion increases levels of CYP2EI but only about two-fold and this effect is lost within 5-10 days of abstinence. No increase in the toxic metabolic activation of paracetamol is observed in chronic alcoholics compared with those who drink less alcohol or who abstain.

Strong evidence that heavy drinkers do not face an increased risk from hepatotoxicity following paracetamol overdose has been obtained in two large retrospective surveys. In a US study of 662 overdose cases, no consistent differences were apparent between patients with or without a history of chronic alcohol use. Similarly, of 553 patients with hepatotoxicity resulting from paracetamol overdose who were admitted to a specialist liver unit in the UK, there was no correlation between alcohol consumption history and the severity of liver damage, irrespective of whether the overdose was deliberate or accidental. It has been suggested that chronic alcoholics would be most vulnerable to paracetamol induced liver toxicity within a few days of withdrawal because liver enzymes may still be elevated. However, there is no evidence that the metabolic activation of paracetamol is any different in recovering alcoholics compared within 48 hours of abstinence and again after approximately 2 weeks, when a decrease in mercapturic acid excretion would have been expected.

Chronic alcoholics have been reported to have decreased intra-hepatic glutathione stores leading to the suggestion that the capacity for glutathione synthesis in the liver may be reduced, thereby compromising NAPQI detoxification. However, a well-controlled, prospective study has demonstrated that therapeutic doses of paracetamol do not cause liver injury in chronic alcoholics. It remains a possibility that chronic alcoholics who are malnourished are at increased risk of paracetamol-induced liver damage following overdosage.

The interaction between alcohol and paracetamol has been reviewed and the conclusion was that there is no evidence of a major toxic interaction between alcohol and paracetamol in humans. Acute liver damage has never been produced by therapeutic doses of paracetamol given as a challenge to chronic alcoholics. Moreover, chronic alcoholics do not appear to be any more susceptible to liver damage following an overdose of paracetamol than patients who are not chronic alcoholics.

Paracetamol Metabolism
Three separate pathways are involved in the metabolism of paracetamol. Approximately 90% of a dose of paracetamol is conjugated with glucuronide or with sulfate and is eliminated safely whilst about 5% is metabolised by liver microsomal mixed-function oxidase enzymes (Prescott, 2001), primarily CYPP450 2El. This latter oxidation of paracetamol leads to the formation of the highly reactive intermediate NAPQI in the liver that is toxic to hepatocytes. Normally, NAPQI is detoxified by conjugation with glutathione and is eliminated in the urine as mercapturic acid and cysteine metabolites. If glutathione reserves in the liver are insufficient to deal with increased levels of NAPQI following paracetamol overdose, liver injury will develop.

Low sodium diet
Two tablets of Paracetamol and Caffeine soluble tablets contain 854 mg of sodium and should not be taken by patients on a low sodium diet.

Interactions:
Concomitant Use of Drugs That Induce CYP Isoenzymes
Anecdotal case reports suggest that concomitant use of paracetamol and drugs that induce CYP enzymes increase the risk of hepatotoxicity in paracetamol overdosage. Drugs that induce the hepatic CYP enzymes include phenobarbitone (and other barbiturates), rifampicin, carbamazepine and phenytoin. The terms enzyme inducers and hepatic mono-oxygenase inducers are synonymous with the term hepatic CYP450 enzyme inducers. However there is insufficient sound clinical evidence to support a major toxic interaction between paracetamol and drugs that induce CYP enzymes. Evidence in support of the interaction is largely anecdotal or has been obtained in animal models raising doubts about its clinical relevance.
It has been noted that rifampicin pre-treatment had no significant effects on the formation of NAPQI or the recovery of thiol metabolites formed by the conjugation of NAPQI with glutathione, suggesting that even when induced the contribution of CYP3A4 to NAPQI formation is negligible. This study also provided convincing evidence of the predominance of CYP2E1 in NAPQI formation in humans, and suggests that the contribution of CYP3A4 is minor.

A review on the data on liver enzyme inducing drugs concluded that phenytoin does not increase the hepatotoxicity of paracetamol and that the enzyme CYP2E1 does not become induced by any of the barbiturates.

The factors influencing paracetamol hepatotoxicity, including chronic administration of liver enzyme inducing drugs, have been reviewed. It was concluded that in animal studies CYP enzyme inducers have been shown to potentiate the hepatotoxicity of paracetamol but that the only clinical evidence for this toxic interaction lies in anecdotal case reports.

Combination:
There do not appear to be any clinically significant pharmacokinetic drug-drug interactions at the proposed dosage regimen, although chronic use of ethanol has been reported to increase the risk of hepatotoxicity following paracetamol overdose. Drugs affecting upper gastro intestinal motility may affect the speed of absorption of paracetamol; both metoclopramide and domperidone increase the speed of absorption. However, this effect is unlikely to be clinically relevant.

Concomitant Use of Anticoagulants
Regular use of paracetamol at a daily dose of 4 g for 14 days enhanced the anticoagulant effect of warfarin. Brief exposure to paracetamol did not significantly alter the anticoagulant response to warfarin. The mechanism by which the effect of oral anticoagulants may be potentiated by paracetamol is unclear. Possible explanations include mediation via the CYP enzyme system and inhibition of enzymes of the vitamin K cycle.

Medications That Increase or Decrease Paracetamol Absorption
Concomitant administration of metoclopramide and paracetamol significantly reduced the time to Cmax for paracetamol in healthy volunteers. Domperidone has also been shown to significantly increase the rate of gastric emptying of paracetamol in 37 healthy volunteers. Conversely, the concomitant administration of paracetamol with cholestyramine markedly reduced absorption of an oral dose of paracetamol 2 g in 14 healthy volunteers.

Pregnancy and Lactation:
Human and animal studies involving paracetamol have not identified any risk to pregnancy or embryo foetal development, or any risk to lactation or the breast-fed offspring. Paracetamol crosses the placental barrier and is excreted in breast milk.
A published study reported links between frequent paracetamol use and wheezing and asthma in adults and children. Data is lacking on possible effects of prenatal exposure on wheezing in early childhood. Findings were that frequent paracetamol use in late pregnancy (20-32 weeks), but not in early pregnancy (<18-20 weeks), was associated with an increased risk of wheezing in the offspring at 30-42 months, particularly if wheezing started before 6 months. Assuming a causal relation, only about 1% of wheezing at 30-42 months was attributable to this exposure.

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. Low concentrations of caffeine are present in breast milk and are not thought to present a hazard. However, the presence of caffeine in milk may potentially have a stimulating effect on breast fed infants.

Overdose:
The major complication of paracetamol overdose is acute hepatic necrosis, although without treatment fewer than 10% of unselected patients are at risk of severe liver damage (Dollery, 1999). It is estimated that approximately 1% of overdose cases develop fulminant hepatic failure. Renal failure from acute tubular necrosis is a further uncommon complication, which may develop in the absence of hepatic failure.

High plasma levels of paracetamol, as found in overdose, give rise to saturation of the phase two metabolic pathways (sulfate and glucuronide), which then leads to an increase in the fraction of the dose metabolised via microsomal CYP mixed function oxidase, and a subsequent increase in the fraction of the dose converted to NAPQL In this situation, a greater proportion of the paracetamol dose would be converted to thio-ether metabolites (i.e. paracetamol cysteine conjugate and paracetamol mercapturic acid conjugate) via reaction with hepatic glutathionine. If diversion of the metabolic pathway to the thio-ether metabolite route increased to such an extent that the levels of hepatic glutathione became depleted, then NAPQI may react with liver protein leading to hepatic cytosis.

Necrosis does not occur unless hepatic glutathione is depleted. Thus, early treatment with agents that facilitate glutathione synthesis, such as N-acetylcysteine (NAC) and methionine, effectively prevent liver damage, renal failure and death following paracetamol overdose.

A caffeine overdose may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions). It should be noted that for clinically significant symptoms of caffeine overdose to occur with Paracetamol and Caffeine soluble tablets, the amount ingested would be associated with serious paracetamol-related toxicity. Fatal poisoning by ingestion of caffeine is rare and would require ingestion of 5-10 g.

The safety profile of caffeine is well established and the current SmPC warns of potential risks of over consumption. The current clinical overview cites a report, where 4262 subjects (albeit adults) reported only one serious adverse event that was considered unrelated to any study treatment. Only 11 serious adverse events, none signalling any new safety information were reported over the five year PSUR period.

In overdose, the danger of paracetamol far exceeds that of caffeine and the issue is adequately documented in the current SmPC.

The European Food Safety Authority has provided a broad overview of caffeine safety. Although the data in adolescents are less than optimal, the safe level of exposure is generally agreed to be 2.5-3mg/kg for children.
The review recommends a maximum consumption of 100mg per day in adolescents. To put the issue in perspective, a single cup of coca cola contains 50mg caffeine, coffee 100mg and some "high energy'' soft drinks as much as 500mg.

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 soluble tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary of safety concerns	
Important identified risks	• Hypersensitivity (Paracetamol, Caffeine) • Hepatic disorders (hepatic failure, hepatic necrosis and hepatic impairment) (Paracetamol) • Use in patients with hepatic impairment (Paracetamol) • Use in patients with severe renal impairment (Paracetamol) • Use in asthmatic patients sensitive to aspirin due to risk of bronchospasm (Paracetamol) • Overdose (Paracetamol, Caffeine) • Blood disorders (thrombocytopenia, agranulocytosis, haemolytic anaemia, neutropenia, leukopenia and pancytopenia) (Paracetamol) • Drug interaction with anticoagulants (Paracetamol) • Drug interaction with enzyme inducers (Paracetamol) • Central Nervous System (CNS) stimulation (including in infants during breastfeeding) (Caffeine)
Important potential risks	• Use in patients with alcohol dependence (Paracetamol) • Serious skin reactions (Stevens-Johnson syndrome and erythema multiforme) (Paracetamol)
Missing information	• Effect on fertility (Paracetamol, Caffeine) • Use in children under 12 years of age (Paracetamol, Caffeine)

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion of the clinical aspects
There are no objections to the approval of this application from a clinical point of view.

V. OVERALL CONCLUSIONS

USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Paracetamol, Codeine Phosphate, and Caffeine Omega 500 mg/30 mg/12.8 mg Soluble Tablets (PL 02855/0246 / UK/H/6164/001/DC). The bridging report submitted by the applicant is acceptable.

OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Paracetamol and Caffeine soluble tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
There are no objections to the authorisation of this product on non-clinical grounds.

EFFICACY
The efficacy of paracetamol and caffeine are well recognised. The applicant has provided a good overall summary of the use of the combination in mild to moderate pain.

SAFETY
The applicant has provided extensive literature to support the safety of the product and no new or unexpected safety concerns arise from this application.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and any non-clinical or clinical safety concerns have been fully resolved. The risk benefit is, therefore, considered to be positive.

PRODUCT LITERATURE

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for this medicine agreed within the decentralised procedure; no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained. Mock-ups of labelling and PIL for product intended for the UK market will need to include the UK statutory warnings as specified in the Human Medicines Regulations 2012 Schedule 25 Pad 4 and Schedule 27 Part 2. In accordance with Schedule 15 of the Human Medicines Regulations 21012, the maximum pack size that could be placed on the market in the UK as a GSL medicine is a pack size of 30 effervescent (soluble) tablets.

VI. REVISION DATE

September 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/6161/001/DC to IE/H/1038/001/DC	N/A	N/A	N/A	Approved 08/08/2019