IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Solpa-Plus Tablets Paracetamol 500mgCodeine Phosphate Hemihydrate 12.8mg
PARACETAMOL
Codeine phosphate hemihydrate
PA1186/011/005

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6163/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 08th August 2019 under procedure number IE/H/1037/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/011/005
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 Member States considered that the application for Paracetamol and Codeine Phosphate Omega 500mg/12.8mg film-coated tablets (PL02855/0245; UK/H/6163/001/DC).), is approvable. This pharmacy medicine (P) is recommended for the relief of acute moderate pain which requires stronger analgesia than paracetamol or ibuprofen or aspirin alone. It is also used for the treatment of dental pain (including pain after extraction), headache, migraine (with and without aura), dysmenorrhea, backache, pain in bones and joints arising from arthritis and rheumatism, neuralgia, strains and sprains and sciatica.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Poland, Republic of Ireland and Romania as Concerned Member States (CMS). This application was made under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

Paracetamol is an analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

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

A satisfactory Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application.

The RMS has been assured that acceptable standards of Good Manufacturing Practice 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 RMS 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.

The Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 -01 December 2016). Following a national phase, the UK granted a Marketing Authorisation (PL 02855/0245) for this product on 15 December 2016.

II. QUALITY ASPECTS

II.1 Introduction

Each tablet contains 500 mg paracetamol and 12.8 mg codeine phosphate hemihydrate, as active ingredients. The excipients present in this product are starch, pre-gelatinised, povidone K25, potassium sorbate (E202), maize starch, talc, magnesium

stearate, stearic acid, microcrystalline cellulose, croscarmellose sodium making up the film core, and the tablet coat composed of lactose monohydrate, hypromellose, macrogol 4000, quinoline yellow (E104), erthyrosine (E127) and titanium dioxide (E171).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of erthyrosine (E127), macrogol 4000 and quinoline yellow (E104) which comply with an in-house specification. The supplier has confirmed that the colouring agents comply with EU requirements for colourings agents.

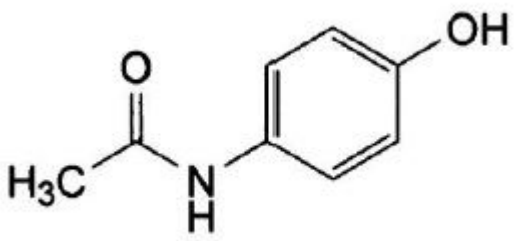
Satisfactory Certificates of Analysis have been provided for these excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packaged in polyvinylchloride (PVC)/aluminium foil blisters in outer cations, containing 6, 10, 12, 16, 20, 24, 30 or 32 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance
INN: Paracetamol
Chemical name(s): N-(4-hydroxyphenyl)acetamide
Structure:

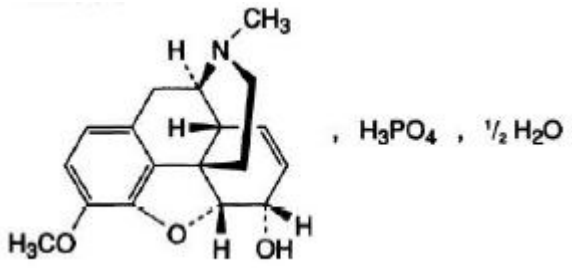


Molecular formula: $C_8H_9N0_2$
Molecular weight: 151.2 g/mol
Appearance: white, crystalline powder.
Solubility: It is sparingly soluble in water; but freely soluble in alcohol and very slightly soluble in dichloromethane.

Paracetamol is the subject of a European Pharmacopoeia monograph.

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

Codeine Phosphate Hemihydrate
INN: Codeine phosphate hemihydrate
Chemical name(s): 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol.
Structure:



Molecular formula: $C_{18}H_{21}NO_3,H_3PO_4, ½H_2O$
Molecular weight: 406.4 g/mol
Appearance: white or almost white, crystalline powder.
Solubility: It is freely soluble in water and slightly soluble in ethanol.

Codeine phosphate hemihydrate is the subject of a European Pharmacopoeia monograph.

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

II.3 Medicinal Product
Pharmaceutical Development
The aim of the development programme was to formulate safe, efficacious and stable tablets containing 500 mg paracetamol and 12.8 mg codeine phosphate hemihydrate.

Dissolution profiles have been provided for one batch of the product compared with another European product to demonstrate comparable dissolution.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on full scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months with storage conditions "Do not store above 25°C" and "Store in original package in order to protect the product from moisture" have been set. These are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.l Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol and codeine phosphate hemihydrate are well-known and the applicant has provided an acceptable overview from limited literature sources. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier. No new non-clinical data have been supplied with this application. This is acceptable.

III.2 Pharmacology
The pharmacology of both paracetamol and codeine are well known and the published literature has been reviewed and discussed in the applicant's non-clinical overview. The combination of these two active substances is well established clinically and the limited combination non-clinical studies have been adequately justified in the applicant's non-clinical overview. Based on the different modes of action of paracetamol and codeine, the combination acts synergistically on acute, moderate pain compared with the individual components.

III.3 Pharmacokinetics
The pharmacokinetic properties of paracetamol and codeine have been reviewed adequately in the applicant's non-clinical overview. The combination effects have been addressed in limited detail in the non-clinical overview. Given the extensive use of each component, and combination of the products in the clinic this approach is acceptable.

III.4 Toxicology

The basis of this application is well established use and the applicant has reviewed published literature on the toxicology of paracetamol and codeine and has justified the absence of new studies on the combination.

The impurities are stated to be within the required limits. The drug substances, paracetamol and codeine are controlled in line with their respective Certificates of Suitability. Limits for drug product impurities are specified and are controlled in line with ICH Q3B and relevant Ph. Eur. monographs.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA) based upon the argument that the proposed product will substitute for identical products on the market.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this product from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Paracetamol and codeine are well-established active substances.
The details of its pharmacokinetics are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. The applicant did not conduct any new research or provide any new data. This is acceptable.

IV.2 Pharmacokinetics

The pharmacokinetics (PK) of paracetamol and codeine are well recognised. The Applicant has updated the pharmacokinetic section of the dossier providing a discussion of the absorption, distribution, metabolism, excretion (ADME) of the constituent actives and the combination. Discussion of the PK in special populations or potential interactions of the combination has also been provided.

IV.3 Pharmacodynamics

The Applicant has provided discussion on the pharmacodynamics of paracetamol and codeine phosphate hemihydrate.

IV.4 Clinical efficacy

The efficacy of paracetamol and codeine phosphate hemihydrate is well recognised. The applicant has provided an overall summary of the use of the combination in acute moderate pain. The dossier has been updated providing examples used with dental pain, bones and joint pain and headache/migraine.
In addition, discussion on efficacy in the special population has been provided.

IV.5 Clinical safety

The safety of paracetamol and codeine phosphate hemihydrate is well recognised. The applicant has addressed the adverse event profile of the single actives and the combination. Data are provided for special populations of interest (adolescents and elderly). The other parts of the summary are acceptable.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder has submitted a risk management plan, 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 Codeine Phosphate Omega 500mg/12.8mg film-coated tablets.

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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identification risks		
Hypersensitivity (Paracetamol, Codeine)	Safety information in the SmPC: **Section 4.3 Contraindications:** Hypersensitivity to the active substances (paracetamol, codeine, opioid analgesics) or to any of the excipients. **Section 4.8 Undesirable effects:** Paracetamol Immune system disorders: Very rare: Anaphylaxis. Rare: Allergies (not including angioedema).	None proposed
Hepatotoxicity (Paracetamol)	Safety information in the SmPC: **Section 4.2 Posology and method of administration** In patients with impaired hepatic function or Gilbert's Syndrome, the dose must be reduced or the dosing interval pro-longed. Adults: The maximum daily dose of paracetamol should not exceed 2g in the following situations: · Adults or adolescents weighing less than 50kg · Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-haemolytic jaundice) · Chronic alcoholism · Dehydration · Chronic malnutrition Method of administration Do not exceed the recommended daily dosage or the specified number of doses because of the risk of liver damage. **Section 4.4 Special warnings and special precautions for use** Patients should be advised not to take other paracetamol containing products. Paracetamol should be administered only with particular caution under the following circumstances: · Hepatocellular insufficiency (Child-Pugh < 9) · Chronic alcoholism · Renal failure (GFR≤50ml/min) · Gilbert's Syndrome (familial non-haemolytic jaundice) · Concomitant treatment with medicinal products affecting hepatic function · Glucose-6-phosphate dehydrogenase deficiency · Haemolytic anaemia · Glutathione deficiency · Dehydration · Chronic malnutrition Immediate medical advice should be sought in the event of overdosage even if the patient feels well because the risk of irreversible liver damage	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.5 Interaction with other medicinal products and other forms of interaction Paracetamol Paracetamol is metabolized in the liver and can therefore interact with other medicines that follow the same pathway or may inhibit or induce this route; causing hepatotoxicity, particularly in overdose. **Section 4.8 Undesirable effects** **Paracetamol** Hepatobiliary disorders Very rare: Hepatic dysfunction. **Section 4.9 Overdose** Paracetamol Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below). There is a risk of poisoning with paracetamol particularly in elderly subjects, young children, patients with liver disease, cases of chronic alcoholism and in patients with chronic malnutrition. Overdosing may be fatal in these cases. Symptoms Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain, or patients may be asymptomatic. Overdose of paracetamol in a single administration in adults or in children can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue. Cardiac arrhythmias and pancreatitis have been reported. Risk Factors: If the patient a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes. Or	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	b) Regularly consumes ethanol in excess of recommended amounts. Or c) Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia. Management Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if >150mg/kg paracetamol has been taken within 1 hour. The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines. Symptomatic treatment should be implemented. **Section 5.2 Pharmacokinetic properties** Paracetamol Biotransformation Paracetamol is mainly metabolised in the liver, following two major metabolic pathways, with formation of glucuronic acid and sulphuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dosages. A minor route, catalysed by the Cytochrome P 450 (mostly CYP2E1), results in the formation of an intermediate reagent (N-acetyl-p-benzoquinone imine) which under normal conditions of use, is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercapturic acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.	
Opioid toxicity (including, higher levels of the active metabolite presented in breast milk in ultra-rapid metaboliser of CYP2D6) (Codeine)	Safety information in the SmPC: **Section 4.2 Posology and method of administration** Children aged less than 12 years: Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine. **Section 4.3 Contraindications:** In patients for whom it is known they are CYP2D6 ultra-rapid metabolizers. The product is contraindicated in: In women who are breastfeeding.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome, due to an increased risk of developing serious and life-threatening adverse reactions. **Section 4.4 Special warning or precautions for use:** Codeine CYP2D6 metabolism Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below:	

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

	Paediatric population Post-operative use in children There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine. Children with compromised respiratory function Codeine is not recommended for use in children in whom respiratory function might be compromised including	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity. Codeine, as with other opioids should be used with caution in patients with impaired respiratory function, hypotension, hypothyroidism, head injury or raised intracranial pressure. **Section 4.6 Fertility, pregnancy and lactation:** Breast-feeding: <Product name> should not be used during breastfeeding. At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.	
Drug dependence (addiction) (Codeine)	Safety information in the SmPC: **Section 4.2 Posology and method of administration** Do not exceed the recommended daily dosage or the specified number of doses because of the risk of liver damage. **Section 4.4 Special warning or precautions for use:** Codeine Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped. **Section 4.8 Undesirable effects:** Codeine Undesirable effects depend upon dose and individual patient metabolism. Psychiatric disorders Not known: Drug dependency after prolonged use of codeine at higher doses. **Section 4.9 Overdose** Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time may lead to physical or psychological dependency.	None proposed
Respiratory depression (Codeine)	Safety information in the SmPC: **Section 4.3 Contraindications:** Codeine The product is contraindicated in:	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	In respiratory depression. **Section 4.4 Special warning or precautions for use:** Codeine CYP2D6 metabolism General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal **Section 4.6 Fertility, pregnancy and lactation** Pregnancy Use during pregnancy should not be used. This includes maternal use during labour because of the potential of codeine to induce respiratory depression in the neonate. **Section 4.9 Overdose:** Codeine Symptoms An overdose of codeine is characterized, in the first phase, by nausea and vomiting. Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large.	
Acute pancreatitis (in patients with a history of cholecystectomy) (Codeine)	Safety information in the SmPC: **Section 4.4 Special warning or precautions for use:** Codeine Patients with a history of cholecystectomy should consult a doctor before using this product as it may cause acute pancreatitis in some patients. **Section 4.8 Undesirable effects:** Codeine Gastrointestinal disorders: Not known: Acute pancreatitis in patients with a history of cholecystectomy.	None proposed
Affectation of the pregnancy (Codeine)	Safety information in the SmPC: **Section 4.6 Fertility, pregnancy and lactation:** Use during pregnancy should be avoided, unless advised by a physician. This includes maternal use during labour because of the potential for respiratory depression in the neonate. The safety of paracetamol-codeine during pregnancy has not been established relative to the possible adverse effects of foetal development.	None proposed
Increased risk of developing serious and life threatening adverse reactions	Safety information in the SmPC: **Section 4.3 Contraindications:**	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
including death in paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome (Codeine)	In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions. **Section 4.6 Special warnings and special precautions for use:** Post-operative use in children There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.	
Risk of opioid toxicity in children less than 12 years of age (Codeine)	Safety information in the SmPC: **Section 4.2 Posology and method of administration** Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine.	None proposed
Important potential risks:		
Use in children with compromised respiratory function including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures (Codeine)	Safety information in the SmPC: **Section 4.4 Special warnings and special precautions for use:** Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.	None proposed
Drug abuse and misuse (Codeine)	Safety information in the SmPC: **Section 4.4 Special warning or precautions for use:** Codeine Prolonged regular use, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped. **Section 4.8 Undesirable effects:** Codeine Undesirable effects depend upon dose and individual patient metabolism. Psychiatric disorders	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Not known: Drug dependency after prolonged use of codeine at higher doses. **Section 4.9 Overdose** Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period of time may lead to physical or psychological dependency.	
Impaired ability to drive safely or operate machinery (Codeine)	Safety information in the SmPC: **Section 4.7 Effects on ability to drive and use machines:** Patients should be advised not to drive or operate machinery if affected by dizziness or sedation.	None proposed
Missing information:		
Effect on fertility (Paracetamol, Codeine)	Safety information in the SmPC: **Section 4.6 Fertility, pregnancy and lactation:** Fertility There are no data available regarding the influence of the product on fertility.	None proposed
Use in children under 12 years of age (Paracetamol, Codeine)	Safety information in the SmPC: **Section 4.2 Posology and method of administration** Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine.	None proposed

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

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V. OVERALL CONCLUSIONS

USER CONSULTATION

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Paracetamol/Codeine phosphate/Caffeine Soluble Tablets (UK/H/6164/001/DC). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with paracetamol and codeine phosphate hemihydrate is considered to have demonstrated the therapeutic value of the compounds. The benefit risk is, therefore, considered to be positive.

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/6163/001/DC to IE/H/1037/001/DC	N/A	N/A	N/A	Approved 08/08/2019