COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Codeïnefosfaat Sandoz
10 mg, 15 mg, 20 mg and 30 mg, tablets
(codeine phosphate hemihydrate)

NL/H/5297/001-004/DC

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This module reflects the scientific discussion for the approval of Codeïnefosfaat Sandoz 10 mg, 15 mg, 20 mg and 30 mg, tablets. The procedure was finalised on 20 July 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
EMA	European Medicines Agency
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Codeïnefosfaat Sandoz 10 mg, 15 mg, 20 mg and 30 mg, tablets, from Sandoz B.V.

The product is indicated for:

- treatment of acute moderate pain that cannot be relieved by other pain medication such as (only) paracetamol or ibuprofen in adults and children older than 12 years of age;
- symptomatic relief of diarrhoea after an insufficient clinical response to loperamide in adults;
- symptomatic relief of a non-productive cough in adults and children older than 12 years of age.

The active substance of this product is codeine phosphate hemihydrate and belongs to the pharmaco-therapeutic group of opium alkaloids and derivatives. Special precautions for disposal and other handling include: any unused medicinal product or waste material should be disposed in accordance with local requirements.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of codeine phosphate 10, 15, 20 and 30 mg tablets. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the community for at least ten years, with recognised efficacy and an acceptable level of safety.

The concerned member state (CMS) involved in this procedure was Czechia.

II. QUALITY ASPECTS

II.1 Introduction

Codeïnefosfaat Sandoz are tablets with 10, 15, 20 or 30 mg codeine phosphate hemihydrate as active substance.

- The 10 mg strength is a white or almost white, biconvex tablet of round shape (diameter 6 mm), debossed ‘COD’ over ‘10’ on one side. Each tablet contains 10 mg codeine phosphate hemihydrate equivalent to 7.37 mg of codeine.

- The 15 mg strength is a white or almost white, biconvex tablet of round shape (diameter 7 mm), debossed 'COD' over '15' on one side. Each tablet contains 15 mg codeine phosphate hemihydrate equivalent to 11.05 mg of codeine.
- The 20 mg strength is a white or almost white, biconvex tablet of round shape (diameter 8 mm), debossed 'COD' over '20' on one side. Each tablet contains 20 mg codeine phosphate hemihydrate equivalent to 14.73 mg of codeine.
- The 30 mg strength is a white or almost white, biconvex tablet of round shape (diameter 9 mm), debossed 'COD' over '30' on one side. Each tablet contains 30 mg codeine phosphate hemihydrate equivalent to 22.10 mg of codeine.

The excipients are: microcrystalline cellulose, lactose monohydrate, potato starch, colloidal anhydrous silica, talc and magnesium stearate.

The tablets are packed in Polyvinylchloride/Aluminium (PVC/Alu) blister or in high density polyethylene (HDPE) container closed with a tamper-resistant polypropylene (pp) cap.

The four tablet strengths are fully dose proportional.

II.2 Drug Substance

The active substance is codeine phosphate hemihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline white powder and is freely soluble in water.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additional requirements has been included for residual solvents in accordance with the CEP and in-house tests for particle size and microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The development started with the 20 mg product strength, which was based on the literature reference product Codeinefosfaat Teva 20 mg, tablets registered since 12 August 1981 in the Netherlands (NL RVG 55443) by Teva Nederland B.V. The main development studies were the characterisation of the marketed product, formulation optimisation studies, dissolution method development and comparative dissolution studies between the 20 mg test product versus the 20 mg marketed product and versus the additional product strengths. The development of the dissolution method is justified and the discriminatory power of the method was demonstrated. The conclusions on the bridging between the test products and the products described in the literature for this well-established-use application, are discussed in the clinical overview submitted by the MAH. The choices of the packaging and manufacturing process are justified and are acceptable. In general, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are weighing, sieving, blending, compression and packaging. The different tablet strengths are manufactured from a common blend. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches of common blend that were used to manufacture three pilot scaled batches of the 10 mg and 20 mg strengths and two pilot scaled batches of the 15 mg and 30 mg strengths. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post-authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements and additional functionality-related characteristics. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification (two methods), dimensions, dissolution, uniformity of dosage units, assay, related substances, microbiological purity and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical except for the related substances. The specification is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from

three pilot scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three scaled batches of each strength stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in PVC-Al blisters or HDPE bottles with PP cap. Stability has been tested according to the ICH stability guidelines. Tests included for the stability study were appearance, hardness, assay, friability, dissolution, assay, related substances and microbiological purity (for initial and end points). At all three storage conditions an increase in impurities was observed, most pronounced at higher storage temperatures. Results for assay were variable, but showed no clear trends. No trend is observed for the studied parameters. All results were within the specified acceptance limits. Photostability studies as described in the ICH were performed and showed that the product is stable when exposed to light. Based on the submitted stability data, a shelf life was granted of 2 years. No specific storage conditions need to be included in the SmPC or on the label.

An in-use stability study was performed on one batch of each strength packed in HDPE bottles stored at 25°C/60% RH. Except for an increase in impurities comparable to the results of the long-term stability studies, no clear trends or changes were observed. Based on these results, no separate in-use shelf-life was set.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

For the excipient lactose monohydrate, scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Codeïnefosfaat Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Codeine is an opiate which exerts its analgesic activity via the μ-opioid receptors. The analgesic action of codeine depends on O-demethylation to morphine, which is mediated in humans by cytochrome P450 2D6 (Lötsch, 2005; Leppert, 2011; DePriest et al., 2015).

In cynomolgus monkey, the constipating effect of opiates may be related to decreased contractile activity, rather than to the increased nonpropulsive segmenting contractions (Ekbom et al., 1980). Codeine prolonged the drug absorption-time and reduced the agitation force in the gastrointestinal tract (Katori et al., 1998). These results with codeine confirmed the stimulatory response of narcotics on the dog small intestine. Codeine phosphate produced a dose dependent increase in the number and duration of circular muscle contractions on the duodenum and jejunum. Moreover, the gastric antrum was relatively unaffected by codeine administration in the dog. These results are similar to those seen in the human gastrointestinal tract, but are in contrast to the inhibitory response of opiates on the rodent gastrointestinal tract. In a study by Fox et al. (1985), it was observed that opiates suppress the electrically induced contractions of the isolated guinea pig ileum and inhibit myoelectric activity of the rat small intestine.

On the basis of an experimental model, it seems unlikely that codeine would reduce stool volume in patients with very severe diarrhoea where all parts of the intestine are continuously exposed to large volumes of fluid (Schiller et al., 1982). According to a recent study on the human mechanism of action, nutrients and codeine were found to decrease motility while codeine was also able to decrease gastric emptying. The effect of codeine on gastric emptying was well correlated with decreased motility as assessed with a novel diagnostic intragastric balloon catheter (VIPUN Gastric Monitoring System) (Goelen et al., 2019).

Overall, the submitted literature does not established the exact mechanisms of action of the anti-diarrhoea effect of codeine. Nevertheless, the experimental data show that codeine reduces gastrointestinal motility and increases absorption of fluids probably by increasing the contact time of luminal fluid with mucosal cells.

The MAH has provided information on interactions with codeine in section 4.5 of the SmPC “Interaction with other medicinal products and other forms of interaction”. Interactions with other drugs, which are generally characteristic for opiates, were provided and discussed in the submitted clinical overview. Additionally, new literature was submitted establishing that: Codeine had a synergistic effect on tramadol in a study (Carnaval et al., 2013). Rosemary essential oil was found to probably have an additive effect to the analgesic action of codeine in mice, maybe via a potential pharmacokinetic action on the CYP enzymes (Raskovic et al., 2015). The dopaminergic system, especially the D1 receptor, may play an important role in the potentiation effect of chlorpheniramine on the reinforcing effects of opiates (Suzuki et al., 1990). This analgesic synergy of L-methadone with selective μ opioid drugs (such as codeine)

and the differences in opioid-mediated actions suggest that these drugs may be acting via different mechanisms (Bolan et al., 2002). Opioid coadministration, studied with codeine and morphine, had a synergistic effect in the acute tonic pain, that may relate to the different pathways of pain transmission and to the different intracellular signal transduction (Miranda et al., 2013). Codeine, diclofenac and fixed-ratio of codeine/diclofenac combinations produced a dose-dependent antinociceptive effect when administered locally, spinally or systemically (Stacher et al., 1986; Ammon et al., 2002).

III.2 Pharmacokinetics

Codeine is a prodrug that undergoes O-demethylation into morphine. This process is mediated by the highly polymorphic gene CYP2D6. Codeine is absorbed from the gastro-intestinal tract, although its bioavailability is low, with a short life-time (Leppert 2011). The substance is metabolised by conjugation with glucuronic acid, O-demethylation to morphine, N-demethylation to norcodeine, and conjugation of morphine and norcodeine with glucuronic acid, with different quantitative ratio of the formed metabolites in different species (TNP 1996). Codeine is mainly excreted via urine (Bodd et al., 1987; Vree & Wissen 1992; Skolnik et al., 2010). The submitted literature on the distribution of codeine to organs and tissues showed that there was a large variability in the measured concentrations and in the calculated ratios of blood/tissue concentrations. There was also a large variability in the calculated ratios of morphine to codeine, codeine-6-glucuronide (C6G) to codeine and norcodeine to codeine in all biological matrices. Moreover, the CYP2D6 genotype was considered as a not-reliable predictor of these ratios. The different blood/tissue concentration ratios showed no systematic relationship with the post-mortem interval. No coherent degradation or formation patterns for codeine, of the metabolites morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were observed upon reanalysis in peripheral blood after storage (Lötsch 2005; Nagar & Raffa, 2008).

It was observed in the literature that codeine passes through the placenta and passes into breast milk (Meny et al., 1993; Koren et al., 2006; Juurlink et al., 2012).

III.3 Toxicology

For acute toxicity the MAH has provided the overview of the available acute toxicity studies based on the publication of Eddy et al. from 1968. Although this overview is not recent, it is considered acceptable. There is a extensive amount of information on the acute toxicity of codeine (in different salt forms) in different species and by different routes of administration. The median lethal dose (LD_{50}) of codeine appears to be higher than the LD_{50} of morphine. Furthermore, codeine causes convulsions at lethal dose levels.

For repeated dose toxicity, the MAH refers to the studies conducted within the framework of the National Toxicology Program (NTP, 1996) which included 2-week, 13-week and 104-week studies with rats and mice administered codeine in fed conditions. The long-term rat study included the toxicokinetic analysis. In the long-term studies, codeine did not induce increased incidence of neoplastic lesions up to the dose levels of 80 mg/kg/day (rats) or 400 mg/kg/day

(mice). The animal survival was not affected. There was an exposure-related decrease in mean body weight of males and females in both species. Other findings in rats included exposure-related decreases in the incidence of benign pheochromocytomas in males and mammary fibroadenomas and adenocarcinomas in females. In mice, the incidences of follicular cell hyperplasia in all exposed groups were significantly greater than in controls, but there were no increases in thyroid gland follicular cell neoplasms. The incidences of eosinophilic foci, foci of fatty change, centrilobular cytomegaly, and centrilobular fatty change were reduced in the 3000 ppm males, and the incidences of hepatocellular adenomas or carcinomas were significantly reduced in both 3000 ppm males and females.

The concentrations of free and conjugated codeine and its metabolites (free and conjugated morphine) were determined in rat plasma in a two-year study. The exposure increased with the dose and decreased as the study progressed, suggesting that codeine did not accumulate. The concentration of conjugated morphine in rat plasma was significantly higher than of codeine, indicating considerably greater exposure of rats to morphine (NTP, 1996; Yuan et al., 1994).

Codeine induced physical dependence in rats, mice and monkeys, as was demonstrated in a number of publicly available studies (NTP, 1996).

For genotoxicity of codeine, the MAH refers to the bacterial gene mutation Ames test and the sister chromatid exchange and chromosome aberration tests in the CHO cells conducted as a part of the NTP studies (NTP, 1996), as well as a publicly available micronucleus test with NRK-49F cell line. These studies do not include *in vivo* testing, which is required according to the applicable ICH guideline (*Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals)*. However, the studies include negative results for the Ames test and chromosome aberration test, which in combination with the negative carcinogenicity test in two species, were considered sufficient to demonstrate that codeine is not genotoxic.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Codeïnefosfaat Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

Codeine phosphate hemihydrate is a well-known substance with an extensive history of use. Therefore, no new studies on pharmacology, pharmacokinetics or toxicology were required. The MAH has instead provided an overview on these aspects based on public literature data. This is acceptable.

IV. CLINICAL ASPECTS

Codeine phosphate hemihydrate is a well-known active substance with established efficacy and tolerability. The dossier is based on well-established use of the active substance. The MAH submitted a clinical overview based on literature for the justification of the indications and posology, which is acceptable.

IV.1 Pharmacokinetics

The pharmacokinetics of codeine are sufficiently discussed by the applicant. The absorption, distribution, metabolism and elimination of codeine is insufficiently supported by literature.

Adsorption, bioavailability and biowaiver

Codeine and its salts are rapidly absorbed from the gastrointestinal tract. On average less than 40% of the orally ingested codeine appears in the systemic circulation, the maximal plasma concentration is attained within 1-2 hours with a plasma half-life of 2.5-3.5 hours (Leppert 2011). Urinary recovery studies as well as similar systemic exposures to metabolites observed after oral and intravenous administration routes, clearly indicate an absorption of over the 90% (Bodd et al., 1987; Vree & Wissen 1992; Skolnik et al., 2010). Therefore, the high first-pass metabolism is primarily accounted for the low systemic bioavailability of codeine. Based on the submitted literature, no food effect on absorption of codeine is expected.

As codeine is highly absorbed, it is classified as a BCS-class I drug substance. Sufficient information on the dose linearity and comparison of the dissolution profiles of the literature reference product (Codeinefosfaat Teva 20 mg, tablets) and test product were submitted. The data justify a biowaiver for the other strengths.

The dissolution studies were performed according to the Guideline On The Investigation Of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1 with the following requirements for the test and reference products:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths are quantitatively proportional
- similarity in in vitro dissolution profiles, i.e. all additional strengths show very rapid dissolution, >85% in 15 min, at all three pH levels of 1.2, 4.5 and 6.8 using paddle apparatus at 50 rpm.

The dissolution studies were performed with 3 pilot batches per strength. The development of the method was justified and its discriminatory power was demonstrated. The results showed that the dissolution of codeine phosphate hemihydrate was pH independent. The dissolution profiles of the reference and test products at pH 1.2 were all similar (more than 85% of the active agent was dissolved within 15 minutes) but there were some variations at pH 4.5 and 6.8 for some strengths. Codeine is well absorbed, therefore the similarity of dissolution at pH 1.2 is the most important to demonstrate *in-vitro* equivalency. The essential

similarity of the 20 mg test and reference product was demonstrated without further mathematical evaluation and the well-established use legal base was applied to compare the 20 mg strength with the other the dose proportional strengths of the new product (10, 15 and 30 mg).

Distribution

Codeine crosses the placenta and is excreted in breast milk. In the SmPC, it is stated that the protein binding of codeine and codeine-6-glucuronide *in vivo* studies was 56.1±2.5% and 34.0±3.6%, respectively. Based on the literature, the estimated volume of distribution in healthy volunteers with normal liver and renal function is between 2.3 L/kg and 5.0 L/kg (Tegeder et al., 1999).

Elimination

Codeine is metabolised in the liver and excreted in the urine, approximately 37% as glucuronide and 10% as unchanged codeine. The plasma half-life is 3-4 hours. It may increase up to 6 hours in case of liver diseases or after intake of an overdose. Codeine is metabolised in the liver by the isoenzymes CYP2D6 and CYP3A4. O-and N-demethylation of codeine eventually leads to the formation of morphine and norcodeine, respectively, and both could be subsequently demethylated into normorphine. In addition, codeine and all of its demethylated derivatives also undergo phase 2 glucuronidation by UGT 2B7 and are excreted almost entirely through the kidney, mainly as conjugates. No interconversion is expected.

Intra- and inter-individual variability, dose proportionality and time dependency

Codeine is metabolised by the highly polymorphic enzyme CYP2D6 into morphine. The MAH provided sufficient information on possible CYP2D6 polymorphism. These polymorphisms cause differences in the activity of CYP2D6, genetic variations can result in a decreased or increased activity of CYP2D6. Consequently the variability of the metabolism of codeine and morphine levels after dosing, variates significantly per individual. This information has been included in sections 4 and 5 of the SmPC. Codeine is dose proportional in the relevant dosage range. Furthermore, codeine showed no time dependency.

Special populations

The MAH submitted pharmacokinetic data for subjects with impaired renal and/or hepatic function. Related information and warnings have been included in the SmPC regarding these two population groups.

Interactions

The possible pharmacokinetic interactions as described in the SmPC are sufficiently discussed and supported by adequate literature.

Bridging to literature

To establish a bridge from the new product to the products studied in the literature, as required in the well-established use (article 10a) application). *In vitro* dissolution profiles of Codeïnefosfaat Sandoz 20 mg tablets were compared with the reference product Codeinefosfaat 20 mg tablet, Teva Nederland B.V. Additionally, dissolution comparisons with

all strengths were provided. See IV.2, Pharmacokinetics for more information regarding the dissolutions tests and biowaiver. The products of the submitted literature varies in formulation and in the composition of the excipients. However, the data showed that the relevant variations in the new product are unlikely to have an effect on absorption and that the formulation plays no role in the *in vivo* delivery and biological use of the active substance, after oral intake of immediate release oral solid dosage forms.

An extensive overview was submitted for the observed pharmacokinetic parameters presented in the literature for different products. No remarkable deviations were observed in the pharmacokinetics for the different formulations when corrected for dose. Additionally, the formulation of the product does comply with the request for a BCS class I drug, supporting that no differences in pharmacokinetics are expected between the different formulations on the market. This is further reinforced by the similarity of the dissolution profiles of the test and reference product.

IV.2 Pharmacodynamics

Most of the submitted publications on the pharmacodynamic effects of codeine were published more than 20 years ago. Considering the pharmacodynamic effects of codeine are well-known for decades and that codeine is used regularly in clinical practice for the treatment of pain, cough, and diarrhoea, it is not expected that many new studies will be conducted on these effects. The submitted scientific evidence on the pharmacodynamic effects of codeine is considered acceptable.

Primary pharmacodynamics

Pain
The MAH has briefly discussed the potency of codeine versus other opioids based on its binding affinity. Codeine is a selective agonist for the μ opioid receptor with far less affinity than opioids used for moderate to severe pain such as oxycodone (Volpe et al., 2011). The mechanism of action and primary pharmacology of codeine in the context of pain management are established.

Cough
In the last decade, there has been a gradual change in opinion on the control of cough, as the research focus has moved more towards the study of human cough. Studies on the voluntary control of cough, placebo effects and the sensation of the urge to cough have helped to develop the idea that cough is much more than a reflex, and that higher centres in the brain play a major role in controlling cough causes and cough suppression by direct central action in the medulla (Eccles, 2009). There are conflicting pharmacological results on the mechanism(s) of antitussive action of codeine, which indicates its high dependency on species and model (Dicpinigaitis et al., 2014). Codeine is believed to exert a relatively specific central inhibitory action on the "cough centre" in the medulla, without causing respiratory depression.

Diarrhoea
The antidiarrheal effect of codeine appears to be due to a combination of delayed mouth-cecum transit plus an additional delay in the ascending colon. This colonic delay may be partially explained by a reduction in postprandial propulsive movements that were seen in the following model of diarrhoea. Enteric coating of a capsule has been used to deliver a bolus of a 99mTc adioisotope to the ileocecal region. This has allowed quantitative assessment of regional colonic transit in a group of healthy subjects whose proximal colonic transit was accelerated by lactulose (20 mL thrice daily). In this experimental model of diarrhoea, codeine delayed transit from mouth to terminal ileum and also delayed transit through the ascending colon (Barrow et al., 1993). Furthermore, codeine delayed whole colon transit, as assessed by geometric centre analysis, which showed the delay to be most marked in the right colon with little effect noted in the left colon. In addition, codeine significantly reduced the number of retrograde movements observed and reduced the colonic response to eating. In other publications (Schiller et al., 1982; O'Brien et al., 1988) it was shown that therapeutic doses of codeine increase the net intestinal absorption (and thereby reduce stool volume) by increasing the contact time of luminal fluid with mucosal cells, but not by increasing the rate of absorption by the mucosal cells. It was also concluded that endogenous opiates do not regulate intestinal absorption in humans. Further, the use of codeine was associated with a significant fall in the total ileostomy output and the ileostomy output of water. The proportion of faecal solids rose and the effluent appeared thicker while the weight of faecal solids remained unchanged (Newton 1978). Codeine administration was also associated with a significant reduction in the ileostomy outputs of potassium. Codeine also increases the pressure in the anal sphincter and increases the continence of infused saline whilst decreasing the sensitivity of the rectum to balloon distension (Hughes 1984).

Secondary pharmacodynamics
The submitted literature on the secondary pharmacodynamics effects of codeine was based on animal studies. These studies showed decreased in heart rates, locomotor behaviour, and respiration. Furthermore, increased abuse liability was observed (Adcock et al., 1988; Carney et al., 1976, Meert & Vermeirsch 2005; Suzuki et al., 1984). The results of several evaluations in rats were also described (Meert & Vermeirsch 2005).

IV.3 Clinical efficacy

Pain
The MAH has provided literature references examining the efficacy of codeine alone or in combination with another analgesic in the treatment of post-operative pain, postpartum uterine pain, episiotomy pain, and musculoskeletal pain.

The submitted data supporting the efficacy of codeine in the treatment of pain concerns studies mostly performed in the 70s and 80s (Bjune et al., 1996; Bloomfield et al., 1977; Bloomfield et al., 1986; Forbes et al., 1986; Giglio et al., 1990; Gilbert et al., 1978; Levin 1978) and do not fulfil the current criteria for studies examining analgesics. The literature shows that the evidence for efficacy of codeine (in combination with another analgesic) in visceral pain is sparse, however the available limited data support its efficacy in the sought indication. The

MAH has not included the two Cochrane library reviews in Issue 4 from 1998. discussing the efficacy of codeine in combination with paracetamol and ibuprofen in the treatment of post-operative pain (Toms et al., 2009; Derry et al., 2015). These reviews conclude the good analgesic efficacy of the combinations in the treatment of post-operative pain. Additionally, recent treatment guidelines (for example from the European Society for Emergency Medicine; EUSEM, 2020) demonstrate that codeine is still considered a treatment option for acute moderate pain, when pain is not relieved by analgesics such as paracetamol or ibuprofen alone. Based on all evaluated literature, the efficacy of codeine in the treatment of pain was considered demonstrated.

The posology for Codeïnefosfaat Sandoz is considered supported by the provided literature and is in line with the established dosing recommendations in the Netherlands (RMS).

Special populations
The MAH submitted literature from four clinical trials in which children or adolescents were included in the patient population. Two of these trials were placebo-controlled studies which examined codeine as an add-on treatment to an non-steroidal anti-inflammatory drugs (NSAID) and as monotherapy. The pain models used i.e. oral surgery and surgical removal of impacted third molars were considered suitable for examining efficacy in acute moderate pain. Patients included in these studies were aged from 15 years and 16 years onwards, respectively. These studies show that while codeine alone did not separate from placebo in all relevant efficacy endpoints, a combination of an NSAID and codeine 60 mg did (Forbes et al., 1986; Giglio et al., 1990; Giglio & Laskin, 1990).

In the guideline for the management of acute pain in emergency situations from the EUSEM (2020), codeine is indicated for children from 12 years onwards. Considering this guideline, the available data in adolescents and the long-standing use of the product in patients aged 12 years onwards, the age limit of 12 years is accepted. Furthermore, in these guidelines there are no limitations for codeine use in the elderly, apart from a recommendation to use a lower dose due to risk of adverse events. The SmPC of the new product includes a warning in section 4.4 on elderly patients due to slower metabolism and elimination of codeine. This is endorsed.

A precise dosing advice cannot be given due to lack of data. Considering the EUSEM guideline (2020), long-standing use of the product and the warning in place in the SmPC, no additional limitations or advice regarding elderly were considered required. In conclusion, the literature provided by the MAH support to some extent the efficacy of codeine in combination with an NSAID in adolescents. Based on the long-standing use of the product in patients aged older than 12 years and elderly, as also apparent from the EUSEM (2020).

<u>Cough</u>
The use of codeine for the symptomatic relief of non-productive cough is considered well-established. The main data in support of its antitussive activity are from early, small scale and poor quality trials performed before the 70s (Eddy et al., 1969). Thereafter, codeine has long been considered as the standard centrally acting antitussive drug. More recent data indicate that codeine is not effective in patients with acute upper respiratory tract infection (Eccles et

al., 1992; Freestone et al., 1996; Freestone et al., 1997) and COPD (Smith et al., 2006). Several reviews on the treatment of cough are described in old and more recently performed trials on the use of codeine (Bolser, 2006; Wee 2008; Chung 2009; Molassiotis et al., 2010). Differences between more recent and older studies may be explained by differences in underlying pathological conditions. In general, reviews on cough treatment emphasise the limited amount of data available on effective treatment for cough and the need for new therapies. Prescription data support the current use of codeine tablets in the EU including in the Netherlands. However, these data do not allow to distinguish between the different licensed indications. No literature data or treatment-specific guidelines for the symptomatic relief of a non-productive cough were provided by the MAH and it may be that these are not available in the public domain. The accumulating evidence indicates that the expected place for codeine in this indication is limited and it cannot be excluded that there is still some use of the product in the cough indication.

The early trials for codeine showed that a single dose of 30-60 mg or a daily dosage of 45-160 mg exerts an antitussive action in patients with various pathological backgrounds. The dose-response study was performed later and this showed a linear dose-response relationship (Sevelius et al., 1971). This last study was performed in a different setting (subjects with obstructive emphysema and chronic bronchitis with a productive cough of more than 5 years of duration). The posology for Codeïnefosfaat Sandoz is in line with currently licensed formulations in the RMS for the same indication and is therefore acceptable.

Use in adolescents (12-18 years)
Literature data on the use of codeine in adolescents is scarce. The submitted data are based on one study in the EMA PRAC recommendation (Kelly et al., 1963; EMA/163792/2015) and an observational study with children aged from 8 months to 17 years, having acute cough due to a respiratory infection (De Blasio et al.,2012). In addition, two studies were submitted on the use of codeine in combination with other antitussives in children below 12 years of age (Jaffé & Grimshaw 1983, Taylor et al., 1993). The limited data provided did not allow to draw firm conclusions on the efficacy of codeine in adolescents for the symptomatic relief of non-productive cough. However, several codeine medicinal products are currently licensed for the use in adolescents and appropriate safety warnings have been taken into account. Based on available data the use in adolescents is considered sufficiently addressed and supported, making this indication also acceptable for the new product.

The age limitation to paediatric patients aged 12 years and above, is in line with a previous PRAC recommendation (EMA/163792/2015). In addition, the use of codeine for cough is not recommended for children from 12 years to 18 years aged with a reduced respiratory function. This was included in the SmPC of the product.

<u>Diarrhoea</u>
Codeine was originally proposed for symptomatic relief of diarrhoea in case of an insufficient response to loperamide in patients aged 12 years and above. Therefore, for this product the indication for diarrhoea was limited to adults.

The MAH submitted several publications concerning reviews and clinical studies on the clinical effects of codeine in patients with diarrhoea. The submitted clinical studies concern double-blinded cross-over studies (King et al., 1982; Palmer et al., 1980) and a patient-blinded prospective study (Shee & Pounder, 1980). The cause of diarrhoea in these publications varied, it was associated with irritable bowel syndrome (Goulston, 1973), it occurred after abdominal surgery (King et al., 1982; Shee & Pounder, 1980), or the cause was unknown or not reported (Shee & Pounder, 1980; Palmer et al., 1980). The clinical effects of codeine were compared to those of loperamide (King et al., 1982; Shee & Pounder, 1980; Palmer et al., 1980) and diphenoxylate (Shee & Pounder, 1980; Palmer et al., 1980). Codeine was provided at daily dosages ranging from 15 mg up to 180 mg per day.

Varying results were obtained in the submitted studies. According to the publication by Shee & Pounder (1980) the clinical effects of codeine by the treatment of chronic diarrhoea were comparable to those of loperamide and diphenoxylate, whereas in the publication by Palmer et al. (1980), the clinical effects of codeine tended to be more pronounced than those of diphenoxylate. The clinical effects with respect to (non-chronic) diarrhoea were comparable to those of loperamide in submitted publications by Shee & Pounder (1980) and Palmer et al. (1980), whereas in the study by King et al. (1982) the effects tended to be more limited than those of loperamide. In this study, both codeine and loperamide significantly decreased the daily output and water content of ileostomy fluid. However, daily losses of sodium and potassium were more pronounced upon codeine than upon loperamide treatment. Moreover, codeine was associated with more side effects compared to loperamide. The results of this study suggest that diarrhoea could be treated better with loperamide than with codeine.

Several international guidelines which are applicable to the European geographic area recommend the use of codeine after failure of loperamide treatment for diarrhoea (WHO 2011, NHS Guideline 2018, Palliative Care Guideline 2019). In line with this, several codeine medicinal products were authorised for symptomatic treatment of diarrhoea after an insufficient response to loperamide (e.g. Codeine phosphate Expharma (HU/H/0608/001-002-003-004/DC)). Based on this, the indication in adults is also applicable for this product.

Codeine at a dosage of 15-60 mg three to four times daily is recommended in several guidelines (WHO, 2011; Schiller et al., 2017; NHS Guideline 2018, Palliative Care Guideline 2019). This dosage has been accepted for codeine medicinal products (e.g. Codeine phosphate Expharma (HU/H/0608/001-002-003-004/DC)) to induce symptomatic relief of diarrhoea after an insufficient response to loperamide. The posology of the new product is in line with this and therefore acceptable.

IV.4 Clinical safety

The MAH submitted a general discussion on the clinical safety of codeine for the indications pain, cough and diarrhoea and provided acceptable literature-based data for the safety assessment.

The MAH has also provided an adequate review of adverse events associated with codeine

and the safety profile is considered acceptable in short-term use. The most common adverse events are those shared with other opioids i.e. nausea, vomiting, constipation and drowsiness. The safety profile is in general reflected in the SmPC sections (4.3 to 4.9). The adverse events presented in the identified pain studies in children and adolescents have been discussed. The most common adverse events reported in children are those reported in adults, i.e. gastrointestinal adverse events such as nausea, nervous system adverse events such as dizziness and drowsiness and skin reactions. Whether there is a difference in adverse event frequency in adolescents compared to adults is not known. Due to the risk of opioid toxicity, as a result of the variable and unpredictable conversion of codeine into morphine in children under 12 years of age, the pain indication is limited to patients older than 12 years of age.

Safety data of codeine in adolescents in the cough indication are scarce and the presented public data are out of date (1983). The safety data for the use of codeine in the cough indication has been updated in 2015 based on the PRAC recommendation EMA/163792/2015 (use restricted to paediatric patients of 12 years and older and not recommended for use in children aged 12 years to 18 years who have problems with breathing). Therefore, recent information on use in paediatrics is taken into account. Despite the limited data in the public domain, the current safety data in the SmPC is considered up-to-date based on regular post-marketing reviews of already licensed products with long-standing use. There are no adverse event data available regarding the elderly. The current SmPC includes a warning in elderly due to slower metabolism and elimination. This is acceptable.

IV.5 Risk Management Plan

The MAH 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 Codeïnefosfaat Sandoz.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

Codeine has been used and is registered for the requested indications in the RMS and the CMS countries for at least ten years. Based upon clinical data and the longstanding clinical experience, the use of codeine in the proposed indications can be considered as well-established with demonstrated efficacy. The posology for the three indications (pain, cough and diarrhoea) is based on wight and is in line with current recommendations. On the basis

thereof, the efficacy of Codeïnefosfaat Sandoz is considered acceptable. Furthermore, the safety profile of codeine in the applicable indications is considered as well-established and acceptable. The adverse events are well characterised and adequately covered by literature-based data.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted of a pilot test with five participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Codeïnefosfaat Sandoz 10 mg, 15 mg, 20 mg and 30 mg, tablets has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the indications as well as the posology of the new product are in line with current codeine use and recommendations in the RMS and CMS countries, in which codeine phosphate has been registered for more than ten years. Based upon clinical data and the longstanding clinical experience, the use of codeine phosphate in the proposed indications can be considered well-established with demonstrated efficacy and safety.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-stablished use has been demonstrated for Codeïnefosfaat Sandoz, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 July 2022.

LITERATURE REFERENCES

Adcock, J. J., Schneider, C., & Smith, T. W. (1988). Effects of codeine, morphine and a novel opioid pentapeptide BW443C, on cough, nociception and ventilation in the unanaesthetized guinea-pig. British journal of pharmacology, 93(1), 93-100.

Ammon, S., Marx, C., Behrens, C., Hofmann, U., Mürdter, T., Griese, E. U., & Mikus, G. (2002). Diclofenac does not interact with codeine metabolism in vivo: A study in healthy volunteers. BMC Clinical Pharmacology, 2(1), 1-10.

Barrow, L., Steed, K. P., Spiller, R. C., Maskell, N. A., Brown, J. K., Watts, P. J., ... & Wilson, C. G. (1993). Quantitative, noninvasive assessment of antidiarrheal actions of codeine using an experimental model of diarrhea in man. Digestive diseases and sciences, 38(6), 996-1003.

Bjune, K., Stubhaug, A., Dodgson, M. S., & Breivik, H. (1996). Additive analgesic effect of codeine and paracetamol can be detected in strong, but not moderate, pain after Caesarean section: Baseline pain-intensity is a determinant of assay-sensitivity in a postoperative analgesic trial. Acta anaesthesiologica scandinavica, 40(4), 399-407.

Bloomfield, S. S., Barden, T. P., & Mitchell, J. (1977). Naproxen, aspirin, and codeine in postpartum uterine pain. Clinical Pharmacology & Therapeutics, 21(4), 414-421.

Bloomfield, S. S., Mitchell, J., Cissell, G., & Barden, T. P. (1986). Flurbiprofen, aspirin, codeine, and placebo for postpartum uterine pain. The American Journal of Medicine, 80(3), 65-70.

Bodd, E., Beylich, K. M., Christophersen, A. S., & Mørland, J. (1987). Oral administration of codeine in the presence of ethanol: a pharmacokinetic study in man. Pharmacology & toxicology, 61(5), 297-300.

Bolan, E. A., Tallarida, R. J., & Pasternak, G. W. (2002). Synergy between μ opioid ligands: evidence for functional interactions among μ opioid receptor subtypes. Journal of Pharmacology and Experimental Therapeutics, 303(2), 557-562.

Bolser DC. Current and future centrally acting antitussives. Respir Physiol Neurobiol. 2006 Jul 28;152(3):349-55.

Carnaval, T. G., Sampaio, R. M., Lanfredi, C. B., Borsatti, M. A., & Adde, C. A. (2013). Effects of opioids on local anesthesia in the rat: a codeine and tramadol study. Brazilian Oral Research, 27, 455-462.

Carney, J. M., Llewellyn, M. E., & Woods, J. H. (1976). Variable interval responding maintained by intravenous codeine and ethanol injections in the rhesus monkey. Pharmacology Biochemistry and Behavior, 5(5), 577-582.

Chung, K. F. (2009). Clinical cough VI: the need for new therapies for cough: disease-specific and symptom-related antitussives. Pharmacology and therapeutics of cough, 343-368.

Dahan, A., Wolk, O., Zur, M., Amidon, G. L., Abrahamsson, B., Cristofoletti, R., ... & Dressman, J. B. (2014). Biowaiver monographs for immediate-release solid oral dosage forms: Codeine phosphate. Journal of Pharmaceutical Sciences, 103(6), 1592-1600.

De Blasio, F., Dicpinigaitis, P. V., Rubin, B. K., De Danieli, G., Lanata, L., & Zanasi, A. (2012). An observational study on cough in children: epidemiology, impact on quality of sleep and treatment outcome. Cough, 8(1), 1-6.

DePriest, A. Z., Puet, B. L., Holt, A. C., Roberts, A., & Cone, E. J. (2015). Metabolism and disposition of prescription opioids: a review. Forensic Sci Rev, 27(2), 115-145.

Derry, S., Karlin, S. M., & Moore, R. A. (2015). Single dose oral ibuprofen plus codeine for acute postoperative pain in adults. Cochrane Database of Systematic Reviews, (2).

Dicpinigaitis, P. V., Morice, A. H., Birring, S. S., McGarvey, L., Smith, J. A., Canning, B. J., & Page, C. P. (2014). Antitussive drugs—past, present, and future. Pharmacological reviews, 66(2), 468-512.

Eccles, R., Morris, S., & Jawad, M. (1992). Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. Journal of clinical pharmacy and therapeutics, 17(3), 175-180.

Eccles, R. (2009). Central mechanisms IV: conscious control of cough and the placebo effect. Pharmacology and therapeutics of cough, 241-262.

Eddy, N. B., Friebel, H., Hahn, K. J., & Halbach, H. (1968). Codeine and its alternates for pain and cough relief: 1. Codeine, exclusive of its antitussive action. Bulletin of the World Health Organization, 38(5), 673.

Eddy NB, Friebel H, Hahn KJ, Halbach H. Codeine and its alternates for pain and cough relief. 3. The antitussive action of codeine--mechanism, methodology and evaluation. Bull World Health Organ. 1969;40(3):425-54.

Ekbom, G., Schulte, W. J., Condon, R. E., Woods, J. H., & Cowles, V. (1980). Effects of narcotic analgesics on bowel motility in subhuman primates. Journal of Surgical Research, 28(4), 293-296.

European Medicines Agency, Pharmacovigilance Risk Assessment Committee (PRAC): Recommends restrictions on the use of codeine for cough and cold in children. EMA/163792/2015; 13 March 2015.

European Society For Emergency Medicine (EUSEM), Guidelines for the management of acute pain in emergency situations, March 2020.

Freestone, C., Eccles, R., Morris, S., & Jawad, M. S. (1996). Assessment of the antitussive efficacy of codeine using cough sound pressure levels as a means of measuring cough. Pulmonary pharmacology, 9(5-6), 365.

Freestone, C., & Eccles, R. (1997). Assessment of the antitussive efficacy of codeine in cough associated with common cold. Journal of pharmacy and pharmacology, 49(10), 1045-1049.

Forbes, J. A., Keller, C. K., Smith, J. W., Zeleznock, J. R., Sevelius, H., & Beaver, W. T. (1986). Analgesic effect of naproxen sodium, codeine, a naproxen-codeine combination and aspirin on the postoperative pain of oral surgery. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 6(5), 211-218.

Fox, D. A., Bauer, R., & Bass, P. (1985). Use of gut cyclic motor activity to evaluate a stimulant (narcotic) and inhibitor (anticholinergic) of gastrointestinal-tract activity in the unanesthetized dog. Journal of pharmacological methods, 13(2), 147-155.

Giglio, J. A., & Laskin, D. M. (1990). Double-blind comparison of meclofenamate sodium plus codeine, meclofenamate sodium, codeine, and placebo for relief of pain following surgical removal of third molars. Journal of oral and maxillofacial surgery, 48(8), 785-790.

Goelen, N., de Hoon, J., Morales, J. F., Varon, C., Van Huffel, S., Augustijns, P., ... & Janssen, P. (2020). Codeine delays gastric emptying through inhibition of gastric motility as assessed with a novel diagnostic intragastric balloon catheter. Neurogastroenterology & Motility, 32(1), e13733.

Goulston, K. (1973). Diagnosis and treatment of the irritable bowel syndrome. Drugs, 6(3), 237-243.

Gilbert, M. M., Sanzari, N. P., Losada, M., & Caruso, F. S. (1978). Double-blind oral analgesic study of butorphanol in musculoskeletal pain: a comparison with codeine and placebo. Journal of International Medical Research, 6(1), 14-23.

Hughes E, Cuthbertson AM, Killingback MK. Colorectal surgery. Br J Surg. 1984;72:156. Edinburgh: Churchill Livingstone.

Jaffé, G., & Grimshaw, J. J. (1983). Randomized single-blind trial in general practice comparing the efficacy and palatability of two cough linctus preparations,'Pholcolix' and 'Actifed' Compound, in children with acute cough. Current medical research and opinion, 8(8), 594-599.

Juurlink, D. N., Gomes, T., Guttmann, A., Hellings, C., Sivilotti, M. L., Harvey, M. A., & Mamdani, M. M. (2012). Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: a retrospective cohort study. Clinical Toxicology, 50(5), 390-395.

Katori, N., Aoyagi, N., & Kojima, S. (1998). Effects of codeine on the agitating force and gastrointestinal transit time in dogs, for use in drug absorption studies. Biological and Pharmaceutical Bulletin, 21(4), 418-420.

Kelly, D. F. (1963). A comparative clinical test of pholcodine with codeine as control. Northwest medicine, 62, 871-874.

King, R. F., Norton, T., & Hill, G. L. (1982). A double-blind crossover study of the effect of loperamide hydrochloride and codeine phosphate on ileostomy output. Australian and New Zealand Journal of Surgery, 52(2), 121-124.

Koren, G., Cairns, J., Chitayat, D., Gaedigk, A., & Leeder, S. J. (2006). Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. The Lancet, 368(9536), 704.

Levin, H. M. (1978, January). Relative potency assay comparing zomepirac sodium, propoxyphene napsylate, propoxyphene napsylate with acetaminophen, codeine, and placebo in patients with episiotomy pain. In CLINICAL PHARMACOLOGY & THERAPEUTICS (Vol. 23, No. 1, pp. 118-118). 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318: MOSBY-YEAR BOOK INC.

Leppert, W. (2011). CYP2D6 in the metabolism of opioids for mild to moderate pain. Pharmacology, 87(5-6), 274-285.

Lötsch, J. (2005). Opioid metabolites. Journal of pain and symptom management, 29(5), 10-24.

Meert, T. F., & Vermeirsch, H. A. (2005). A preclinical comparison between different opioids: antinociceptive versus adverse effects. Pharmacology Biochemistry and Behavior, 80(2), 309-326.

Meny, R. G., Naumburg, E. G., Alger, L. S., Brill-Miller, J. L., & Brown, S. (1993). Codeine and the breastfed neonate. Journal of Human Lactation, 9(4), 237-240.

Miranda, H. F., Noriega, V., Zepeda, R. J., Sierralta, F., & Prieto, J. C. (2013). Systemic synergism between codeine and morphine in three pain models in mice. Pharmacological Reports, 65(1), 80-88.

Molassiotis, A., Bryan, G., Caress, A., Bailey, C., & Smith, J. (2010). Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: a systematic review of the literature. Respiratory Medicine CME, 3(4), 199-206.

Nagar, S., & Raffa, R. B. (2008). Looking beyond the administered drug: metabolites of opioid analgesics. J Fam Pract, 57(Suppl 6), S25-S32.

National Toxicology Program. (1996). NTP toxicology and carcinogenesis studies of codeine (CAS No. 76-57-3) in F344 rats and B6C3F1 mice (feed studies). National Toxicology Program technical report series, 455, 1-275.

Newton, C. R. (1978). Effect of codeine phosphate, Lomotil, and Isogel on ileostomy function. Gut, 19(5), 377-383.

National Health Service (NHS) England, Guideline 2018, Management of systemic anti-cancer therapy, induced diarrhoea in adult patients v2.3.

O'Brien, J. D., Thompson, D. G., McIntyre, A., Burnham, W. R., & Walker, E. (1988). Effect of codeine and loperamide on upper intestinal transit and absorption in normal subjects and patients with postvagotomy diarrhoea. Gut, 29(3), 312-318.

Palliative care, pain & symptom control guidelines for adults, Greater Manchester and Eastern Cheshire Strategic Clinical Networks, fifth edition 2019.

Palmer, K. R., Corbett, C. L., & Holdsworth, C. D. (1980). Double-blind cross-over study comparing loperamide codeine and diphenoxylate in the treatment of chronic diarrhea. Gastroenterology, 79(6), 1272-1275.

Raskovic, A., Milanovic, I., Pavlovic, N., Milijasevic, B., Ubavic, M., & Mikov, M. (2015). Analgesic effects of rosemary essential oil and its interactions with codeine and paracetamol in mice. Eur Rev Med Pharmacol Sci, 19(1), 165-72.

Sevelius, H., McCoy, J. F., Colmore, J. P. Dose response to codeine in patients with chronic cough. Clinical Pharmacology & Therapeutics, 1971, 12(3), 449–455.
Shee, C. D., & Pounder, R. E. (1980). Loperamide, diphenoxylate, and codeine phosphate in chronic diarrhoea. British Medical Journal, 280(6213), 524.

Schiller, L. R., Davis, G. R., Santa Ana, C. A., Morawski, S. G., & Fordtran, J. S. (1982). Studies of the mechanism of the antidiarrheal effect of codeine. The Journal of Clinical Investigation, 70(5), 999-1008.

Schiller, L. R., Pardi, D. S., & Sellin, J. H. (2017). Chronic diarrhea: diagnosis and management. Clinical Gastroenterology and Hepatology, 15(2), 182-193.

Skolnik, S., Lin, X., Wang, J., Chen, X. H., He, T., & Zhang, B. (2010). Towards prediction of in vivo intestinal absorption using a 96-well Caco-2 assay. Journal of pharmaceutical sciences, 99(7), 3246-3265.

Smith, J., Owen, E., Earis, J., & Woodcock, A. (2006). Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. Journal of Allergy and Clinical Immunology, 117(4), 831-835.

Stacher, G., Steinringer, H., Schneider, S., Mittelbach, G., Winklehner, S., & Gaupmann, G. (1986). Experimental pain induced by electrical and thermal stimulation of the skin in healthy man: sensitivity to 75 and 150 mg diclofenac sodium in comparison with 60 mg codeine and placebo. British journal of clinical pharmacology, 21(1), 35-43.

Suzuki, T., Masukawa, Y., & Misawa, M. (1990). Drug interactions in the reinforcing effects of over-the-counter cough syrups. Psychopharmacology, 102(4), 438-442.

Suzuki, T., Shimada, M., Yoshii, T., & Yanaura, S. (1984). Induction of physical dependence on codeine in the rat by drug-admixed food ingestion. The Japanese Journal of Pharmacology, 34(4), 441-446.

Taylor, J. A., Novack, A. H., Almquist, J. R., & Rogers, J. E. (1993). Efficacy of cough suppressants in children. The Journal of pediatrics, 122(5), 799-802.
Toms, L., Derry, S., Moore, R. A., & McQuay, H. J. (2009). Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. Cochrane Database of Systematic Reviews, (1).

Tegeder, I., Lötsch, J., & Geisslinger, G. (1999). Pharmacokinetics of opioids in liver disease. Clinical pharmacokinetics, 37(1), 17-40.

Volpe, D. A., Tobin, G. A. M., Mellon, R. D., Katki, A. G., Parker, R. J., Colatsky, T., ... & Verbois, S. L. (2011). Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. Regulatory Toxicology and Pharmacology, 59(3), 385-390.

Vree, T. B., & Wissen, C. P. V. V. (1992). Pharmacokinetics and metabolism of codeine in humans. Biopharmaceutics & drug disposition, 13(6), 445-460.

Wee B. Chronic cough. Curr Opin Support Palliat Care. 2008 Jun;2(2):105-9.

World Health Organization (WHO), 2011; 18th Expert committee on the selection and use of essential medicines, WHO Technical Report Series 965, Section 17.5.3. Antidiarrhoeal (symptomatic) medicines in adults, March 2011.

Yuan, J., Dunnick, J. K., Barnes, E. R., & Findlay, J. W. (1994). Codeine toxicokinetics in rats during a two-year dosed feed study. Drug metabolism and disposition, 22(1), 14-20.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-