IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Co-codamol 15 mg/500 mg Film-coated Tablets
Paracetamol
Codeine phosphate hemihydrate
PA22871/020/001

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

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Co-codamol 15 mg/500 mg film-coated tablets, from Azure Pharmaceuticals Ltd on 12th August 2022, indicated in adult and adolescent patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC and is referred to as a well-established use application.

Ireland was the Reference Member State in the decentralised procedure and Malta was the sole Concerned Member State.

This is a prescription-only medicinal product.

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

Name of the product	Co-codamol 15 mg/500 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Codeine phosphate hemihydrate and paracetamol
Pharmacotherapeutic classification (ATC code)	N02BE51
Pharmaceutical form and strength(s)	15 mg/500 mg film-coated tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/020/001
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1138/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Co-codamol 15 mg/500 mg film-coated tablets.

II.2 Drug substance

The active substances are codeine phosphate hemihydrate and paracetamol, established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each film-coated tablet contains 15 mg of codeine phosphate hemihydrate and 500 mg of paracetamol.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Co-codamol 15 mg/500 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The active substances in combination, paracetamol and codeine, for the treatment of acute moderate pain has been available on the European/Irish market for several decades. Preclinical data have been superseded by clinical experience, as such, no pre-clinical assessment has been made on the application.

The nonclinical data have been collected from the published scientific literature, which is based on the results of experiments conducted by numerous independent investigators, there has been no well structured testing strategy. Therefore the GLP status of the reported studies is unknown.

III.2 Pharmacology

The pharmacology of paracetamol and codeine are well established.

Paracetamol

Paracetamol possesses analgesic and antipyretic properties along with a weak anti-inflammatory activity. It has a long history of beneficial use regarding the treatment of mild to moderate pain and fever. Although the exact mechanism of action of paracetamol is not clearly defined, there are several potential mechanisms of action including a central site of action, prostaglandin inhibition, and cannabinergic and serotonergic effects. The most significant adverse effect of paracetamol is its hepatotoxic potential at high doses. This is the result of the limited capacity of the non-toxic pathways of paracetamol metabolism, and an accumulation of the toxic intermediate metabolite NAPQI following administration of high doses.

Codeine

Codeine phosphate is an opioid agonist used as an oral analgesic, antidiarrhoeal and as an antitussive agent. Codeine is metabolized to morphine by O-demethylation in the liver. Codeine and other opioids act on the brain stem respiratory centres reducing their responsiveness to increases in carbon dioxide tension, resulting in respiratory depression. The antitussive mechanisms of narcotic antitussives are not fully understood. Presynaptic μ-opioid receptors probably contribute to this action. The secondary pharmacodynamic effects of codeine in experimental animal species include decreased locomotor behavior, respiration and GI motility; as well as increased abuse liability.

III.3 Pharmacokinetics

Paracetamol

Both paracetamol and codeine are well absorbed orally. Paracetamol is widely distributed throughout most tissues of the body. Paracetamol is metabolised primarily in the liver. The two main metabolic pathways are glucuronide conjugation and sulphate conjugation. A minor pathway, catalysed by CYP450, is the formation of the reactive intermediate compound NAPQI. Paracetamol induced toxicity is mainly based on the accumulation of NAPQI forming the basis for metabolic interactions with other drugs. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

Codeine

Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral potency of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10% of orally administered codeine is demethylated to morphine, which may account for some of its analgesic activity.

III.4 Toxicology

The animal toxicological studies reviewed from the available published literature indicate that both paracetamol and codeine, when administered chronically, at high dosage, have well defined toxic effects. In this respect, codeine is associated with CNS depression and reproductive toxicities; paracetamol can cause hepatic, renal, and testicular damage. The information available on acute and chronic toxicity indicates that paracetamol and codeine are unlikely to be associated with significant toxic effects when used at typical therapeutic doses.

Paracetamol

The most significant adverse effect of paracetamol is its hepatotoxic potential. This is the result of the limited capacity of the non-toxic pathways of paracetamol metabolism, and an accumulation of the toxic intermediate metabolite NAPQI following administration of high doses. The risks of liver damage resulting from overdosage, especially in patients taking concomitant alcohol, since they may be especially at risk as their livers may form more of the toxic metabolite NAPQI There is some evidence from animal studies that long-term use at high (hepatotoxic) doses maybe associated with effects on male fertility. Genotoxic effects of paracetamol at the chromosomal level have been demonstrated. However, since there is convincing experimental evidence of the existence of dose thresholds for the genotoxicity of paracetamol, these safety factors are satisfactory and it seems unlikely that normal therapeutic doses of paracetamol would cause any genotoxicity.
The normal therapeutic use of paracetamol is not associated with genotoxic or carcinogenic risks.
Experimental animal studies do not suggest increased malformations from therapeutic use of paracetamol during pregnancy. In rats orally administered 500 mg/kg or 1000 mg/kg paracetamol inhibited sexual behaviour and fertility. This was attributed to paracetamol's effects on male reproductive competence. Paracetamol was to an increase in pre-implantation losses resulting from oligozoospermia, impairments of normal and hyper-activated sperm motility, and reduction in the fertilizing potential of spermatozoa. Embryo foetal development studies showed that paracetamol did not increase foetal skeleton malformations compared with untreated control, and it is well tolerated by foetal and maternal organism. In rats, following intrauterine exposure to paracetamol there were no signs of maternal toxicity and no effects on parturition, litter size and birth weight. In the male pups exposed to paracetamol, the AGD index was significantly reduced and the number of retained nipples was significantly increased.

Codeine

Codeine is associated with CNS and respiratory depression. Induction of physical dependence on codeine has been demonstrated in male Sprague-Dawley rats.

Results from genotoxicity studies using codeine in the *Salmonella* assay and in mice revealed no genotoxicity.

Codeine studies revealed no carcinogenic activity in rats, although thyroid gland follicular cell hyperplasia was increased in exposed male and female mice.

Oral administration of codeine to mice has resulted in developmental toxicity, codeine also increased the number of resorptions in mice. Codeine was not teratogenic in rabbits but was embryotoxic to rats. In addition, codeine displayed

embryo-foetal toxicities, causing skeletal abnormalities in mice. In codeine-treated rats, the mortality rate of neonates was 7.3% at birth compared to 0% in controls; and their body weights (male and female) were slightly decreased compared to control. Codeine crosses the placenta and is excreted in milk.

III.5 Ecotoxicity/environmental risk assessment

Since Co-codamol 15mg/ 500 mg Tablets 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. An appropriate justification for the absence of studies was provided by the applicant.

III.6 Discussion on the non-clinical aspects

As paracetamol and codeine are well-known active substances, this is a bibliographic application with no new non-clinical studies conducted by the applicant. The submitted overview of the available non-clinical pharmacodynamic, pharmacokinetic and toxicological data is acceptable. Nonclinical data, where available for each component, reveal no special hazard for humans based on studies of repeat dose toxicity, genotoxicity and carcinogenic potential. Paracetamol and codeine are well known constituents of medicinal products and their safety profile is well documented from long-term clinical use worldwide.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application is based on well-established use and therefore the clinical dossier is based upon published literature. Paracetamol and codeine phosphate hemihydrate are well-known active substances with an established efficacy and safety profile both alone and in combination.

IV.2 Pharmacokinetics

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 30 minutes to two hours after oral administration. 90- 100% of administered drug can be recovered in the urine within the first day. Practically none is excreted unchanged, most is conjugated in the liver with glucuronic acid or sulphuric acid.

Codeine and its salts are absorbed rapidly from the gastrointestinal tract with peak
plasma levels occurring about one hour after oral administration. Codeine is metabolised in the liver and excreted in the urine mainly as a conjugate of glucuronic acid. Approximately 10% of administered codeine is demethylated to form morphine.

Concurrent administration of both drugs does not interfere with the normal metabolic processes of each agent.

IV.3 Pharmacodynamics

Paracetamol has analgesic and antipyretic effects that do not differ significantly from those of aspirin. Its anti-inflammatory action is weak and it has practically no anti- platelet effect. The mechanism of action is unclear, although it is believed to exert its action by inhibition of prostaglandin synthesis.

Codeine is a centrally acting weak analgesic with uses similar to those of morphine, although it is much less potent as an analgesic and has only mild sedative effects. Codeine exerts its effects through μ opioid receptors, although codeine has a low affinity for these receptors, and its analgesic effect is due to its conversion to morphine; approximately 10% of administered codeine is demethylated to form morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

IV.4 Clinical Efficacy

The applicant has provided several appropriate literature references demonstrating that the efficacy of paracetamol/codeine phosphate hemihydrate is well established in the proposed indications.

IV.5 Clinical Safety

The safety profile of paracetamol/codeine phosphate hemihydrate is well established. Undesirable effects listed in the SmPC are:
The following undesirable effects have been reported following the use of paracetamol:
blood dyscrasias including thrombocytopenia, leucopenia, neutropenia and agranulocytosis, but these were not necessarily causally related to paracetamol. Hypersensitivity, including skin rash and angioedema, may also occur.
Very rare cases of serious skin reactions have been reported.
There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

The following undesirable effects have been reported following the use of codeine:
nausea, vomiting, dizziness and drowsiness. These effects are more likely to be experienced by the ambulatory patient and thus may be alleviated if the patient lies down.
Other side effects of codeine, which may occur, include bradycardia, miosis, constipation, abdominal pain (rarely codeine-induced pancreatitis has been reported in patients with a history of cholecystectomy), allergic reactions, light-headedness, headache, respiratory depression (with high doses), dyspnoea, hallucination, confusion, euphoria, dysphoria, urinary retention, urticaria and pruritus.
Regular prolonged use of codeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.

Prolonged use of a painkiller for headaches can make them worse.

Pharmacovigilance System
The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

Risk Management Plan
The applicant 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 Co-Codamol 15 mg/500 mg.
Routine risk minimization activities are considered sufficient. The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatoxicity at therapeutic doses of paracetamol in patients with risk factors for hepatotoxicity (paracetamol) • Drug abuse, misuse and dependence (codeine) • Central nervous system depression, including sedation and respiratory depression (codeine)
Important potential risks	• None
Missing information	• None

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects
The clinical aspects of this medicinal product are well established and acceptable.

V. OVERALL CONCLUSIONS

Co-codamol 15 mg/500 mg film-coated tablets have a proven chemical-pharmaceutical quality and a well-established and favourable efficacy and safety profile. The applicant has appropriately demonstrated this profile using appropriate bibliographic references.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Co-codamol 15 mg/500 mg film-coated tablets has demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

22.06.2027