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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Ilvico Cold and Flu Film-Coated Tablets
PARACETAMOL
CAFFEINE
BROMPENIRAMINE MALEATE
PA 0417/018/001

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) 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 IMB 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 IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Ilvico Cold and Flu Film-Coated Tablets, from Seven Seas Limited for the relief of symptoms associated with the common cold, influenza and upper respiratory tract infection.

This application for a marketing authorisation was submitted in accordance with Article 8(3) of Directive 2001/83/EC and is referred to as a line extension application.

The active substances are known.
The product will be supplied through pharmacies only and will not be subject to medical prescription.
The pharmaceutical form is a film-coated tablet with the active substances
Paracetamol 325mg
Caffeine 30mg
Brompheniramine 3mg
per tablet.

The original Ilvico coated tablets PA 417/10/1 which contains Paracetamol, Caffeine, Brompheniramine Maleate and Ascorbic acid was authorised on 12th June 1984. This application is a line extension to the above authorisation, and will replace same.

No scientific advice was sought or given as the active ingredients are well established and known.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB’s website at www.imb.ie

Name of the product	Ilvico Cold and Flu Film-Coated Tablets
Name(s) of the active substance(s) (INN)	PARACETAMOL CAFFEINE BROMPHENIRAMINE MALEATE
Pharmacotherapeutic classification (ATC code)	RO5X
Pharmaceutical form and strength (s)	Film-Coated Tablets 325mg/30mg /3mg
Marketing Authorisation Number (s) in Ireland (PA)	PA 0417/018/001
Marketing Authorisation Holder	Seven Seas Ltd

II QUALITY ASPECTS

II.1. Introduction

This application is for Ilvico Cold and Flu Film-Coated Tablets.

II.2 Drug substance

The active substances are Paracetamol, Caffeine and Brompheniramine Maleate 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 are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification have been provided

II.3 Medicinal product

P.1 Composition

Active substance

Paracetamol Ph. Eur.	325 mg
Caffeine Ph. Eur.	30 mg
Brompheniramine Maleate Ph. Eur.	3 mg

Excipients

- Microcrystalline Cellulose Ph. Eur.
- Sodium Carboxymethyl Starch Ph. Eur.
- Crospovidone Ph. Eur.
- Hypromellose Ph. Eur.
- Cellulose Powder Ph. Eur.
- Magnesium Stearate Ph. Eur.
- Glycerol Ph. Eur.
- Colloidal Anhydrous Silica Ph. Eur.
- Hypromellose Ph. Eur.
- Titanium Dioxide Ph. Eur.
- Macrogol 4000 Ph. Eur.
- Macrogol 6000 Ph. Eur.
- Talc Ph. Eur.

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 ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, 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(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as packaged in blisters

Evidence has been provided that the blister material complies with 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 demonstrating the stability of the product for 3 years when stored below 25°C.

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 Ilvico Cold and Flu film-coated tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

The active substances have been available on the European market for greater than 10 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is necessary.

There are no preclinical concerns with the active ingredients or excipients in this product.

The IMB has been assured that GLP standards were followed in an appropriate manner in the studies conducted.

III.2 Pharmacology

Not applicable.

III.3 Pharmacokinetics

Not applicable.

III.4 Toxicology

Studies of chronic toxicity in animals show that high Paracetamol doses produce testicular atrophy and inhibition of spermatogenesis; the importance of this fact in humans is unknown.

III.5 Ecotoxicity/environmental risk assessment

Not applicable as actives and excipients contained in this product are well known and have been marketed for many years.

III.6 Discussion on the non-clinical aspects

This is a line extension and there are no additional non-clinical concerns from PA 417/10/1.

IV CLINICAL ASPECTS

IV.1 Introduction

A Risk Management Plan is not necessary.

The proposed schedule for submission of PSURs will be on a 3 yearly basis.

Ilvico Cold and Flu Film-Coated Tablets have well known active substances with established efficacy and tolerability. This medicinal product is the same as the originator product on the European market.

The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

It is quickly and completely absorbed after oral administration, reaching maximum plasmatic peak between 3-4 hours. Plasmatic bioavailability is 60-80%, linking with proteins at 10%. It metabolises mainly through the liver, being eliminated mainly through the kidney as inactive metabolites. The average plasmatic life is between 1.5 -2.5 hours, being completely eliminated after 24 hours. Maximum pharmacological effect is achieved at 4-6 hours.

IV.3 Pharmacodynamics

Pharmacotherapeutic Group: - Code ATC: RO5X

Paracetamol is an analgesic pharmacopoeia that also possesses antipyretic properties. The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly inhibiting the synthesis of prostaglandin at the central nervous system level and to a lower degree blocking the generation of the pain impulse at peripheral level. The peripheral action may also be due to the inhibition of the prostaglandin synthesis or to the inhibition of the synthesis, or of the action, of other substances that sensitise the nociceptors to mechanical or chemical stimulations.

Probably Paracetamol produces the antipyretic effect acting at central level over the hypothalamic centre regulating temperature, to produce a peripheral vasodilatation that gives place to an increase of perspiration and to flow of blood in the skin and loss of heat. The action at central level probably is related with the inhibition of the prostaglandin synthesis in the hypothalamus.

Brompheniramine maleate: is a highly effective antagonist of the H1 receptors of Histamines. From the different studies in this field it is known that the antihistaminic effect reduces capillary permeability and the permeability of cellular membranes producing a diminution of the secretion and congestion of the inflamed mucous membranes of the superior respiratory tract.

This diminution of permeability, that appears to be independent of the histamine and the allergic process, appears independently of whatever is the cause of the increase of permeability. The experimental use of Brompheniramine in animals has evidenced antitussive effects and stimulation of blood circulation. At the same time it has a slight sedative effect.

Caffeine stimulates circulation and strengthens the analgesic and antipyretic effects of Paracetamol.

IV.4 Clinical Efficacy

The uses of paracetamol, caffeine and brompheniramine maleate in the symptomatic treatment of the common cold, influenza and upper respiratory tract infections are well established.

IV.5 Clinical Safety

The Pharmaceutical Class to which this product belongs is "Cold and Influenza Treatments". The adverse effects characteristic of this pharmacological class are known and are usually of a non-serious nature when the product is used at the recommended dosage levels. However, Serious Adverse Events may occur.

Side effects (adverse reactions) are rare when it is taken at the recommended dosage. Skin rashes, blood disorders and acute inflammation of the pancreas have occasionally occurred in people taking paracetamol on a regular basis for long periods of time.

At recommended dosages, paracetamol is recognised as not irritating to the stomach, nor does it affect blood coagulation as much as Non-Steroidal Anti-inflammatory Drugs (NSAIDs) or affect the function of the kidneys.

Paracetamol has not been found to cause euphoria or to alter mood in any way, and has a very low risk of addiction, dependence, tolerance and withdrawal. However, Paracetamol may damage the liver if overdosed.

A Risk Management Plan is not necessary.

The proposed schedule for submission of PSURs will be on a 3 yearly basis.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

Paracetamol is an analgesic and antipyretic.

Caffeine is a central nervous system stimulant.

Brompheniramine Maleate is a histamine H1 receptor antagonist.

Together, these active ingredients are able to relieve the symptoms associated with the common cold, influenza and upper respiratory tract infections and have been used to do so for many years.

V OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendation

The uses of paracetamol, caffeine and brompheniramine maleate in the symptomatic treatment of the common cold, influenza and upper respiratory tract infections are well established.

The Pharmaceutical Class to which this product belongs is “Cold and Influenza Treatments”. The adverse effects characteristic of this pharmacological class are known and are usually of a non-serious nature when the product is used at the recommended dosage levels.

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

The IMB, on the basis of the data submitted, considered that Ilvico Cold and Flu Film-Coated Tablets demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

