IPAR

HEALTH PRODUCTS REGULATORY AUTHORITY

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion
Panadol Cold & Flu Relief Orange Effervescent Tablets
Paracetamol 500 mg
Caffeine 65 mg
PA0678/105/002

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.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Panadol Cold & Flu Relief Orange Effervescent Tablets, Paracetamol 500mg / Caffeine 65mg from GlaxoSmithKline, on 13th February 2015 for for the relief of symptoms associated with influenza and colds such as sore throat, headache, aches and pains, drowsiness and fever.

The Application was submitted as a new National application under article 8(3), and section 1.3 as a change to existing marketing authorisation to Panadol cold and Flu relief tablets PA 678/105/1 Glaxosmithkline consumer healthcare Ireland ltd. As this is an effervescent tablet the changes are to pharmacokinetics and change or addition of a new pharmaceutical form.

The method of sale and supply is as a non prescription medicine available through pharmacy outlets and non pharmacy outlets which can be promoted to the public and health care professionals.

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

Name of the product: Panadol Cold & Flu Relief Orange Effervescent Tablets, Paracetamol 500mg / Caffeine 65mg Name(s) of the active substance(s) (INN): Paracetamol, Caffeine Pharmacotherapeutic classification (ATC code): ATC Code: N02BE51 Pharmaceutical form and strength(s): Effervescent Tablets, Paracetamol 500mg / Caffeine 65mg Marketing Authorisation Number(s) in Ireland (PA): PA 678/105/002 Marketing Authorisation Holder: GlaxoSmithKline Consumer Health Ireland Ltd MRP/DCP No. n/a Reference Member State: n/a Concerned Member State: n/a

II QUALITY ASPECTS

II.1. Introduction

This application is for Panadol Cold & Flu Relief Orange Effervescent Tablets, Paracetamol 500mg / Caffeine 65mg.

II.2 Drug substance

The active substances are Paracetamol and Caffeine, both are established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with these specifications have been provided.

II.3 Medicinal product

P.1 Composition

Panadol Cold & Flu Relief Orange Effervescent Tablets, Paracetamol 500mg / Caffeine 65mg are round, flat, off-white to yellow effervescent tablets (25 mm in diameter) with speckles. The tablets have a faultless surface and a break line mark on one side. The score line is not for dividing into equal doses.

Each tablet contains 500 mg of paracetamol and 65 mg of caffeine. It also contains following excipients: Sodium hydrogen carbonate, Sorbitol (E420), Ascorbic acid, Sodium laurilsulfate, Citric acid (anhydrous), Sodium carbonate (anhydrous),

Povidone, Dimethicone, Acesulfame Potassium (E 950), Orange Flavour (contains sodium and sulphites), Aspartame (E 951), Carmine (E120) and Riboflavin sodium phosphate (E101a)

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/*Ancillary Substances*)

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(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 Aluminium foil/paper laminated strips packed in to an outer cardboard carton. Packs of 12, 16 and 24 tablets. There are either 2 or 4 tablets per blister strip.

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 demonstrating the stability of the product for 36 months when stored below 30°C and stored in the original package in order to protect from moisture.

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 Panadol Cold & Flu Relief Orange Effervescent Tablets, Paracetamol 500mg / Caffeine 65mg.

III NON-CLINICAL ASPECTS

III.1 Introduction

No new preclinical data have been supplied with this application and none are required for an application of this type.
A preclinical expert report has been written by a suitably qualified person and is satisfactory.
The marketing authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.

This active substance has been available on the European/Irish market for a number of years the EU reference birth date

is 24 Jun 1969. No new preclinical data have been supplied with this applications are none are required for applications of this type.

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

III.5 Ecotoxicity/environmental risk assessment

No change in ecotoxicity or risk to the environment is expected.

IV CLINICAL ASPECTS

Clinical Background

Paracetamol has been widely available as an over-the-counter analgesic since the 1950s. The maximum recommended adult dose is 1.0 g every 4-6 hr up to a maximum of 4 g in 24 hours.

The proposed product contains an established combination of paracetamol and caffeine, and this combination is widely available.

Caffeine acts as an analgesic adjuvant which enhances the clinical efficacy of paracetamol.

GlaxoSmithKline data on file and published data support the efficacy and safety profile of products containing this combination.

The Clinical Overview has adequately reviewed all the relevant clinical documentation relevant to this application. In view of the widespread use of paracetamol and the nature of the paracetamol and caffeine formulation, the data presented here are considered adequate in support of this application.

Indications
Paracetamol and Caffeine 500 mg / 65 mg Tablets are a mild to moderate analgesic and antipyretic. The product is recommended for the relief of symptoms associated with influenza and colds such as sore throat, headache, aches and pains, drowsiness and fever.

Dose and Dose Regimen
Each tablet contains 500 mg paracetamol and 65 mg caffeine. The maximum recommended dose of paracetamol and caffeine is two tablets (500 mg paracetamol, 65 mg caffeine in each tablet) every 6 hours, the maximum of 8 tablets should not be exceed in 24 hours.

This medicinal product is not recommended for use in children under 12 years of age.

Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication. The restrictions related to the use of paracetamol and caffeine products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug.

IV.2 Pharmacokinetics

Overview

In an open, randomised, three-way crossover study in healthy volunteers, the pharmacokinetic parameters of standard paracetamol and caffeine 500 mg / 65 mg tablets – (PANADOL EXTRA) , standard paracetamol 500 mg tablets – (PANADOL) and paracetamol and caffeine 500 mg /65 mg soluble tablets – (Panadol Extra Soluble) were compared at a two tablet dose.

The study has demonstrated bioequivalence between PANADOL EXTRA (Paracetamol and Caffeine) and PANADOL (Paracetamol) and demonstrated that caffeine does not affect the pharmacokinetics of paracetamol and that paracetamol does not affect the pharmacokinetics of caffeine.

The pharmacokinetics of both paracetamol and caffeine, alone and in combination, are well established and has been adequately reviewed by the Clinical Expert.
It has been established that no pharmacokinetic interaction occurs between paracetamol and caffeine.

Pharmacodynamics and mechanism of action
The primary pharmacodynamics of paracetamol and caffeine alone and in combination are well described and has been adequately reviewed by the Clinical Expert.

IV.4 Clinical Efficacy

The superior analgesic efficacy of paracetamol 500 mg/caffeine 65 mg compared to the single actives and placebo has previously been demonstrated in clinical studies. This has been adequately reviewed in the Clinical Overview. Caffeine acts as an analgesic adjuvant which enhances the efficacy of paracetamol.

Paracetamol
The antipyretic activity of paracetamol is thought to be mediated by central prostaglandin synthetase inhibition. This may also play a role in the analgesic effect though the precise mechanism remains unclear. Paracetamol does not have an anti-inflammatory effect and, unlike NSAIDs, does not inhibit peripheral prostaglandin sysnthesis and serious gastrointestinal adverse events are not associated with this active.

Caffeine
Caffeine is a methylxanthine and has a mild stimulant effect. The specific mechanism by which it acts as an analgesic adjuvant remains unclear, but may be mediated via adenosine antagonism (adenosine being one of the kinins released in association with pain), inhibition of COX-2 synthesis or by affecting the emotional response to pain.

IV.5 Clinical Safety

The overall safety profile of products containing paracetamol and caffeine is well established with extensive safety monitoring conducted on all currently marketed formulations. The safety profile of this combination has been adequately reviewed in the Clinical Overview. There are currently no safety concerns regarding this combination.

Pharmacovigilance & Risk Management Plans
An overview of GlaxoSmithKline's organisation and processes for conducting pharmacovigilance activities has been provided and is consistent with regulatory requirements.

In accordance with the EURD list the frequency of PSURS will be every 13 years and the data lock point is 01-June-2012 to 24-Jun-2025.

The birth date is based on the EU reference date of 24 Jun 1969.

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

V OVERALL CONCLUSIONS

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 for Panadol Cold & Flu Relief Orange Effervescent Tablets, Paracetamol 500mg / Caffeine 65mg the MAH has provided adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The pharmacokinetics of both paracetamol and caffeine, alone and in combination, are well established and have been

adequately reviewed by the clinical expert.
It has been established that no pharmacokinetic interaction occurs between paracetamol and caffeine.

Paracetamol 500mg / Caffeine 65mg is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The HPRA, on the basis of the data submitted considered that Panadol Cold & Flu Relief Orange Effervescent Tablets, Paracetamol 500mg / Caffeine 65mg has a positive benefit risk ratio and there has granted a marketing authorisation.