# IPAR

IRISH MEDICINES BOARD

**PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE**

Scientific discussion

Panadeine Extra Strength Tablets
Paracetamol 500mg
Codeine phosphate hemihydrate 12.8 mg
PA0678/026/003

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 Panadeine Extra Strength tablets paracetamol 500mg codeine phosphate hemihydrate 12.8mg, from GlaxoSmithkline Consumer Healthcare (Ireland) ltd. on 29th June 2012 for the relief of rheumatic pain, backache, headaches, migraine, toothache, sore throat, dysmenorrhoea, feverishness and the symptoms of colds and influenza.

This application for a marketing authorisation was submitted in accordance with Annex II of regulations (EC) no. 1084/2003 and is referred to as a 'line extension' application. This is a line extension to the Marketing Authorisation Holder's product Panadeine Tablets paracetamol 500 mg/codeine phosphate hemihydrate 8 mg, which is an authorised medicinal product in Ireland, PA678/26/1.

The tablets are red, film-coated capsule-shaped tablets and are presented in pack sizes of 12 and 24 tablets for non-prescription use. Packs containing up to 100 tablets may be available on prescription.

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 | Panadeine Extra Strength |
| Name(s) of the active substance(s) (INN) | PARACETAMOL / CODEINE PHOSPHATE HEMIHYDRATE |
| Pharmacotherapeutic classification (ATC code) | N02AA59 |
| Pharmaceutical form and strength(s) | Film-coated tablets; 500 mg /12.8 mg |
| Marketing Authorisation Number(s) in Ireland (PA) | PA0678/026/003 |
| Marketing Authorisation Holder | GlaxoSmithKline Consumer Healthcare (Ireland) Limited |

# II QUALITY ASPECTS

## II.1. Introduction

This application is for:
Panadeine extra strength tablets
paracetamol 500mg
codeine phosphate hemihydrate 12.8mg

## II.2 Drug substance

The active substances are paracetamol and codeine phosphate hemihydrate 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 meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with these specifications have been provided.

## II.3 Medicinal product

P.1 Composition

The tablets are red film-coated, capsule shaped tablets embossed with “Extra”.

Composition
The two active substances in the product are paracetamol & codeine phosphate hemihydrate. Other ingredients are: pregelatinised starch, povidone, potassium sorbate, maize starch, talc, magnesium stearate, stearic acid, microcrystalline cellulose, sodium croscarmellose, lactose monohydrate, hypromellose, quinolone yellow aluminium lake, macrogol, erythrosine aluminium lake and titanium dioxide.

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 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 film-coated 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 has 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 film-coated tablets packed into opaque PVC / aluminium blister strips in an outer carton.

Evidence has been provided that the materials used in the blister strip comply 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 three 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 Panadeine Extra Strength paracetamol 500 mg/ codeine phosphate hemihydrate 12.8 mg tablets

## III NON-CLINICAL ASPECTS

## III.1 Introduction

The active substances, paracetamol and codeine phosphate, are considered to fulfil the definition of products with well-established use for the proposed indications on the European market. Therefore, no preclinical studies have been submitted. A review of the literature on the non-clinical pharmacology of these substances alone and when combined has been provided. This is acceptable for this type of application.

These ingredients, both alone and in combination, have a long history of safe and effective use in the treatment of mild to moderate pain and no adverse events associated with their use, as directed, would therefore be expected to occur. This is reflected in the widespread use of the drugs internationally, including use in self−medication.

## III.2 Pharmacology

### Paracetamol

Paracetamol has analgesic and antipyretic effects similar to those of aspirin, though unlike aspirin, it has only weak anti−inflammatory activity. The antipyretic activity of paracetamol is thought to be due to selective inhibition of prostaglandin synthesis in the central nervous system (CNS) . The analgesic action of paracetamol is not fully understood, but central inhibition of cyclooxygenase-3 (COX-3) may be relevant.

### Codeine Phosphate Hemihydrate

Codeine is an opium alkoid with well−established analgesic and antitussive properties. The analgesic action of codeine is much less potent than that of morphine and it has a relatively mild sedative effect. The principal action of codeine appears to be to alter the perception of pain and the emotional effects evoked by pain. Other sensory modalities seem not to be effected. Codeine has an exceptionally low affinity for opioid receptors, and its analgesic effect is due to its metabolism to morphine. Approximately 10% of an administered dose of codeine is *O*−demethylated to morphine. Morphine exerts its effects as a selective agonist of the μ opioid receptor .

## III.3 Pharmacokinetics

### Paracetamol

At recommended therapeutic dosage, paracetamol is well tolerated. It is rapidly and almost completely absorbed from the gastrointestinal tract and reaches a maximum plasma concentration within 30 to 60 minutes. Paracetamol has a plasma half−life of about two hours, is uniformly distributed throughout most body tissues and shows variable binding to plasma proteins.

Metabolism of paracetamol occurs principally in the liver: the drug is extensively conjugated with glucuronic acid (60%), sulphuric acid (35%) or cysteine (3%). In children, sulphation is the primary pathway until the age of 10 to 12 years. Conjugated drug is almost completely eliminated in the urine within 24 hours.

### Codeine Phosphate Hemihydrate

Codeine is well absorbed by the gastrointestinal tract and has a large volume of distribution in man. Following oral administration the maximum plasma concentrations of codeine and its metabolites is achieved within one to two hours and the plasma half−life is between two and four hours. Once absorbed, codeine is metabolised by *O*- and *N*−demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone .

Codeine and its metabolites are excreted almost entirely in inactive forms by the kidney, mainly as conjugates with glucuronic acid . Some elimination is also seen via the pulmonary and biliary systems and the digestive tract.

### III.4 Toxicology

In view of the long experience of use of paracetamol in man, much of the animal toxicology information is regarded as irrelevant to a consideration of the clinical safety of the drug. At recommended therapeutic dosage, paracetamol is generally well tolerated.

Adverse reactions following ingestion of recommended therapeutic doses of paracetamol are rare. Occasional instances of mild allergic reaction have been reported and, even more rarely, haematological disturbance. It should be noted that patients hypersensitive to aspirin (acetylsalicylic acid) are only rarely sensitive to paracetamol.

Studies in animals have revealed no adverse effects on reproduction and no teratogenic effects of paracetamol at doses well in excess of the human therapeutic dose. Controlled epidemiological data from human studies has shown no association between paracetamol ingestion and birth defects.

**Codeine**

Morphine and related opioids produce a wide spectrum of unwanted effects including, respiratory depression, nausea, vomiting, dizziness, mental clouding, dysphoria, pruritis, constipation, increased pressure on the biliary tract, urinary retention, and hypotension. All opioid analgesics are metabolised by the liver and should be used with caution in patients with hepatic disease . In therapeutic doses codeine is much less liable than morphine to product adverse effects, although constipation may occur with long-term use.
Codeine has been in use as an analgesic for many years with no evidence of genotoxic or carcinogenic effects.

### III.5 Ecotoxicity/environmental risk assessment

It is considered that the introduction of paracetamol and codeine phosphate hemihydrate to the environment through use and proper disposal of Panadeine Extra Strength Tablets raises no significant environmental concerns. Many paracetamol-containing and codeine phosphate hemihydrate-containing products are already approved and marketed in a number of countries, and the further authorisation and sales of this product are not expected to change the overall environmental exposure.

### III.6 Discussion on the non-clinical aspects

Due to the established safety profile of the active ingredients in this combination, this product falls into the category of a combination product not requiring additional animal safety studies. This view is based on substantial data from animals that indicate the drug substances in this formulation are associated with low toxicity.

## IV CLINICAL ASPECTS

### IV.1 Introduction

This marketing authorisation seeks approval for the use of Panadeine Extra Strength Tablets [500 mg Paracetamol Ph. Eur/ 12.8 mg Codeine Phosphate Hemihydrate Ph Eur] as a non-prescription product for the relief of rheumatic pain, backache, headaches, migraine, neuralgia, toothache, sore throat, dysmenorrhoea, feverishness and the symptoms of colds and influenza.

This is a combination product containing 500 mg paracetamol Ph Eur and 12.8 mg codeine phosphate hemihydrate Ph Eur as active ingredients in each tablet. The tablets are red, film-coated capsule-shaped tablets and are presented in pack sizes of 12 and 24 tablets for non-prescription use. The proposed pack sizes comply with the restrictions on the sale of paracetamol-containing products which were introduced in Ireland in 1997. The daily oral dose for adults (including the elderly) and children 12 years and over is two tablets taken every four to six hours, up to four times a day. The product should not be taken for more than three days without consulting a doctor. Panadeine Extra Strength Tablets is not recommended for children under 12 years of age except on medical advice.

The active ingredient combination is not novel. Both active ingredients are well-established for the proposed indications and are already available in OTC products in combination, in various pharmaceutical forms and strengths.

PANADEINE Soluble Tablets which contain 500 mg Paracetamol/ 8 mg Codeine Phosphate Hemihydrate has been registered in Ireland as a non-prescription product since April 1990 (PA678/26/2).
No bioavailability or bioequivalence studies have been conducted on the proposed product which contains 500 mg paracetamol and 12.8 mg codeine.

**IV.2 Pharmacokinetics**

**Paracetamol**

Oral paracetamol is readily absorbed from the upper small intestine to give peak plasma concentrations of 15−20 μg/ml in 30 to 120 minutes after oral administration of a 1 g dose in adults. The speed of gastric emptying modifies the rate of absorption. Plasma protein binding is minimal and there is distribution to all tissues. There is limited first-pass metabolism of paracetamol after oral administration and about 80% of a 1 g dose is bioavailable.

Paracetamol is metabolised primarily in the liver. After a 1 g oral dose in adults, 50−60 % is recovered in the urine as the glucuronide conjugate, 25 − 35 % as the sulphate conjugate, up to 5 % as unchanged paracetamol and 2 - 5 % as the cysteine or mercapturate metabolites. The latter are formed from the combination of glutathione with the oxidation metabolite of paracetamol, N−acetyl−p−benzoquinoneimine (NAPQI). Excretion via the urine is rapid and the plasma half-life after oral administration is about 2.3 hours.

In overdose situations, the detoxification of a minor metabolite, N-acetyl-p-benzoquinoneimine, by conjugation with glutathione is saturated and this leads to its accumulation and resultant liver damage.

There do not appear to be any clinically significant pharmacokinetic drug-drug interactions at the proposed dosage regimen, although chronic use of ethanol has been reported to increase the risk of hepatotoxicity following paracetamol overdose. Drugs affecting upper gastro-intestinal motility may affect the speed of absorption of paracetamol; both metoclopramide and domperidone increase the speed of absorption. However, this effect is unlikely to be clinically relevant.

**Codeine**

Codeine is well absorbed from the gastrointestinal tract following oral administration and has a large volume of distribution of approximately 3-6 L/kg. Ingestion of codeine phosphate produces peak plasma-codeine concentrations in approximately one hour.

Codeine is metabolised by the liver and its metabolites are excreted mainly as inactive glucuronide conjugates in the urine. A small fraction (approximately 10%) of administered codeine is *0*-methylated to morphine, and free and conjugated morphine can be found in the urine after therapeutic doses of codeine. The plasma half-life of codeine is about 2 to 4 hours. There are no significant differences in codeine pharmacokinetics following single or multiple-oral dose administration.

It is reported in the review by Gutstein and Akil that the conversion of codeine to morphine is effected by the CYP2D6 (cytochrome P450 2D6). Genetic polymorphisms in CYP2D6 can lead to an inability to convert codeine to morphine, thus making codeine ineffective as an analgesic in approximately 10% of Caucasians. For example, Chinese people produce less morphine from codeine than do Caucasians and are also less sensitive to the effects of morphine. This may be due to decreased production of morphine 6-glucuronide. Other polymorphisms can lead to enhanced metabolism and thus increased sensitivity to the effects of codeine. For example, CYP 2D6 gene duplication is estimated to occur in 1% of people in Finland and Denmark, 10% of people in Greece and Portugal and 29% of Ethiopia leading to increased production of morphine from codeine compared to most people.

**Paracetamol - Codeine in combination**

A study incorporating codeine up to 30 mg with a dose of paracetamol of 1000 mg showed this had no effect on paracetamol absorption. Thus, the combination of products in the proposed product does not modify the bioavailability of paracetamol.

## IV.3 Pharmacodynamics

### Paracetamol

Paracetamol is an effective analgesic and antipyretic with little anti-inflammatory action. The antipyretic activity of paracetamol is thought to be mediated by its ability to selectively inhibit prostaglandin synthesis in the central nervous system. The precise mechanism for the analgesic properties of paracetamol remains to be established. Data suggest that central prostaglandin synthetase inhibition is likely to be of primary importance. Paracetamol is a weak inhibitor of COX−1 and COX-2 leading to the suggestion that there may be another form of COX that is more sensitive to inhibition by paracetamol.

A third distinct COX isoenzyme has been described, COX-3, which is inhibited by paracetamol and expressed in specific tissues with highest levels in human cerebral cortex and heart. Whether this is the target for paracetamol is uncertain. Paracetamol does not exhibit a clinical anti-inflammatory effect.

The analgesic effect has been shown to be dose dependent with 1000 mg being more effective than lower doses and therefore useful for more severe pain. The onset of analgesic action occurs within 30 minutes, peaks at approximately 2 hours and last 3-4 hours. Paracetamol and aspirin are equally effective on a mg per mg basis.

### Codeine

Codeine is a weak opioid analgesic used for somatic (deep) pain. Codeine is an opiate receptor agonist and produces its analgesic effects by binding to μ opioid receptors leading to inhibition of nociceptive reflexes. This action is entirely different from the mode of action of paracetamol, thus enabling their combination to produce enhanced analgesia. Codeine also binds weakly to κ opioid receptors. Other effects of codeine are through its CNS action to inhibit the cough centre and thus act as an anti-tussive and, through its actions on the gastrointestinal tract, to inhibit motility and cause constipation.

Other opiate effects such as respiratory depression and alteration of endocrine and autonomic nervous systems are not likely to be observed at the dosage of codeine contained in Panadeine Extra Strength.

## IV.4 Clinical Efficacy

Paracetamol is widely used as an analgesic for relief of mild to moderate pain and as an antipyretic. Single doses of paracetamol 500-1000 mg have been shown to be effective in the relief of pain and/or fever in a variety of clinical conditions such as dental pain, episiotomy, headache, migraine, neuralgia, dysmenorrhoea, muscle ache, musculoskeletal pain, osteoarthritis, sore throat and fever.

The applicant provided a detailed review of the literature, including published trials for the indications outlined, to support the efficacy of paracetamol.

The analgesic activity of codeine lies mainly in its metabolites. It is recognised in standard therapeutic textbooks and monographs as an analgesic for mild to moderate pain and as a cough-suppressant.: Codeine is often used in the post-partum period for pain associated with episiotomy and caesarean section.

### Clinical Efficacy of Paracetamol and Codeine

The combination of paracetamol and codeine has received official recognition in the UK by the adoption of a British Approved Name of co−codamol, with a codeine/paracetamol ratio of 8/500.

Compound analgesic opioid preparations for OTC use for mild to moderate pain and pyrexia generally contain 500 mg paracetamol in a fixed combination with a low dose of opioid analgesic, either 8 mg or 12.8 mg codeine per tablet.

A meta-analysis of published clinical studies reported that the difference in analgesic effect between paracetamol-codeine combinations and paracetamol alone is small, but statistically significant . Twenty four trials which evaluated

analgesic efficacy in post-surgical pain (21), post-partum pain (1), osteoarthritis pain (1) and experimentally-induced pain (1) were included in the meta-analysis. Dosages in the trials ranged from 400 to 1000 mg paracetamol and 10 to 60 mg codeine and only the single dose studies were combined for analysis of analgesic efficacy. Pooled efficacy results indicated that codeine added to paracetamol provided a 5% increase in analgesia on the sum pain intensity difference. Li Wan Po and Zhang who conducted a similar overview also concluded that codeine added to the analgesic efficacy of paracetamol.

However, in their meta-analysis of six head to head comparison trials, a significant pooled estimate of a 6.7 point difference in the sum of pain intensity difference (95% confidence interval 3.2 to 10.3) between paracetamol-codeine combination and paracetamol was not translated into a significant increase in the proportion of patients obtaining moderate to excellent pain relief (response rate ratio 1.14 (0.97 to 1.34). Li Wan Po and Zhang commented that deciding what change is clinically important is often difficult and that better reporting of patients' assessment of how their treatments have affected their symptom or condition would ease the interpretation of data from clinical trials and facilitate evidence based practice.

## IV.5 Clinical Safety

The applicant provided a review of the safety of paracetamol and codeine products which included GSK safety update reporting for products containing paracetamol and codeine, information on Co-codamol (paracetamol and codeine–containing products) from the UK Medicines and Healthcare products Regulatory Agency (MHRA) Adverse Drug Reaction Online Information Tracking (ADROIT) database, a summary of the MHRA's report on OTC codeine/dihydrocodeine-containing medicines which was issued in 2005 and a review of published literature.

### Paracetamol

With recommended therapeutic doses (500 mg to 1000 mg orally, up to a maximum of four times a day), paracetamol is well tolerated and side effects are uncommon. The accepted adverse event profile demonstrates an occasional skin rash and allergic reaction. Reports of generalised anaphylactic type reaction are exceedingly rare.

Blood dyscrasias have been reported very rarely in association with paracetamol though they are usually reversible and few appear, if any, to be causally related.

Paracetamol has been associated with several cases of thrombocytopenia although a causative role for paracetamol has not been proven. A link between paracetamol and analgesic nephropathy has been suggested, but phenacetin has been identified as the major risk factor. Although paracetamol is a metabolite of phenacetin, there is no evidence that paracetamol alone causes analgesic nephropathy.

There have been reports of liver toxicity in conjunction with the consumption of therapeutic quantities of paracetamol. However, in the majority of cases either consumption was excessive or there were other pre-existing factors (e.g. chronic alcoholism) that predisposed to liver damage. There are no consistent clinical findings that link paracetamol to hepatotoxicity at therapeutic doses and this is supported by biochemical data. A single dose of at least 15 g of paracetamol is required to deplete hepatic glutathione in an adult to the point where liver damage could occur , so it is highly unlikely that a 1000 mg dose of paracetamol could cause severe or fatal liver damage. A warning is provided in the proposed SPC that the hepatotoxicity of paracetamol may be increased in patients taking enzyme-inducing drugs, although the risk appears to be small.
The paracetamol content of the product is 500 mg per tablet. This is equivalent to a standard (500 mg) tablets. The tablets are presented in blister packs in cartons containing 12 or 24 tablets.

### Codeine

At therapeutic doses the commonest adverse effects of codeine are constipation, nausea and vomiting. Dizziness and drowsiness may present depending on the dosage administered and individual susceptibility. Codeine has been reported to reduce peristalsis, increase tone and segmentation in the bowel and has the potential to raise colonic pressure, however at the doses recommended for Panadeine Extra Strength such effects are unlikely.

Opioids can depress respiratory function which can complicate respiratory difficulties associated with head injury. Carbon dioxide retention can cause dilatation of intracranial vessels and thus exacerbate cerebral oedema. In large doses codeine can cause respiratory depression and histamine release, which can cause bronchoconstriction and vasodilation.

Codeine is metabolised to morphine, which has the potential to precipitate or exacerbate asthmatic attacks and so is generally not recommended for patients with a history of asthma, however the level of codeine in Panadeine Extra Strength is unlikely to elicit such effects.

Codeine may potentiate the central depressive effects of central nervous system depressants, including alcohol.

### Risk Management Plan (RMP)

A RMP is not required for this application in line with relevant legislation.

GlaxoSmithKline (GSK) confirms that the services of Qualified Persons responsible for pharmacovigilance of Consumer Healthcare (GSK CH) are available, and that it has the necessary means for the collection and notification of any adverse reaction occurring in the Community or in a third country. A detailed description of the pharmacovigilance system employed by GSK CH was provided in Module 1.8 of the CTD.

The schedule for Periodic Safety Update Reports (PSUR) submission should be routine.

### IV.6 Discussion on the clinical aspects

The active substances, paracetamol and codeine phosphate, are considered to fulfil the definition of products with well-established use for the proposed indications on the European market. Therefore, no new preclinical nor clinical studies have been submitted. A review of the literature on the non-clinical pharmacology and clinical pharmacology, efficacy and safety of these substances alone and when combined has been provided. This is acceptable for this type of application.

The proposed indications included neuralgia. However, it was considered that evidence to support this indication was lacking and furthermore, this is not an indication that is self-limiting and that can be readily diagnosed by the patient. This indication was withdrawn by the applicant.

## V OVERALL CONCLUSIONS

### Benefit/Risk Assessment and Recommendation

The drug substances, Paracetamol and Codeine Phosphate Hemihydrate are well established chemical entities that have been used for numerous non-prescription drug products for more than 30 years. This type of formulation has been self-administered by the general public for the symptomatic relief of mild to moderate pain for many years. The safety and efficacy in use of this type of combination without prescription is therefore generally well understood. In excess of 20,000 clinical publications exist that relate to the use of paracetamol and codeine phosphate hemihydrate.

The drug product therefore fully complies with the definition within Directive 2001/83/EC, as amended by 2004/27/EC and other amending directives, for a drug product with “well-established use”.

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 Panadeine Extra Strength tablets demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.