IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Paracetamol/Ibuprofen Vale 500 mg/150 mg powder for oral solution in sachet
Paracetamol
Ibuprofen lysine
PA1535/018/001

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 Paracetamol/Ibuprofen Vale 500mg/150mg powder for oral solution in sachet, from Vale Pharmaceuticals Limited, on 29th August 2025 for the short-term symptomatic treatment of mild to moderate pain in adults. This product is especially suitable for pain which has not been relieved by ibuprofen or paracetamol alone.

This application is submitted via a Decentralised Procedure (DCP) under Article 8(3) of Directive 2001/83/EC with the Reference Member State (RMS) being Ireland and the following concerned member states (CMSs):
IE/H/1291/001-002/DC – BG, CY, CZ, MT, RO, SK

It is a mixed application with bioavailability studies comparing the new sachet formulation with the authorised tablet form and clinical trials with the tablet formulation providing safety and efficacy data supporting the indications.

Legal status: Product not subject to prescription and supply in pharmacies only.

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	Paracetamol/Ibuprofen Vale 500mg/150mg powder for oral solution in sachet
Name(s) of the active substance(s) (INN)	Paracetamol, Ibuprofen lysine
Pharmacotherapeutic classification (ATC code)	N02BE51
Pharmaceutical form and strength(s)	500mg/150mg powder for oral solution in sachet
Marketing Authorisation Number(s) in Ireland (PA)	PA1535/018/001
Marketing Authorisation Holder	Vale Pharmaceuticals Limited
MRP/DCP No.	IE/H/1291/001/DC
Reference Member State	IE
Concerned Member State	BG, CY, CZ, MT, RO, SK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Paracetamol/Ibuprofen Vale 500mg/150mg powder for oral solution.

II.2 Drug substance

The active substances are paracetamol and Ibuprofen lysine, established active substances. Paracetamol is described in the European Pharmacopoeia, but Ibuprofen lysine is not monographed in Ph. Eur. or in a pharmacopoeia of a member state. Both active substances are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

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

II.3 Medicinal product

P.1 Composition

Each sachet contains Paracetamol 500 mg and Ibuprofen (as lysine) 150 mg for Paracetamol/Ibuprofen Vale 500mg/150mg powder for oral solution.

Each sachet contains Paracetamol 1000 mg and Ibuprofen (as lysine) 300 mg for Paracetamol/Ibuprofen Vale 1000mg/300mg powder for oral solution.

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/*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 oral powders, 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 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 Paracetamol/Ibuprofen Vale 500mg/150mg powder for oral solution and Paracetamol/Ibuprofen Vale 1000mg/300mg powder for oral solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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

III.2 Pharmacology

Paracetamol is an analgesic and antipyretic agent that has little anti-inflammatory activity. It
has been used clinically for more than a century, having been introduced into use in 1893 to treat fever, headaches, and other minor aches and pains.

Unlike other common analgesics such as aspirin and ibuprofen, paracetamol has relatively little anti-inflammatory activity. The mechanism by which paracetamol reduces fever and pain is still unclear, however it is known to reduce the production of prostaglandins via cyclooxygenase-2 (COX-2) inhibition and lessen pain. It is metabolised to AM404, a compound that can modulate pain by inhibiting the uptake of anandamide, activation of the TRPV1 receptor and inhibiting sodium channels. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that has been in clinical use since 1969 to treat pain and fever. It is a dual COX-1 and COX-2 inhibitor and reduces the production of prostaglandins.

Co-administration of paracetamol and ibuprofen has been shown to act synergistically in reducing pain in mice models of pain, inflammation and arthritis. In a systematic literature review, combination treatment with both active substances was associated with equivalent or superior pain relief in 6 of 8 studies reviewed.

Safety Pharmacology

In relation to safety pharmacology, the Applicant reviewed the available literature on key target organs of toxicity for both compounds, focusing on the gastrointestinal (GI) tract, kidneys, liver and cardiovascular system. In one study paracetamol and ibuprofen co-treatment was associated with greater renal toxicity than either compound alone in both rats and mice. A GLP-compliant 7-day oral combination toxicity study was performed in rats to investigate this. Animals received a dose of 80 mg/kg of paracetamol and 24 mg/kg of ibuprofen daily over 7 days, similar to the maximum dose a 60 kg patient would take daily. There was no evidence of kidney toxicity in animals treated with either compound, or in those treated with both. Ibuprofen is known to target the GI tract and can even lead to peptic ulcers and GI bleeding. It is less clear if paracetamol causes GI effects. A review of published literature provided conflicting information on the effect of combined treatment. In a 7-day oral toxicity study in rats there was no evidence of GI toxicity.
A review of available data did not suggest an increased level of toxicity with co-administration of paracetamol and ibuprofen in any other target organs.

III.3 Pharmacokinetics

No dedicated pharmacology studies were conducted with paracetamol and ibuprofen combination. Both paracetamol and ibuprofen are readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 20 to 70 minutes after oral administration. Paracetamol is rapidly absorbed following oral administration, by passive diffusion throughout the gastrointestinal tract. In humans, approximately 75 to 95% of an oral dose was absorbed.
Although administration of paracetamol with food slowed the absorption, the extent of absorption was not affected. There appear to be no age or sex-related effects on bioavailability. The Tmax typically occurs about one hour after dosing and the Cmax ranges from 15 to 30 µg/mL following 500 to 1000 mg doses. Because of the high clearance of paracetamol (4 to 5 mL/min/kg after intravenous administration) resulting primarily from conjugation, the half-life is quite short, ranging from 2 to 3 hours. As a result of this short half life it is necessary to dose the drug on at least a three times a day (TID) basis to maintain plasma concentrations.
Like paracetamol, ibuprofen is rapidly absorbed with an absolute bioavailability approaching
100%. The volume of distribution is small due to the physicochemical properties of the molecule and high protein binding to albumin. As a result of extensive oxidative metabolism and glucuronidation, the half-life is quite short, about two hours, and so repeat daily doses (e.g. TID) are necessary to maintain adequate plasma concentrations. The high protein binding is also concentration dependent, and as a result, total drug exposures do not rise in proportion to the administered dose. The pharmacokinetics of ibuprofen in children is similar to that of young middle aged adults.

Paracetamol is not extensively bound to plasma proteins and is independent of paracetamol concentration, with estimates ranging from 5 to 43%. Paracetamol is distributed into most body tissues. Paracetamol readily crosses into the cerebrospinal fluid and into the brain, where it exhibits its main analgesic effect. Paracetamol readily crosses cell membranes and has a volume of distribution of about 0.9 L/kg in humans. There are no particular tissues where paracetamol accumulates.
Ibuprofen is highly bound (90-99%) to plasma proteins. In humans, more than 99% of ibuprofen in serum is protein-bound; despite this, displacement interactions with other drugs are not clinically significant and the doses of oral anti-coagulants and oral hypoglycemic agents do not need to be altered when such drugs are co-administered with ibuprofen. In vitro experiments with human connective tissue have shown that radioactively labelled ibuprofen can bind to skin, muscle, subcutaneous, tendon and joint capsule tissues. Of these tissues, binding was highest in muscle and lowest in tendon tissue.

Both paracetamol and ibuprofen are metabolised primarily by the liver. Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation Paracetamol metabolites include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdosage and if left untreated has the potential to cause severe and even irreversible liver damage. Paracetamol is metabolised differently by premature infants, newborns, and young children compared with adults, the sulfate conjugate being most predominant. The details of the metabolic pathways for paracetamol both and ibuprofen are further discussed in the clinical section as most relevant information is available.

The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. A formal study using human liver enzymes to investigate such a possibility failed to find any potential drug interaction on the metabolic pathway.
The elimination half-life of paracetamol from plasma varies from about 1 to 3 hours. The main route of elimination from the body is in the urine, mainly as inactive glucuronide and sulfate conjugates. Less than 5% of a paracetamol dose is excreted unchanged. The elimination half-life of ibuprofen from plasma is in the range of 1.9 to 2.2 hours. Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion.

The potential for drug-drug interactions (DDIs) was reviewed in the literature. Clinical studies with combined administration of paracetamol and ibuprofen confirmed that there was no pharmacokinetic interaction of relevance. This supersedes the available information in animals and no additional studies were needed.

III.4 Toxicology

Single, orally administered doses of at the maximum tolerated dose of paracetamol of 1000 mg/kg and ibuprofen of 300 mg/kg results in little additional toxicity than when either drugs are administered alone. The only effects of co-administering single oral combined doses of paracetamol and ibuprofen at a ratio matching for the proposed product were a greater incidence of staining on the head (a nonspecific manifestation of stress or ill health) than administration of either drug alone, and a slower recovery from transient paracetamol-related weight loss.

In a 7 day oral toxicity study in rats, no additional toxicity to the kidneys and GI tract was observed in animals treated with the combination of paracetamol and ibuprofen versus either compound alone. No genotoxicity or carcinogenicity studies were undertaken for the fixed-dose combination. The Ibuprofen is considered not to present a genotoxic or carcinogenic hazard to human subjects. Paracetamol also is not considered to present a genotoxic hazard to human subjects at therapeutic doses. Paracetamol has also produced negative results in well-conducted lifetime carcinogenicity studies in mice and rats; however, a 1999 IARC review concluded that there was inadequate evidence to classify the carcinogenic potential of paracetamol in humans. There is nothing in the available information on paracetamol and ibuprofen to suggest an increased or novel risk of genotoxicity or carcinogenicity with co-administration of the two drugs.

Limited nonclinical information is available in relation to the reproductive and developmental toxicity of paracetamol or ibuprofen. When administered to pregnant rats and rabbits during the period of organogenesis, ibuprofen reportedly does not affect fetal development in either species. When administered to pregnant mice throughout gestation, paracetamol reportedly results in reduced birth weights. When administered to mice throughout gestation and lactation, paracetamol reportedly resulted in reduced pup growth. Clinical experience with the administration of each drug has appropriately informed the warnings in the SmPC, thus further nonclinical studies were not necessary.

III.5 Ecotoxicity/environmental risk assessment

The use of Paracetamol/Ibuprofen 500/150 mg film-coated tablets and Paracetamol/Ibuprofen sachets, containing either Paracetamol 1000 mg/Ibuprofen 300 mg or Paracetamol 500 mg/Ibuprofen 150 mg, in accordance with the SmPCs, will not significantly increase environmental exposure to paracetamol and ibuprofen; hence no additional environmental risk is presented by these medicinal products.

- Considering the above data, paracetamol and ibuprofen are not expected to pose a risk to the environment.
- Considering the above data, paracetamol and ibuprofen should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

III.6 Discussion on the non-clinical aspects

The nonclinical package for the proposed product is supported by a literature review for the active substances, supplemented by oral toxicity studies and clinical experience with the administration of both compounds. Additional nonclinical studies would not provide additional useful information. The nonclinical package is therefore acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

IV.2 Pharmacokinetics

Absorption
Both paracetamol and ibuprofen, are readily absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration. In clinical trials comparing the absorption of the hot drink sachet formulation to the equivalent fixed-dose combination tablets, the hot drink sachet formulation demonstrated a higher peak plasma concentration of paracetamol and ibuprofen when taken during fasting.

Absorption and bioavailability, distribution, metabolism, elimination, dose proportionality and time dependence, target/special populations, interactions, relationship between concentration and effect. The rate and absorption of both paracetamol and ibuprofen from the combination product is slightly delayed following administration after food.

Distribution
As for any product containing paracetamol, it is distributed into most body tissues.
Ibuprofen is highly bound (90-99%) to plasma proteins.

Metabolism
Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less than 5% is excreted unchanged. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione; however, it can accumulate following paracetamol overdose and if left untreated has the potential to cause severe and even irreversible liver damage.
Paracetamol is metabolised differently by premature infants, newborns, and young children compared with adults, the sulphate conjugate being most predominant.

Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. A formal study using human liver enzymes to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways.
In another study, the effect of ibuprofen on the oxidative metabolism of paracetamol was evaluated in healthy volunteers under fasting conditions. The study results indicated that ibuprofen did not alter the amount of paracetamol undergoing oxidative metabolism, as the amount of paracetamol and its metabolites (glutathione-, mercapturate-, cysteine-, glucuronide- and sulfate-paracetamol) were similar when administered alone, as paracetamol, or with the concomitant administration of ibuprofen. This study clears any added hepatic risks from the hepatotoxic metabolite, NAPQI, from paracetamol if administered with ibuprofen.

Elimination
Paracetamol elimination half-life varies from about 1 to 3 hours.
Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life if ibuprofen is around 2 hours.

Pharmacokinetic relationship
A specific study to investigate possible effects of paracetamol on the plasma clearance of ibuprofen and vice versa did not identify any drug interactions.

Clinical trials
In bioavailability trials comparing the absorption of the sachet formulation to the equivalent fixed-dose combination tablets, the sachet formulation demonstrated a higher peak plasma concentration of paracetamol and ibuprofen when taken during fasting. The higher peak concentration (C max) and time to reach peak concentration (T max) for the sachet formulation is expected due to the specific formulation (hot drink) where all the ingredients are completely dissolved in the solution prior to oral administration and thus conferring a rapid absorption from the gastrointestinal tract. The overall exposure for both medicines is bioequivalent to the tablet formulation. The Applicant provided sufficient evidence of assurance that the higher Cmax would not lead to any difference in safety or efficacy. The rate and absorption of both paracetamol and ibuprofen from the hot drink sachet formulation was shown to be slightly delayed following administration after food. To minimise any potential side effects, it is therefore recommended to take the sachet formulation after food.

IV.3 Pharmacodynamics

Mechanism of action
Although the exact site and mechanism of analgesic action of paracetamol is not clearly defined, it appears that it induces analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-Daspartate and substance P.

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The medicine's therapeutic effects as an NSAID result from its inhibitory effect on the enzyme cyclo-oxygenase, leading to reduction in prostaglandin synthesis. The exact mechanism of action of ibuprofen is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthesise inhibition.

IV.4 Clinical Efficacy

Clinical trials
To support efficacy and safety of the product, an overview of 4 studies that evaluated the efficacy of the oral tablet formulations was provided. Compared to placebo or paracetamol or ibuprofen only treatment, treatment with the fixed dose combination of paracetamol and ibuprofen at both doses had the greatest response rate/analgesic effect, lowest maximum VAS pain scores, the longest time to rescue medication and the lowest percentage of patients requiring rescue medication. All studies presented were consistent in their conclusions.

The tablets were shown to be bioequivalent in the pharmacokinetic parameters AUC0-t and AUC0-∞, to the new sachet formulation and therefore support the relevance of these studies.

Literature
The Applicant provided a systematic review of scientific literature which demonstrated that the analgesic efficacy of paracetamol in combination with ibuprofen administered enterally or otherwise is superior to that of either drug used alone as measured in a variety of different pain models.

IV.5 Clinical Safety

Safety data from completed studies including a bioavailability study where the sachet formulated product was used were provided.

The safety and adverse event profile are in line with that expected for paracetamol and ibuprofen.

As stated previously, in bioavailability trials comparing the absorption of the sachet formulation to the equivalent fixed-dose combination tablets, the sachet formulation demonstrated a higher peak plasma concentration (Cmax) of paracetamol and ibuprofen when taken during fasting. The Applicant provided sufficient evidence of assurance that the higher Cmax would not lead to any difference in safety or efficacy. The rate and absorption of both paracetamol and ibuprofen from the hot drink sachet formulation was shown to be slightly delayed following administration after food. To minimise any potential side effects, it is therefore recommended to take the sachet formulation after food.

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 Easolief DUO 500mg/150mg & 1000mg/300mg powder for oral solution.

Safety Specification

List of important risks and missing information	
Important identified risks	none
Important potential risks	none
Missing information	none

Based on consideration of the identified risks, the potential risks and the need for additional information on the medicinal product, it is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

Overdose (accidental and intentional) and risk to exposure to multiple products containing paracetamol/NSAIDs will be reviewed, as part of routine pharmacovigilance, as an adverse reaction of special interest within PSURs for this product, along with routine analysis of all individual case safety reports, including fatal, serious and non-serious cases

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

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

Paracetamol and ibuprofen are well-known analgesics. The Applicant has submitted completed studies and a literature review which support efficacy and safety of use of the combination sachet containing paracetamol and ibuprofen for the short-term treatment of mild to moderate pain in adults.

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 Paracetamol/Ibuprofen Vale 500mg/150mg for oral solution in sachet demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

01.07.2030