IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Paracetamol 500mg/5ml Oral Solution
PARACETAMOL
PA0281/243/001

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

This product was initially authorised under procedure number UK/H/6069/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 20/06/2018 under procedure number IE/H/0624/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/243/001
Marketing Authorisation Holder: Pinewood Laboratories Ltd

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the application for Paracetamol 500mg/5ml Oral Solution (PL 29831/0593; UK/H/6069/001/DC) could be approved. The product is a prescription only medicine (POM) and is indicated in the treatment of mild to moderate pain in adults and adolescents over 16 years old who are unable to receive other paracetamol formulations such as lower strength liquid preparations, effervescent tablets or tablets.

The product may be referred to as 'Paracetamol Oral Solution' in the remainder of this report.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The application for Paracetamol 500mg/5ml Oral Solution was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance (paracetamol) of well-established use. Paracetamol has been widely used in the EU for many years.

The active substance, paracetamol, is an acetanilide derivative. It is one of the most widely used analgesics for mild to moderate pain, and most forms are available world-wide without a prescription.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

The RMS has been assured that acceptable standards of good manufacturing practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates issued by the inspection services of the Irish competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

The UK and Ireland considered that the application could be approved at the end of procedure (Day 157) on 28 April 2016. After a subsequent national phase, a licence was granted in the UK on 20 May 2016.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

The application is submitted in accordance with Article 10a of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is presented as a clear amber solution.

Each 5ml of oral solution contains 500mg of paracetamol. The product also contains pharmaceutical excipients namely, propylene glycol (E1520), glycerol (E422), macrogol 400, citric acid monohydrate, sodium citrate, methylparahydroxybenzoate (E218), propylparahydroxybenzoate (E216), peppermint flavour, sucralose, sunset yellow (E110) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The product is supplied in amber (Type III) soda glass 150ml, 200ml and 500ml bottles, each with a closure consisting of a 28mm white, child-resistant tamper evident cap with expanded polyethylene (EPE) liner. The bottle is provided in an outer cardboard carton.

A 5ml dispensing oral syringe and bottle adapter are supplied with each pack.

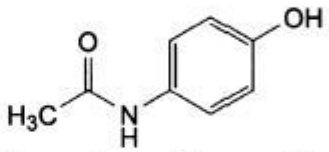
Not all packs sizes are marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food.

II.2 Drug Substance

Paracetamol

International Non-proprietary Name (INN):	Paracetamol
Chemical name:	N-(4-hydroxyphenyl)acetamide
Molecular formula:	$C_8H_9NO_2$
Mr:	151.2
Structural formula:	



Description:	White or almost white crystalline powder.
Solubility:	Sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

Paracetamol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, paracetamol, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, oral solution containing 500mg/5ml of paracetamol. Suitable pharmaceutical development data have been provided for this application.

With the exception of peppermint flavour and sunset yellow (E110), all excipients comply with their respective European Pharmacopoeia monographs. Peppermint flavour and sunset yellow (E110) are controlled to their respective in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated at production scale and has shown satisfactory results.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years for the unopened product and 3 months once the product has been opened, with the special storage conditions, 'Store below 25°C. Do not refrigerate or freeze. Store in the original bottle.' has been accepted.

Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this type of application.

II.4 Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well known and are adequately described in the applicant's non-clinical overview. No new non-clinical data were submitted and none are required for an application of this type.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacokinetics
The pharmacokinetic properties of paracetamol are well known and adequately described in the applicant's non-clinical overview.

III.3 Pharmacodynamics
The pharmacodynamic properties of paracetamol are well known and are adequately described in the applicant's non-clinical overview.

III.4 Toxicology
The toxicological properties of paracetamol are well known and are adequately described in the applicant's non-clinical overview.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). It is agreed that the risks to the environment are not expected to increase as the proposed product will be used to substitute other currently marketed forms of paracetamol.

III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for this application, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV. CLINICAL ASPECTS

IV.1 Introduction

The legal basis of this application is a well-established medicinal use application according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic literature.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

No new clinical pharmacokinetic data have been submitted and none are required for an application of this type. The pharmacokinetic profile of paracetamol is well-known. Adequate bibliographic clinical pharmacokinetic data have been provided to support the application. An adequate summary of the pharmacokinetic profile of paracetamol has been provided. A summary of the pharmacokinetic profile of paracetamol is provided below:

Paracetamol is a weak acid with a high pKa. After oral administration, paracetamol is rapidly and completely absorbed with a T_{max} between 15 minutes and 2 hours. The absolute oral bioavailability is about 80%, mainly due to first pass metabolism. Dose proportionality has been demonstrated for oral doses in the range 5-20 mg/kg. Food increases T_{max} but does not affect the AUC.

The extent of binding of paracetamol to plasma proteins is low (10-25%). The volume of distribution is around 0.9 L/kg. It is non-ionised at physiological pH and freely crosses the placenta and blood-brain barrier.

In adults, paracetamol is extensively metabolised in the liver by glucuronidation (50-60%), sulfation (25-30%) and oxidation (<10%). The major metabolites are inactive sulfate and glucuronide conjugates, which are excreted in the urine. The sulfate conjugation pathway is completely saturated following overdose. A small fraction of the dose is converted by cytochrome P450-dependent mixed function oxidase to N-acetyl-P-benzoquinoneimine (NAPQI), a reactive potentially cytotoxic alkylating intermediate which is normally conjugated with glutathione and excreted in the urine as mercapturic acid and cysteine conjugates of paracetamol. Glutathione is depleted following overdosage and the reactive metabolite binds covalently to hepatic macromolecules, causing irreversible damage and necrosis.

Total clearance is 5ml/min/kg. The mean plasma half-life is 2.3 hours in healthy volunteers with a range of 1.00-3.00 hours. It is not prolonged to a clinically significant extent in the elderly.

Around 2.5% of a therapeutic dose is excreted unchanged in the urine.

Paracetamol pharmacokinetics has been investigated in patients with renal and hepatic disease. In patients with severe acute and decompensated chronic liver disease the half-life was considerably prolonged. Therapeutic doses of paracetamol do not exacerbate stable chronic liver disease, and the

metabolism of paracetamol is normal in these patients. Plasma concentrations of paracetamol and its glucuronide and sulfate conjugates are increased in patients with moderate renal failure and in patients on dialysis.

The applicant has summarised the known drug-drug interactions of paracetamol, with reference to standard drug reference texts.

IV.3 Pharmacodynamics

The clinical pharmacology of paracetamol is well-known. An adequate summary of the pharmacodynamic profile of paracetamol to support the application has been presented in the clinical overview. A summary of the pharmacodynamics profile of paracetamol is provided below:

Paracetamol is an analgesic and an antipyretic. It is believed to exert its action via inhibition of prostaglandin synthesis, and interaction with serotonergic and cannabinoid pathways. Paracetamol inhibits COX1 and COX2.

The therapeutic range is usually stated to be within the plasma concentration range of 10-20 µg/mL for both analgesia and antipyresis. Several studies report a time delay of 1-2 hours between T_{max} and maximum temperature reduction.

IV.4 Clinical Efficacy

No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of paracetamol is well-established.

The applicant has submitted a clinical overview and bibliographic references to support the clinical efficacy of paracetamol in the treatment of mild to moderate pain.

The applicant refers to a review (2002) which compared the efficacy of paracetamol to NSAIDs in postoperative pain. A total of 36 studies involving 3362 patients were included. The results were heterogeneous; some studies demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) were superior to paracetamol, whereas other studies showed that efficacy was comparable. In five studies, paracetamol was superior to placebo. In three studies of postoperative analgesia after orthopaedic surgery a model of moderate-severe pain, the efficacy of paracetamol was comparable to NSAIDs.

The applicant also refers to a further review (2004) of the efficacy of paracetamol. This review looked at single doses ranging from 325 mg to 1500 mg in 2561 patients, and included comparisons with placebo. The author concluded that paracetamol is effective in the treatment of postoperative pain, including after dental surgery.

Concerning headache, the applicant refers to a review (2010) of the efficacy of paracetamol in acute migraine, alone or in combination with an anti-emetic. The review included ten studies, including a total of 2769 patients. Paracetamol was superior to placebo for the treatment of moderate to severe pain, for all efficacy outcomes. In addition, paracetamol 1000 mg in combination with metoclopramide 10 mg was not significantly different to oral sumatriptan for 2 hour headache relief.

The applicant also refers to a published meta-analysis (2004) of ten studies of the efficacy of paracetamol in osteoarthritis. The studies included comparisons with placebo. NSAIDs were shown to be more effective than paracetamol.

IV.5 Clinical Safety

No new safety data were supplied or required for this bibliographic application. The safety profile of paracetamol is well-known. The submitted bibliographic data is considered adequate to support the

clinical safety of paracetamol when used by the general adult and elderly population in the proposed indications.

Adverse effects of paracetamol are rare and usually mild, although haematological reactions (including thrombocytopenia, leucopenia, pancytopenia, neutropenia, and agranulocytosis) and serious skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalised exanthematous pustulosis) have been reported. More mild rashes and other hypersensitivity reactions also occur occasionally.

Some studies have suggested an association between paracetamol and asthma. However, overall a strong link between paracetamol and asthma is judged unlikely.

Two systematic reviews have found that the rate of adverse events following paracetamol administration is not significantly different to that of placebo.

Acute oral overdosage is relatively common, and is particularly serious due to the narrow margin between therapeutic and toxic doses. Acute hepatic necrosis, and more rarely renal tubular necrosis, may result. Early treatment with agents which facilitate glutathione synthesis can prevent the development of hepatotoxicity.

The applicant discusses that there is a theoretical increased risk of hepatotoxicity with therapeutic doses of paracetamol in the elderly. Mitchell (2011) showed that older frail hospitalised patients treated with paracetamol for five days do not have an increased risk of liver enzyme elevation compared to younger patients. However there is a lack of definitive evidence, and the applicant concludes that older frail patients will be at increased risk of drug-induced liver injury compared to younger patients, at therapeutic doses.

IV.6 Risk Management Plan

The Marketing Authorisation Holder (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 Paracetamol Oral Solution.

The MAH identified the following as safety concerns:

Summary of safety concerns	
Important identified risks	**Overdose and hepatotoxic effects of paracetamol** Risk groups of patients susceptible to overdose and hepatotoxic effects of paracetamol are: • Patients with severe hepatic dysfunction. • children and adolescents under 16 years, • patients with severe renal impairment, • patients with noncirrhotic alcoholic liver disease and use in patients with alcoholic dependence • concomitant use of paracetamol-containing products • medication errors - incorrect use of syringe, or intentional overdose. • Frequency of use and duration of treatment **Concomitant medication** - The hepatotoxicity of Paracetamol, particularly after overdosage, may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants and alcohol. - The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect. **Hypersensitivity to the active substance or to any of the excipients.**
Important potential risks	• Medication errors • Use in patients with asthma. • Use for more than three days. • Use in elderly patient population • Use during pregnancy and breastfeeding
Missing information	Fertility data

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. This is satisfactory.

IV.7 Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

V. USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to the PILs for Paracetamol Adult 500 mg/5 ml Oral Suspension (Rosemont Pharmaceuticals Limited; for scientific content) and

Maximum Strength Ibuprofen 400mg Film-Coated Tablet (Wockhardt UK Limited; for design and layout). The bridging report submitted by the applicant has been found acceptable.

V. OVERALL CONCLUSIONS

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Paracetamol Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of paracetamol are well-known, no additional data were required.

EFFICACY
No new clinical data were submitted and none were required for this type of application.

The published literature supports the efficacy of the product in the proposed indication and posology. The efficacy of paracetamol is well-known. The presented evidence for well-established use of the active substance is sufficient.

SAFETY
The safety profile of paracetamol is well-known. The literature review identified no new or unexpected safety issues or concerns.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.

VI. REVISION DATE

02/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/6069/1/DC to IE/H/0624/1/DC			
MAH transfer				04/01/2021