Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Paracetamol 1000 mg Effervescent Tablets

(paracetamol)

UK Licence No: PL 31603/0021

Apollo Generics Limited

LAY SUMMARY

Paracetamol 1000 mg Effervescent Tablets

This is a summary of the Public Assessment Report (PAR) for Paracetamol 1000 mg Effervescent Tablets (PL 31603/0021). It explains how Paracetamol 1000 mg Effervescent Tablets were assessed and their authorisation recommended, as well as their condition of use. It is not intended to provide practical advice on how to use Paracetamol 1000 mg Effervescent Tablets.

This product will be referred to as Paracetamol Effervescent Tablets throughout the remainder of this public assessment report.

For practical information about using Paracetamol Effervescent Tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Paracetamol Effervescent Tablets and what are they used for?
Paracetamol Effervescent Tablets are a 'hybrid medicine'. This means that Paracetamol Effervescent Tablets are similar to a 'reference medicine', containing the same active substance, but in a different strength, already authorised in the European Union (EU), called Panadol Actifast Soluble Tablets or Panadol Soluble 500 mg Tables (PL 44673/0083; GlaxoSmithKline Consumer Healthcare (UK) Trading Limited). The reference product will be referred to as Panadol Actifast Soluble Tablets throughout the remainder of this PAR.

Paracetamol Effervescent Tablets belongs to a group of medicines called analgesic and antipyretic medicines. Paracetamol Effervescent Tablets are used for the relief of headache, tension headache, migraine, backache, rheumatic and muscle pain, toothache and period pain. They also relieve sore throat and the fever, aches and pains of colds and flu.

How do Paracetamol Effervescent Tablets work?
Paracetamol Effervescent Tablets contain the active ingredient, paracetamol, which belongs to a group of medicines called analgesics (painkillers). Paracetamol works by relieving pain and brings down high temperatures (reduces fever).

How are Paracetamol Effervescent Tablets used?
The pharmaceutical form of this medicine is an effervescent tablet which is dissolved in water and taken by mouth (oral).

The patient should always use this medicine exactly as described in the package leaflet or as advised by their doctor or pharmacist. If unsure, the patient should ask their doctor or pharmacist.

The recommended dose of this medicine is as follows:

Adults
Take ½ to 1 tablet dissolved in a tumbler of water every 4 hours as needed. Do not take more than 4 tablets in 24 hours. The tablet can be divided into equal doses.

Use in children and adolescents
Not recommended for children under the age of 16 years.

If the patient takes more Paracetamol Effervescent Tablets than the recommended dose then they should talk to their doctor at once as too much paracetamol can cause delayed, serious liver damage. If the symptoms continue or headaches become persistent, the patient must see their doctor.

This medicine can be obtained without a prescription.

For further information on how to use Paracetamol Effervescent Tablets see section 3 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Paracetamol Effervescent Tablets have been shown in studies?
Because Paracetamol Effervescent Tablets are a hybrid medicine and, when taken in equal doses, are considered to be therapeutically equivalent to the reference product, Panadol Actifast Soluble Tablets (PL 44673/0083; GlaxoSmithKline Consumer Healthcare (UK) Trading Limited), their benefits and risks are taken as being the same as those of the reference medicine.

What are the possible side effects from Paracetamol Effervescent Tablets?
The most common side effects with Paracetamol Effervescent Tablets are:

- Allergic reactions which may be severe such as skin rash and itching sometimes with swelling of the mouth or face or shortness of breath.
- Skin rash or peeling, or mouth ulcers.
- Breathing problems. These are more likely if you have experienced them before when taking other painkillers such as ibuprofen and aspirin.
- Unexplained bruising or bleeding
- Nausea, sudden weight loss, loss of appetite and yellowing of the eyes and skin.

For a full list of all the side effects reported with Paracetamol Effervescent Tablets see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website. For the full list of restrictions, see the package leaflet.

Why were Paracetamol Effervescent Tablets approved?
The MHRA decided that the benefits of Paracetamol Effervescent Tablets are greater than the risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Paracetamol Effervescent Tablets?
A Risk Management Plan has been developed to ensure that Paracetamol Effervescent Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Paracetamol Effervescent Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Paracetamol Effervescent Tablets
A Marketing Authorisation was granted in the UK on 20 July 2018.

The full PAR for Paracetamol Effervescent Tablets follows this summary.
For more information about treatment with Paracetamol Effervescent Tablets read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in September 2018.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Apollo Generics Limited a Marketing Authorisation for the medicinal product Paracetamol Effervescent Tablets (PL 31603/0021) on 20 July 2018. This product is available from pharmacies without a prescription (P). Paracetamol Effervescent Tablets are recommended for the treatment of most painful and febrile conditions, for example, headache including migraine and tension headaches, toothache, backache, rheumatic and muscle pains, dysmenorrhoea, sore throat, and for relieving the fever, aches and pains of colds and flu.

This application was submitted as an abridged national application, according to Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference product for this hybrid application is Panadol Actifast Soluble Tablets, which were originally authorised on 12 January 1982 to the Marketing Authorisation Holder (MAH) SmithKline Beecham (SWG) Limited (PL 00071/0072R). A subsequent change of ownership procedure took place on 27 April 2016 to the current Marketing Authorisation Holder (MAH) GlaxoSmithKline Consumer Healthcare (UK) Trading Limited (PL 44673/0083).

Paracetamol is an analgesic used in the relief of mild to moderate pain. It is an antipyretic and it has minimal anti-inflammatory effects. Paracetamol has analgesic and antipyretic effects. It is only a weak inhibitor of prostaglandin biosynthesis, although there is some evidence to suggest that it may be more effective against enzymes in the CNS than those in the periphery. This fact may partly account for its ability to reduce fever (a central action) and to induce analgesia. It is one of the most popular and most commonly used analgesic and antipyretic drugs around the world, available without a prescription, both in mono- and multi-component preparations. It is the drug of choice in patients that cannot be treated with non-steroidal anti-inflammatory drugs (NSAIDs), such as people with bronchial asthma, peptic ulcer disease, hemophilia, salicylate-sensitized people, children under 12 years of age, pregnant or breastfeeding women.

No new non-clinical or clinical studies were conducted, which is acceptable given that this application was based on being a hybrid medicinal product of the reference product that has been licenced for over 10 years.

Comparable physicochemical parameters between the reference and proposed product were provided. As the product is a solution at the time of administration, no therapeutic equivalence study between the reference product Panadol Actifast Soluble Tablets (PL 44673/0083; GlaxoSmithKline Consumer Healthcare (UK) Trading Limited) and the proposed product has been conducted. A biowaiver is considered appropriate for this application in line with the note for guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) and is adequately supported by the comparative quality data provided.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

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

A Marketing Authorisation was granted in the UK on 20 July 2018.

II QUALITY ASPECTS

II.1 Introduction

The finished product is formulated as an effervescent tablet containing 1000mg of paracetamol.

Other pharmaceutical excipients present are povidone, ascorbic acid, citric acid, lactose monohydrate, sorbitol, sodium hydrogen carbonate, sodium saccharin, L-leucine, lemon flavour and sulfurous acid.

This medicinal product contains the following excipients with known effects:
Sodium 330 mg / 14.4 mmol
Lactose monohydrate 150 mg
Sorbitol 200 mg

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the lemon flavouring which is controlled by an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

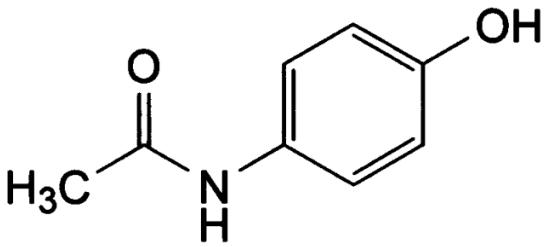
The finished product is packaged in white polypropylene tubes closed with a polyethylene cap containing silica gel desiccant. Each tube contains 10 effervescent tablets and are packaged in boxes.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN:	Paracetamol
Chemical Name:	N-(4-hydroxyphenyl)acetamide

Structure:



Molecular formula:	$C_8H_9NO_2$
Molecular weight:	151.2 g/mol
Appearance:	White crystalline powder
Solubility:	It is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in dichloromethane

Paracetamol is the subject of a European Pharmacopoeia monograph.

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

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop safe, efficacious effervescent tablets containing 1000 mg of paracetamol that could be considered as a hybrid medicinal product of the currently licensed product, Panadol Actifast Soluble Tablets (PL 44673/0083; GlaxoSmithKline Consumer Healthcare (UK) Trading Limited).

The physicochemical properties of the proposed product versus the reference product have shown that the products are comparable.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as required for human consumption.
This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on production scale batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing. Paracetamol Effervescent Tablets placed on the market will be packed in child-resistant packaging.

The data from these studies support a shelf life of 4 years for this product with special storage conditions of “Do not store above 30°C. Keep the polypropylene tube tightly closed. Store in the original container to protect from the moisture and light.”

Suitable post approval stability commitments to continue stability testing on batches of finished product in appropriate packaging for marketing have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report 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 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. Since Paracetamol Effervescent Tablets are intended to be used in place of similar products, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical point of view therefore grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS
IV.1 Introduction
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of paracetamol are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
Paracetamol has now been classified as a 'Biopharmaceutical classification system class I compound' (BSC). According to the BCS, drugs can be divided into categories based on their solubility and permeability. Drugs, which show good solubility and permeability, are indexed into class I. These drugs are generally suitable for a biowaiver. Therefore, no bioequivalence study was conducted or required. A biowaiver is considered appropriate for this application in line with the note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) and is adequately supported by the comparative quality data provided.

IV.3 Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for this application and none have been submitted.

IV.5 Clinical safety
No new clinical safety data are required for this application and none have been submitted.

IV.6 Risk Management Plan (RMP)
The applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The applicant shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the national competent authority
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report (PSUR) and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisation is recommended.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Paracetamol 500 mg Effervescent Tablets (PL 31603/0018). The bridging report submitted by the applicant is acceptable.

IV OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 balance is, therefore, considered to be positive.

Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
The SmPC and PIL are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved text version of the labelling for this medicine is presented below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
{Carton}

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol 1000mg Effervescent Tablets
Paracetamol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each effervescent tablet contains paracetamol 1000mg

3. LIST OF EXCIPIENTS

Sodium content 330mg per tablet. Also includes sorbitol (E420), lactose monohydrate and sulphurous acid (a source of sulfur dioxide E220). See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Effervescent Tablets.

10 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

HOW TO TAKE: For oral use. The tablets must be dissolved in water before taking.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the site and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not take anything else containing paracetamol while taking this medicine.
Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.
Immediate medical advice should be sought in the event of an overdose, even if you feel well.

Consult your doctor before taking this medicine, if you have liver or kidney disease, including alcoholic liver disease or if you are on a low sodium diet.

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Keep the tube tightly closed.

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Apollo Generics Limited
Unit 6 The Gallery
Furness Avenue
Formby, Liverpool
L37 3NP

12. MARKETING AUTHORISATION NUMBER(S)

PL 31603/0021

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

For use in mild pain and fever

Adults: Take ½ - 1 tablet in at least half a tumbler of water, up to 4 times daily as required. Maximum of 4 tablets in any 24 hour period.

Do not give to children under 16 years.

Do not take more frequently than every 4 hours.

Read the package leaflet before use.

16. INFORMATION IN BRAILLE

Paracetamol 1000 mg effervescent tablets

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING {TUBE}

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol 1000 mg Effervescent Tablets
Paracetamol

2. METHOD OF ADMINISTRATION

For oral use. The tablets must be dissolved in water before taking.

Read the package leaflet before use.

3. EXPIRY DATE

EXP (MM/YYYY)

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 Effervescent Tablets

6. OTHER

Keep out of the sight and reach of children.

Each tablet contains paracetamol 1000mg.
Do not take with any other paracetamol containing products.
Sodium content 330mg per tablet. Also includes sorbitol (E420), lactose monohydrate and sulphurous acid (a source of sulfur dioxide E220). See the leaflet for further information.

Apollo Generics Limited, Formby, Liverpool, L37 3NP, UK

PL 31603/0021

Do not store above 30°C. Keep the tube tightly closed.

Store in the original package.

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Approval/ non approval**	**Assessment report attached Y/N (version)**