Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

UKPAR

Paracetamol 500mg Effervescent Tablets (GSL)
Paracetamol 500mg Effervescent Tablets (Pharmacy)

(paracetamol)

UK Licence Number: PL 31603/0018-0019

Apollo Generics Limited

LAY SUMMARY

Paracetamol 500mg Effervescent Tablets

This is a summary of the Public Assessment Report (PAR) for Paracetamol 500mg Effervescent Tablets (PL 31603/0018) and Paracetamol 500mg Effervescent Tablets (PL 31603/0019). It explains how Paracetamol 500mg Effervescent Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Paracetamol 500mg Effervescent Tablets.

The product will be referred to as 'Paracetamol Effervescent Tablets' throughout the remainder of this public assessment report (PAR).

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 'generic medicine'. This means that Paracetamol Effervescent Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Panadol ActiFast Soluble Tablets (SmithKline Beecham (SWG) Limited).

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?
The active ingredient is paracetamol which is a pain killer and also reduces a person's temperature when they have a fever.

How are Paracetamol Effervescent Tablets used?
The pharmaceutical form of this medicine is an effervescent tablet and the route of administration is oral (by mouth). Before swallowing the tablets should be dissolved in a tumbler of water.

Dose
1 to 2 tablets every 4 – 6 hours, up to a maximum of 4 doses in 24 hours.

No more than 8 tablets should be taken in 24 hours.

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

This medicine is not recommended in children under 10 years.

Please read section 3 of the package leaflet for detailed dosing recommendations including use in children aged 10-15 years, the route of administration, and the duration of treatment.

For further information on how Paracetamol Effervescent Tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained without a prescription.

What benefits of Paracetamol Effervescent Tablets have been shown in studies?
Paracetamol Effervescent Tablets are a generic medicine, and are considered to be therapeutically equivalent, to the reference medicine Panadol ActiFast Soluble Tablets (SmithKline Beecham (SWG) Limited).

What are the possible side effects of Paracetamol Effervescent Tablets?
Because Paracetamol Effervescent Tablets are a generic medicine their benefits and possible side effects are taken as being the same as those of the reference medicine Panadol ActiFast Soluble Tablets (SmithKline Beecham (SWG) Limited).

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 are Paracetamol Effervescent Tablets approved?
It was concluded that, in accordance with EU requirements, Paracetamol Effervescent Tablets have been shown to have comparable quality and to be therapeutically equivalent to Panadol ActiFast Soluble Tablets (SmithKline Beecham (SWG) Limited). The benefits are greater than the risks and it was recommended that Paracetamol Effervescent Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Paracetamol Effervescent Tablets?
A risk management plan (RMP) 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 (SmPC) 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 19 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

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Apollo Generics Limited, a marketing authorisation for the medicinal product Paracetamol Effervescent Tablets (PL 31603/0018) and Paracetamol Effervescent Tablets (PL 31603/0019). Paracetamol Effervescent Tablets (PL 31603/0018) is a general sales list medicine (GSL), whereas Paracetamol Effervescent Tablets (PL 31603/0019) is a pharmacy medicine (P).

Paracetamol Effervescent Tablets are indicated 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. Paracetamol is a mild analgesic and antipyretic.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference product for this application is Panadol ActiFast Soluble Tablets (PL 00071/0072R; SmithKline Beecham (SWG) Limited) which was first authorised in the UK in 1982. On 27 April 2016 this Marketing Authorisation changed ownership to GlaxoSmithKline Consumer Healthcare (UK) Trading Limited as 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 studies were submitted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been in clinical use 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 00071/0072R; SmithKline Beecham (SWG) Limited) and the proposed product has been conducted. A biowaiver is considered appropriate for this application as per Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98) 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 these products.

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.

II QUALITY ASPECTS

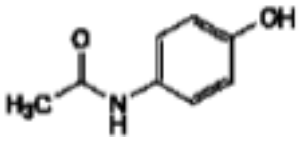
II.1 Introduction

The finished product is an effervescent tablet containing 500mg paracetamol per tablet. Other ingredients consist of the pharmaceutical excipients povidone, ascorbic acid, citric acid, lactose, sorbitol, sodium hydrogen carbonate, sodium saccharin, L-Leucine, and lemon flavour

The finished product for general sale (PL 31603/0018) is packaged in a carton containing 1 tube of 16 effervescent tablets, protected from moisture by a silica gel capsule, whereas the finished product for supply through pharmacies (PL 31603/0019) is also packaged in carton containing 2 tubes with 16 effervescent tablets in each tube, 32 tablets in total.

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

All aspects of the manufacture and control of the active substance, paracetamol, are covered by the 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. Appropriate stability will be generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a safe, efficacious, film-coated tablet containing 500mg paracetamol per tablet that is a generic version of the reference product Panadol ActiFast Soluble Tablets (SmithKline Beecham (SWG) Limited). The development of the product has been described, the choice of excipients is justified, and their functions explained.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with their respective European Pharmacopeia monographs.

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on commercial batch sizes have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. 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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with the special storage conditions “Store below 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 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)
Since Paracetamol Effervescent Tablets are intended for generic substitution, 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 viewpoint.

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.

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 as per Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98) and is adequately supported by the comparative quality data provided.

IV.2 Pharmacokinetics

No new pharmacokinetics data were submitted and none were required for an application of this type, see section IV.1 above for more information.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

With the exception of the safety data collected during the bioequivalence study, no new data on safety have been submitted and none are required for applications of this type. No new or unexpected adverse events were observed in the bioequivalence study.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

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), which is acceptable.

The MAH 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 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 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 a marketing authorisation is recommended for this application from a clinical viewpoint.

V User consultation

The package leaflet has been evaluated, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to understand and act upon the information that it contains.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products 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 biowaiver has been accepted is, therefore, considered to be positive.

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

The MAH has submitted the following approved labelling for this medicine which is presented below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
{Carton}

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol 500mg Effervescent Tablets
Paracetamol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each effervescent tablet contains 500mg paracetamol

3. LIST OF EXCIPIENTS

Sodium content 316mg per tablet. Also contains sorbitol (E420), lactose monohydrate and sulphurous acid (a source of sulfur dioxide E220). See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

16 Effervescent 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 SIGHT 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.
Talk to a doctor at once if you take too much of this medicine, 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 31603/0018

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

For use in mild pain and fever

Adults, the elderly and children aged 16 years and over: Take 1 - 2 tablets in at least half a tumbler of water, up to 4 times daily as required. Maximum of 8 tablets in any 24 hour period.

Children aged 10 – 15 years: 1 tablet dissolved in water up to 4 times daily as required. Maximum of 4 tablets in any 24 hour period. **Do not give to children under 10 years.**

Do not take more frequently than every 4 hours.

Read the package leaflet before use

16. INFORMATION IN BRAILLE

Paracetamol 500 mg effervescent tablets

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING {TUBE}

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol 500 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

16 Effervescent Tablets

6. OTHER

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Each tablet contains paracetamol 500mg.
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.
Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Sodium content 316mg per tablet. Also contains 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 31603/0018

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

Store in the original package.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
{Carton}

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol 500mg Effervescent Tablets
Paracetamol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each effervescent tablet contains 500mg paracetamol

3. LIST OF EXCIPIENTS

Sodium content 316mg per tablet. Also contains sorbitol (E420), lactose monohydrate and sulphurous acid (a source of sulfur dioxide E220). See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

16 Effervescent Tablets
32 Effervescent 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 SIGHT 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.
Talk to a doctor at once if you take too much of this medicine, 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 31603/0019

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, the elderly and children aged 16 years and over: Take 1 - 2 tablets in at least half a tumbler of water, up to 4 times daily as required. Maximum of 8 tablets in any 24 hour period.

Children aged 10 – 15 years: 1 tablet dissolved in water up to 4 times daily as required. Maximum of 4 tablets in any 24 hour period. **Do not give to children under 10 years.**

Do not take more frequently than every 4 hours.

Read the package leaflet before use

16. INFORMATION IN BRAILLE

Paracetamol 500 mg effervescent tablets

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING {TUBE}

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol 500 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

16 Effervescent Tablets

6. OTHER

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Each tablet contains paracetamol 500mg.
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.
Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Sodium content 316mg per tablet. Also contains 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 31603/0019

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)