Public Assessment Report

Decentralised Procedure

Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets

(Paracetamol and diphenhydramine hydrochloride)

Procedure No: UK/H/6235/001/DC

UK Licence Number: PL 30306/0766

Actavis Group PTC ehf.
LAY SUMMARY

Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets
(paracetamol 500mg and diphenhydramine hydrochloride 25 mg)

This is a summary of the Public Assessment Report (PAR) for Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets (PL 30306/0766; UK/H/6235/001/DC). It explains how Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated 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 and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets.

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

For practical information about using Paracetamol and diphenhydramine hydrochloride Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Paracetamol and diphenhydramine hydrochloride Tablets and what are they used for?
Paracetamol and diphenhydramine hydrochloride Tablets are a ‘generic medicine’. This means that Paracetamol and diphenhydramine hydrochloride Tablet are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Panadol Night or Panadol NightPain (GlaxoSmithKline Consumer Healthcare (UK) Trading Limited, UK).

Paracetamol and diphenhydramine hydrochloride Tablets are used to provide relief of the fever, aches and pains associated with colds and flu, headaches, backache, rheumatic and muscle pains, period pains and toothache which is causing difficulty in getting to sleep.

How do Paracetamol and diphenhydramine hydrochloride Tablets work?
This medicine contains two active substances, paracetamol and diphenhydramine hydrochloride. Paracetamol is a painkiller and diphenhydramine hydrochloride is an antihistamine that causes sleepiness or drowsiness making it useful when pain is keeping the patient awake.

How are Paracetamol and diphenhydramine hydrochloride Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

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

For bedtime use only.

Swallow Paracetamol and diphenhydramine hydrochloride Tablets with water.

Adults (including the elderly) and adolescents 16 years and over:
- Take 2 tablets about 20 minutes before bedtime.
- Do not take more than 2 tablets per night.

When taking Paracetamol and diphenhydramine hydrochloride Tablets at bedtime, the patient may take other tablets containing paracetamol during the day but do not take more than 4,000 mg paracetamol (including this product) in any 24 hours with at least 4 hours between doses.
Adolescents 12 years to 15 years:
- Take 1 tablet about 20 minutes before bedtime.
- Do not take more than 1 tablet per night.

When taking Paracetamol and diphenhydramine hydrochloride Tablets at bedtime, the patient may take other tablets containing paracetamol during the day but do not take more than 3,000 mg paracetamol (including this product) in any 24 hours with at least 4 to 6 hours between doses.

The patient should not take Paracetamol and diphenhydramine hydrochloride Tablets for more than 7 consecutive nights without consulting their doctor.

Not recommended for children under 12 years except under medical advice.

Do not exceed the stated dose.
If symptoms persist the patient should contact their doctor.

Prolonged use except under medical supervision may be harmful.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Paracetamol and diphenhydramine hydrochloride 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 be obtained without a prescription.

What benefits of Paracetamol and diphenhydramine hydrochloride Tablets have been shown in studies?
Because Paracetamol and diphenhydramine hydrochloride Tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Panadol Night or Panadol NightPain (GlaxoSmithKline Consumer Healthcare (UK) Trading Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Paracetamol and diphenhydramine hydrochloride Tablets?
Because Paracetamol and diphenhydramine hydrochloride Tablets are a generic medicine and as they are bioequivalent to the reference medicine Panadol Night or Panadol NightPain (GlaxoSmithKline Consumer Healthcare (UK) Trading Limited, UK), its possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Paracetamol and diphenhydramine hydrochloride Tablets, see section 4 of the package leaflet available on the MHRA website.

Why were Paracetamol and diphenhydramine hydrochloride Tablets approved?
It was concluded that, in accordance with EU requirements, Paracetamol and diphenhydramine hydrochloride Tablets have been shown to have comparable quality and to be bioequivalent to Panadol Night or Panadol NightPain (GlaxoSmithKline Consumer Healthcare (UK) Trading Limited, UK). Therefore, the MHRA decided that, as for Panadol Night or Panadol NightPain (GlaxoSmithKline Consumer Healthcare (UK) Trading Limited, UK); the benefits are greater than the risks and recommended that Paracetamol and diphenhydramine hydrochloride Tablets can be approved for use.
What measures are being taken to ensure the safe and effective use of Paracetamol and diphenhydramine hydrochloride Tablets?

A risk management plan (RMP) has been developed to ensure that Paracetamol and diphenhydramine hydrochloride Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Paracetamol and diphenhydramine hydrochloride 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 and healthcare professionals will be monitored and reviewed continuously.

Other information about Paracetamol and diphenhydramine hydrochloride Tablets

Agreement for granting a Marketing Authorisation was given on 05 May 2017 by the UK and EU member states Bulgaria, Hungary, Ireland, Iceland, Poland and Romania.

A Marketing Authorisation was granted in the UK on 02 June 2017.

The full PAR for Paracetamol and diphenhydramine hydrochloride Tablets follows this summary.

For more information about treatment with Paracetamol and diphenhydramine hydrochloride Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2017.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th></th>
<th>Introduction</th>
<th>Page 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 7</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 9</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 12</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 12</td>
</tr>
<tr>
<td></td>
<td>Annex 1 – Table of content of the PAR update for MRP and DCP</td>
<td>Page 20</td>
</tr>
</tbody>
</table>
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Actavis Group PTC ehf, a marketing authorisation for the medicinal product, Paracetamol and diphenhydramine hydrochloride Tablets (PL 30306/0766; UK/H/6235/001/DC). The product is a pharmacy medicine (P) indicated for the short term treatment of bedtime symptoms of pain, for example arising from colds and flu, rheumatic and muscle pain, backache, toothache, headache and period pain which is causing difficulty in getting to sleep.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Bulgaria, Hungary, Ireland, Iceland, Poland and Romania as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for the purpose of establishing the expiration of the data protection period is “Panadol Night film-coated tablets” authorised in Ireland on 18th September 1998 with GlaxoSmithKline Consumer Healthcare (Ireland) Limited as marketing authorisation holder. The reference medicinal product in the UK is Panadol Night or Panadol NightPain, which was first authorised to SmithKline Beecham (SWG) Limited (PL 00071/0423) in the UK on 19 January 1996. However this marketing authorisation (MA) was cancelled following a change of ownership application transferring the MA to GlaxoSmithKline Consumer Healthcare (UK) Trading Limited (PL 44673/0076) on 27 April 2016. The above product authorised in Ireland is cited as the European reference medicinal product in all other CMS involved in this procedure. The reference medicinal product used for the bioequivalence study is Panadol Night authorised in Ireland.

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 central nervous system (CNS) than those in the periphery. This fact may partly account for its ability to reduce fever (a central action) and to induce analgesia.

Diphenhydramine is an ethanolamine class antihistamine that acts predominantly as a competitive but reversible inhibitor of histamine at the H1 receptor sites. However, like most H1 antihistamines it has additional sedative anticholinergic (antimuscarinic) and local anaesthetic properties.

One bioequivalence study (conducted under fasting conditions) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS 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 RMS 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS and CMS considered that the application could be approved at the end of procedure on 05 May 2017. After a subsequent national phase, a licence was granted in the UK on 02 June 2017.

II QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains paracetamol 500 mg and diphenhydramine hydrochloride 25 mg as the active ingredients. Other ingredients consist of the pharmaceutical excipients:

**Tablet core**
Cellulose, microcrystalline, crospovidone, Type A, povidone K29-32, stearic acid and anhydrous colloidal silica.

**Tablet coating**
Partially hydrolysed polyvinyl alcohol, titanium dioxide (E171), talc, macrogol/PEG 3350, methacrylic acid-ethyl acrylate copolymer type A, brilliant blue FCF (E133), indigo carmine (E132) and sodium bicarbonate.

The finished product is packed into the following presentations and pack sizes:
- polyvinyl chloride (PVC)/polyvinilidene chloride (PVdC)/aluminium blisters and is available in pack sizes of 8, 12, 16 or 24 tablets.
- High-density polyethylene containers sealed with foil and closed with a child resistant polypropylene cap in a pack size of 50 tablets.

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

II.2 Drug Substances
(1) Paracetamol
INN: Paracetamol
Chemical name: \( N-(4\text{-Hydroxyphenyl})\text{acetamide}. \)
Structural formula:

![Structural formula of paracetamol](image)

Molecular formula: \( \text{C}_8\text{H}_9\text{NO}_2 \)
Molecular mass: 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.

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.
(2) Diphenhydramine hydrochloride
INN: Diphenhydramine hydrochloride
Chemical name: 2-(Diphenylmethoxy)-N,N-dimethylethanamine hydrochloride.

Structural formula:

![Structural formula of Diphenhydramine hydrochloride](image)

Molecular formula: C<sub>17</sub>H<sub>22</sub>ClNO
Molecular mass: 291.8 g/mol
Appearance: White or almost white, crystalline powder.
Solubility: Very soluble in water, freely soluble in ethanol (96 per cent).

Diphenhydramine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious film-coated tablets containing paracetamol 500 mg and diphenhydramine hydrochloride 25 mg per tablet, that are generic versions of the reference product Panadol Night or Panadol NightPain (SmithKline Beecham (SWG) Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film-coating material which complies with a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

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 processes have been validated at commercial scale batch size and have shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. 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 18 months for the blisters with the storage condition ‘Store below 25°C’ and 2 years for the containers with no special storage conditions. The in-use shelf life for the containers is 6 months after first opening.’.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**

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

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**III NON-CLINICAL ASPECTS**

**III.1 Introduction**

As the pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol and diphenhydramine hydrochloride 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)**

A short justification for the absence of a full ERA has been provided. The generic statement argues that as the proposed product is a generic there would be no resultant increase in overall environmental exposure. The justification for absence of an environmental risk assessment is acceptable.

**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 clinical pharmacology of paracetamol and diphenhydramine hydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of paracetamol and diphenhydramine hydrochloride.

Based on the data provided, Paracetamol and diphenhydramine hydrochloride Tablets (Actavis Group PTC ehf, Iceland) can be considered bioequivalent to Panadol Night (GlaxoSmithKline Consumer Healthcare (Ireland) Limited, Ireland).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY 1
A double blinded, randomised, single dose, three way crossover oral bioequivalence study of the applicant’s fixed dose combination of the applicant’s test product Paracetamol and diphenhydramine hydrochloride Tablets (Actavis Group PTC ehf, Iceland) versus the reference product Panadol Night (GlaxoSmithKline Consumer Healthcare (Ireland) Limited, Ireland) in healthy, adult, human subjects under fasting conditions.

A second reference product taken from the Canadian market (reference product 2) was also used in this three way crossover bioequivalence study. However, for the scope of this application only the European reference product, Panadol Night (GlaxoSmithKline Consumer Healthcare (Ireland) Limited, Ireland) will be taken into consideration (reference product 1).

Following an overnight fast of at least 10 hours, subjects were administered a single oral dose of investigational medicinal product (1 x 500 mg paracetamol / 25 mg diphenhydramine hydrochloride tablet of test product or reference product 1 or 1 caplet of reference product 2) with 240 mL of water under fasting conditions.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours for the analyte salicylic acid and 48 hours after each administration. The washout period between the treatment phases was 5 days. The pharmacokinetic results are presented below:
Table: Summary statistics for the pharmacokinetic parameters for paracetamol are presented below (ratio and 90% Confidence Intervals):

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Ratio (%)</th>
<th>90% Confidence Intervals</th>
<th>Intra-%CV</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower 90% CI (%)</td>
<td>Upper 90% CI (%)</td>
<td></td>
</tr>
<tr>
<td>LnAUC_{0\rightarrow t} (μg.hr/mL)</td>
<td>99.20</td>
<td>94.87</td>
<td>103.73</td>
<td>9.97</td>
</tr>
<tr>
<td>LnAUC_{0\rightarrow \infty} (μg.hr/mL)</td>
<td>101.33</td>
<td>97.82</td>
<td>104.97</td>
<td>7.50</td>
</tr>
<tr>
<td>LnC_{max} (ng/mL)</td>
<td>102.57</td>
<td>96.02</td>
<td>109.56</td>
<td>14.79</td>
</tr>
</tbody>
</table>

C_{max} maximum plasma concentration
AUC_{0\rightarrow t} area under the plasma concentration-time curve from zero to t hours
AUC_{0\rightarrow \infty} area under the plasma concentration-time curve from zero to \infty hours

Table: Summary statistics for the pharmacokinetic parameters for diphenhydramine are presented below (ratio and 90% Confidence Intervals):

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Ratio (%)</th>
<th>90% Confidence Intervals</th>
<th>Intra-%CV</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower 90% CI (%)</td>
<td>Upper 90% CI (%)</td>
<td></td>
</tr>
<tr>
<td>LnAUC_{0\rightarrow t} (ng.hr/mL)</td>
<td>98.34</td>
<td>94.20</td>
<td>102.66</td>
<td>9.61</td>
</tr>
<tr>
<td>LnAUC_{0\rightarrow \infty} (ng.hr/mL)</td>
<td>98.28</td>
<td>94.03</td>
<td>102.72</td>
<td>9.88</td>
</tr>
<tr>
<td>LnC_{max} (ng/mL)</td>
<td>97.87</td>
<td>91.84</td>
<td>104.30</td>
<td>14.26</td>
</tr>
</tbody>
</table>

Study Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for paracetamol and diphenhydramine lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Panadol Night (GlaxoSmithKline Consumer Healthcare (Ireland) Limited, Ireland).
IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 and diphenhydramine hydrochloride Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Concomitant use with CNS depressants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concomitant use with Monoamine Oxidase Inhibitors (MAOIs)</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity and skin reactions</td>
</tr>
<tr>
<td></td>
<td>Deliberate or unintentional overdose</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity when used in combination with other products containing paracetamol, in patients with alcoholic liver disease, or in patients with hepatic impairment or renal impairment</td>
</tr>
<tr>
<td></td>
<td>Interaction with anticoagulants; increased risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>Patients prone to seizure</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm, including risk in asthmatic patients sensitive to aspirin or NSAIDs</td>
</tr>
<tr>
<td></td>
<td>Driving and using machines</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>Use in patients &lt;12 years of age</td>
</tr>
<tr>
<td>Missing information</td>
<td>Use in pregnancy and lactation</td>
</tr>
</tbody>
</table>

Routine risk minimisation and pharmacovigilance measures are satisfactory.

IV.7 Discussion on the clinical aspects
There are no objections to the approval of this application from a clinical viewpoint.

V User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI 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 and diphenhydramine hydrochloride is
considered to have demonstrated the therapeutic value of the compounds. The product is bioequivalent to the marketed reference product and the benefit-risk balance is considered similar and positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

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 following text is the approved label text for this medicine, no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**BLISTER CARTON**

1. **NAME OF THE MEDICINAL PRODUCT**

Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains paracetamol 500 mg and diphenhydramine hydrochloride 25 mg.

3. **LIST OF EXCIPIENTS**

Also contains: brilliant blue FCF (E133). Please see enclosed leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

8 Film-coated Tablets
12 Film-coated Tablets
16 Film-coated Tablets
24 Film-coated Tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use
Please 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**

Contains: Paracetamol

Do not take anything else containing paracetamol while taking this medicine.

Talk to a doctor at once if you take too much of this medicine, even if you feel well.

8. **EXPIRY DATE**

EXP
9. **SPECIAL STORAGE CONDITIONS**

Store below 35°C

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

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

MA Holder: Actavis Group PTC eft, Reykjavikurvegi 76-78, Hafnarfjörður, 220, Iceland

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 30306/0766

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

P

15. **INSTRUCTIONS ON USE**

For the relief of the fever, aches and pains associated with colds and flu, headaches, backache, rheumatic and muscle pains, period pains and toothache which is causing difficulty in getting to sleep.

The recommended dosage:
Adults (16 years and over): swallow 2 tablets with water, 20 minutes before you go to bed.
Children aged 12 to 15 years: swallow 1 tablet with water, 20 minutes before you go to bed.

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

Do not take with any other antihistamine-containing products.
Do not give to children under 12 years

16. **INFORMATION IN BRAILLE**

Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets

17. **UNIQUE IDENTIFIER – 2D BARCODE**

<2D barcode carrying the unique identifier included>

18. **UNIQUE IDENTIFIER – HUMAN READABLE DATA**

< PC: (number)
SN: (number)
NN: (number)>
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>MA Holder: Actavis Group PTC ehf</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
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<tr>
<td>EXP</td>
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<tr>
<td><strong>4. BATCH NUMBER</strong></td>
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<tr>
<td>Lot</td>
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<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains paracetamol 300 mg and diphenhydramine hydrochloride 25 mg.

3. LIST OF EXCIPIENTS

Also contains brilliant blue FCF (E133). Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

50 Film-coated Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Please 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

Contains Paracetamol

Do not take anything else containing paracetamol while taking this medicine.

Talk to a doctor at once if you take too much of this medicine, even if you feel well.

8. EXPIRY DATE

EXP
Shelf life after first opening the bottle: 6 months

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: Actavis Group PTC ehf, Reykjavíkurvegi 76-78, Hafnarfjörður, 220, Iceland

12. MARKETING AUTHORISATION NUMBER(S)

PL 30306/0766

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

For the relief of the fever, aches and pains associated with colds and flu, headaches, backache, rheumatic and muscular pains, period pains and toothache which is causing difficulty in getting to sleep.

The recommended dosage:
Adults (16 years and over): swallow 2 tablets with water, 20 minutes before you go to bed.
Children aged 12 to 15 years: swallow 1 tablet with water, 20 minutes before you go to bed.

Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

Do not take with any other antihistamine-containing products.

Do not give to children under 12 years

16. INFORMATION IN BRAILLE

Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<PC: {number}>

SN: {number}

NV: {number}>
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**LABEL FOR TABLET CONTAINER**

1. **NAME OF THE MEDICINAL PRODUCT**

Paracetamol and diphenhydramine hydrochloride 500mg/25mg Film-coated Tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains paracetamol 500 mg and diphenhydramine hydrochloride 25 mg.

3. **LIST OF EXCIPIENTS**

Also contains brilliant blue FCF (E133).
Please see the enclosed leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

50 Film-coated Tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use
Please 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**

Contains Paracetamol
Do not take anything else containing paracetamol while taking this medicine.
Talk to a doctor at once if you take too much of this medicine, even if you feel well.

8. **EXPIRY DATE**

EXP
Shelf life after first opening the bottle: 6 months

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

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Do not take with any other antihistamine-containing products.

Do not give to children under 12 years

16. INFORMATION IN BRAILLE

N/A

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

- PC: (number)
- SN: (number)
- NS: (number)
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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