Public Assessment Report

Decentralised Procedure

Paracetamol 500mg/5ml Oral Solution

(paracetamol)

Procedure No: UK/H/6069/001/DC

UK Licence No: PL 29831/0593

Wockhardt UK Limited
LAY SUMMARY

Paracetamol 500mg/5ml Oral Solution
(Paracetamol)

This is a summary of the Public Assessment Report (PAR) for Paracetamol 500mg/5ml Oral Solution (PL 29831/0593; UK/H/6069/001/DC). It explains how the application for Paracetamol 500mg/5ml Oral Solution was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Paracetamol 500mg/5ml Oral Solution.

For practical information about using Paracetamol 500mg/5ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Paracetamol Oral Solution’ in this report.

What is Paracetamol Oral Solution and what is it used for?
Paracetamol Oral Solution is a medicine with ‘well-established use’. This means that the medicinal use of the active substance (paracetamol) of Paracetamol Oral Solution is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

This medicine is a higher strength Paracetamol Oral Solution.

Paracetamol Oral Solution is used in adults and adolescents over 16 years old in the treatment of mild to moderate pain when the patient cannot take other paracetamol formulations such as lower strength liquid paracetamol, effervescent tablets or tablets.

How does Paracetamol Oral Solution work?
Paracetamol Oral Solution contains the active substance paracetamol. Paracetamol belongs to a group of medicines called pain-killers or analgesics.

How is Paracetamol Oral Solution used?
Paracetamol Oral Solution should be taken by mouth only. This medicine should be taken as advised by the patient’s doctor or pharmacist. If unsure, the patient should read the label and ask his/her doctor or pharmacist.

How to take
• This medicine contains 500mg of paracetamol in one 5ml dose.
• The bottle should be shaken for at least 10 seconds before use.
• The patient should always use the oral dosing syringe supplied with the pack. Please refer to the package leaflet for instructions on how to use the oral dosing syringe to measure and take a dose.

How much to take
Adults and adolescents over 16:
• 500mg (5ml) to 1000mg (10ml) up to three to four times a day, as required. Maximum daily intake should not exceed 4g (40ml).

How often to take
• Take a dose of this medicine every 4 to 6 hours when needed.
• Do not take more than 4 doses in 24 hours.
Do not exceed the stated dose.

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

Paracetamol Oral Solution can only be obtained with a prescription.

What benefits of Paracetamol Oral Solution have been shown in studies?

As paracetamol is a well-known substance and its use in the treatment of mild to moderate pain in adults and adolescents over 16 years old is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of paracetamol in the treatment of mild to moderate pain in adults and adolescents over 16 years old.

What are the possible side effects of Paracetamol Oral Solution?

Like all medicines Paracetamol Oral Solution can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Paracetamol Oral Solution, see section 4 of the package leaflet.

Also, for the full list of restrictions, see the package leaflet for Paracetamol Oral Solution.

Why is Paracetamol Oral Solution approved?

The MHRA concluded that, in accordance with EU requirements, the benefits of Paracetamol Oral Solution outweigh the identified risks and recommended that the product be approved for Paracetamol Oral Solution.

What measures are being taken to ensure the safe and effective use of Paracetamol Oral Solution?

A Risk Management Plan has been developed to ensure that Paracetamol Oral Solution is 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 Oral Solution, 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 Oral Solution

Ireland and the UK agreed to grant a Marketing Authorisation for Paracetamol Oral Solution on 28 April 2016. A Marketing Authorisation was granted in the UK to Wockhardt UK Limited on 20 May 2016.

The full PAR for Paracetamol Oral Solution, solution follows this summary.

For more information about treatment with Paracetamol Oral Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2016.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I Introduction Page 5
II Quality aspects Page 5
III Non-clinical aspects Page 7
IV Clinical aspects Page 8
V User consultation Page 11
VI Overall conclusion, benefit/risk assessment and recommendation Page 12
Annex 1 - Table of content of the PAR update for MRP and DCP Page 18
Scientific discussion

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

Mr: 151.2

Structural formula:

![Structural formula of Paracetamol](image)

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.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.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 $T_{\text{max}}$ 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 $T_{\text{max}}$ 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 $T_{\text{max}}$ 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:

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<th>Summary of safety concerns</th>
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<td><strong>Important identified risks</strong></td>
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**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.**

<table>
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<th>Important potential risks</th>
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<td>- Medication errors.</td>
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<td>- Use in patients with asthma.</td>
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<td>- Use for more than three days.</td>
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<tr>
<td>- Use in elderly patient population.</td>
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<td>- Use during pregnancy and breastfeeding.</td>
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**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.

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.
Paracetamol 500mg/5ml Oral Solution

Each 5ml of solution contains 500mg of paracetamol
Contains glycerol, propylene glycol, methylparaben (E218), propylparaben (E216) and sunset yellow (E110). Read the package leaflet for further information.

Contains Paracetamol
Do not take any other paracetamol-containing products while taking this medicine
Do not exceed the stated dose
Talk to a doctor at once if you take too much of this medicine, even if you feel well
Keep out of the sight and reach of children

Store below 25°C. Do not refrigerate or freeze. Store in the original bottle. Once opened the product should be used within 3 months
Dose: As directed by your doctor
Read the package leaflet before use
Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor
Use the syringe supplied in the pack to measure the prescribed dose

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

107576/1 221881 MH/DRUGS/AD/091
Paracetamol 500mg/5ml Oral Solution

Each 5ml of solution contains 500mg of paracetamol.

Contains: paracetamol, propylene glycol, methylparaben, propylparaben, and E102.

Read the package leaflet for further information.

For oral use

Paracetamol 500mg/5ml Oral Solution (sugar free)

Contains Paracetamol

Do not take any other paracetamol-containing products while taking this medicine.

Do not exceed the stated dose.

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

Keep out of the sight of and reach of children.

Store below 25°C.

Do not refrigerate or freeze.

Keep in the original bottle.

Once opened, the product should be used within 3 months.

Dosage: As directed by your doctor.

Read the package leaflet before use.

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

Use the syringe supplied in the pack to measure the prescribed dose.

POM

Prescribing Notes:

600mm x 600mm

should be kept unprinted and blank

without pre-printed text or colour

for the year, expiry date,

Batch Number & (2D code)

Marketing Authorization Holder:

Wockhardt UK Ltd, Ash Road North,

Wrexham, LL13 1WX, UK.

PL 2983/0195

PA 131346/011

UK/H/6069/001/DC
Each 5ml of solution contains 500mg of paracetamol. Contains glycerol, propylene glycol, methylparahydroxybenzoate (E218), propylparahydroxybenzoate (E216), sunset yellow (E110).

Read the package leaflet for further information.

Contains Paracetamol
Do not take any other paracetamol-containing products while taking this medicine.

Do not exceed the stated dose.
Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Keep out of the sight and reach of children.

Store below 25°C, Do not refrigerate or freeze. Store in the original bottle. Once opened the product should be used within 3 months.

Dose: As directed by your doctor. Read the package leaflet before use.

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

Use the syringe supplied in the pack to measure the prescribed dose.

Marketing Authorisation Holder: Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK 107572/1 221800 MH/DRUGS/AD/091.
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

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