**Public Assessment Report**

**National Procedure**

**<NAME(S) OF PRODUCT(S) FROM SmPC(S)>**

**<active substance(s)/common name(s)>**

**<PRODUCT LICENCE NUMBER(S)>**

**<MAH Name>LAY SUMMARY**

**<PLEASE NOTE THAT THIS LAY SUMMARY IS INTENDED TO BE INFORMATIVE TO THE PATIENT AND SHOULD CONTAIN NON-PROMOTIONAL INFORMATION TO HELP PATIENTS UNDERSTAND MORE ABOUT THEIR MEDICINES.>**

**< name of product(s) from SmPC(s), including pharmaceutical form and strength(s)> i.e. <X>**

**<active substance(s)/common name(s)>**

This is a summary of the Public Assessment Report (PAR) for <X>. It explains how this product/these products was/were assessed and its/their authorisation recommended, as well as its/their conditions of use. It is not intended to provide practical advice on how to use this product/these products.

<*If necessary, include shortened name and the following text*:

This product/These products will be referred to as <XX> in this lay summary for ease of reading.> (***Note****: if shortened name is to be used, XX should replace all mentions of X in text below.)*

For practical information about using <X>, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

**What is <X> and what is it used for?**

This application/These applications is/are for a medicine that is a “fixed combination”. This means that the medicine is composed of two or more active substances that are already in clinical use.

<X is used in the treatment of/X can be used by patients who…>

*<Include the relevant information on indications, e.g. copy the relevant information from PIL section “What X is and what is it used for”. Note that the PL is directed to the patient, rewrite accordingly if necessary.>*

**How does <X> work?**

<*Copy the relevant information from Section 1 of the PL “What X is and what is it used for”.>*

**How is <X> used?** **<AVOID USING GRAPHICS, TEXT ONLY>**

The pharmaceutical form of this medicine is <pharmaceutical form> and the route of administration is <route of administration>.

*<This section should include: pharmaceutical form(s); main dosing recommendations; route/method of administration; duration of treatment if specified; need for any specific monitoring of certain parameters or for diagnostic tests; prescription status.>*

For further information on how <X> is used, refer to the PIL and Summary/Summaries of Product Characteristics (SmPC(s)) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**Either:**

<This medicine can only be obtained with a prescription.>

**Or:**

<This medicine can be obtained without a prescription.>

**Either (if being administered by the patient themselves):**

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

**Or (if being administered by a healthcare practitioner):**

<The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.>

**What benefits of <X> have been shown in studies?**

**Either**

As the active substances in this medicine are already in clinical use, data were provided from studies to show the benefits of these when given in one fixed combination medicine. These studies showed…

*<A brief description should be provided of what the studies showed for the fixed combination versus placebo or active comparator.>*

**What are the possible side effects of <X>?**

For the full list of all side effects reported with this medicine/these medicines, see Section 4 of the PIL or the Summary/Summaries of Product Characteristics (SmPC) available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at <https://yellowcard.mhra.gov.uk> or search for ‘MHRA Yellow Card’ online. By reporting side effects, patients can help provide more information on the safety of this medicine.

**Either**

The most common side effects with <X> (which may affect more than 1 in 10 people) are….

*<The list of side effects should be taken from Section 4 of the Patient Information Leaflet>*

**Or**

Because<X>is a line extension of the existing product(s) <Y>, its benefits and possible side effects are taken as being the same as <Y>.

**Why was <X> approved?**

It was concluded that the data provided from studies using this/these fixed-combination product(s) showed that <X> is effective in the treatment of… Furthermore, the side effects observed with use of this product/these products are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

*If applicable include the following statement:*

**Either**

<X> has been authorised under “exceptional circumstances”. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. Any new information on < X> will be reviewed every year and this report will be updated as necessary.>

<<X> has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. See section below “What measures are being taken to ensure the safe and effective use of <X>?”

**What measures are being taken to ensure the safe and effective use of <X>?**

**<PLEASE COMPILE FROM RELEVANT SECTIONS OF THE RISK MANAGEMENT PLAN>**

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for <x> The RMP details the important risks of <x>, how these risks can be minimised, any uncertainties about <x> (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for <x>:

Important identified risks: <complete as applicable or state “None”>

Important potential risks: <complete as applicable or state “None”>

Missing information: <complete as applicable or state “None”>

<or>

<if applicable: There are no safety concerns associated with use of <x>.>

<if applicable: describe additional risk management measures (also mentioned in the AR), such as obligations to provide educational materials, establish patient registries, or carry out further studies e.g. in specific populations or for long-term safety/efficacy data.>

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients.  Side effects of <x> are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this/these application(s) and are satisfactory.

**Other information about <X>**

A Marketing Authorisation/Marketing Authorisations for <X> was/were granted in the United Kingdom (UK) on <date of issue of the Marketing Authorisation(s)>.

The full PAR for <X> follows this summary.

This summary was last updated in February 2024.

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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) considered that the application(s) for <Name(s) of the product(s) from the SmPC> (<Product licence number(s)>) could be approved.

The product is indicated for the treatment of the following:

*<Include the relevant information on indications, copied from the SmPC(s)>*

<Name(s) of the active substances> ….

*<Include a summary of the mechanism of action of each active substance, taken from the Overview of the assessment report (MRP/DCP) or from the national assessment report/Module 2 summaries or Section 5.1 of the SmPC>*

This/These application(s) was/were approved under Regulation 55 of The Human Medicines Regulation 2012, as amended (previously Article 10b of Directive 2001/83/EC, as amended), as (a) fixed combination application(s)*.<A description of the data required for this application should be provided here, on a case-by-case basis>*

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this/these application(s) and are satisfactory.

**<For applications referred to CHM>**Advice was sought from the Commission of Human Medicines (CHM) on <state dates(s) of CHM discussions> because….

*<A brief description of the main non-clinical/clinical reason(s) (but not quality as commercially confidential) that the application(s) was/were referred to CHM should be given and how the issue(s) was resolved.>*

A national marketing authorisation(s) were granted in the United Kingdom (UK) on <state date of UK national licence(s) grant>.

II QUALITY ASPECTS

**II.1 Introduction**

This/These product(s) consist(s) of…

*<Include the relevant information from Section 2 of the SmPC(s) that describes each product>*

In addition to <state active substance(s)>, this/these product(s) also contain the excipients <list excipients, as per Section 6.1 of the SmPC(s)>.

The finished product(s) is/are packaged in <list packaging, as per Section 6.5 of the SmPC(s)>. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

**II.2 ACTIVE SUBSTANCE(S)**

**rINN: <state active substance rINN>**

Chemical Name: <state chemical name, as per the Quality assessment report or Module 3.2.S>

Molecular Formula: <state molecular formula, as per the Quality assessment report or Module 3.2.S>

Chemical Structure: <provide chemical structure, as per the Quality assessment report or Module 3.2.S>

Molecular Weight: <state molecular weight, as per the Quality assessment report or Module 3.2.S>

Appearance: <state appearance, as per the Quality assessment report or Module 3.2.S>

Solubility: <state solubility, as per the Quality assessment report or Module 3.2.S>

**Either**

<Name of active substance> is the subject of a European Pharmacopoeia monograph.

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

*<Please note that if the packaging and retest period have not been covered by the EDQM certificate, these will have been assessed by the Quality assessor and so the following should be added>*

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

**Or**

<The information related to the active substance was provided in an ASMF.  The Active substance is the subject of a Ph.Eur. monograph.>

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

*<Repeat the above for each active substance in the medicinal product(s)>*

**II.3 DRUG PRODUCT(S)**

**Pharmaceutical development**

A satisfactory account of the pharmaceutical development has been provided.

***<If any physico-chemical comparisons with the individual products are made (such as dissolution and impurity profiles), these should be stated here.***

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

**Either**

No excipients of animal or human origin are used in the finished product(s).

**Or**

With the exception of <state excipient>, no excipients of animal or human origin are used in the final products. *<State whether any EDQM certificates have been provided for the excipients of animal origin>*

<If appropriate: The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.>

<If appropriate: Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.>

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

**Manufacture of the product(s)**

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product(s), along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification(s)**

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of <INSERT SHELF LIFE FROM SMPC>, with the storage conditions <INSERT STORAGE CONDITIONS FROM THE SMPC>, is acceptable.

**<ADDITIONAL SHELF-LIFE/STORAGE CONDITIONS, SUCH AS FROM IN-USE STABILITY STUDIES OR AFTER RECONSTITUTION CAN BE ADDED HERE.>**

**<If applicable>** 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**

The grant of (a) marketing authorisation(s) is recommended.

III NON-CLINICAL ASPECTS

**III.1 Introduction**

**Either**

As this/these application(s) are for a combination of active substances that are already in clinical use, no new non-clinical data were submitted and none were required.

**Or**

The following non-clinical studies were submitted with this/these applications:

***<A list of studies should be provided>***

All studies were conducted in accordance with current Good Laboratory Practice (GLP).

**III.2 Pharmacology**

**Either**

No new pharmacology data were provided and none were required for this/these application(s).

**Or**

***<A summary of the main conclusions from the pharmacology studies should be provided here>***

**III.3 Pharmacokinetics**

**Either**

No new pharmacokinetic data were provided and none were required for this/these application(s).

**Or**

***<A summary of the main conclusions from the pharmacokinetic studies should be provided here>***

**III.4 Toxicology**

**Either**

No new toxicology data were provided and none were required for this/these application(s).

**Or**

***<A summary of the main conclusions from the toxicology studies should be provided here>***

**III.5 Ecotoxicity/Environmental Risk Assessment**

**Either**

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application(s) is/are for a product(s) that are intended to be used in place of other products that are already marketed, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation(s) for the proposed product(s).

**Or**

An Environmental Risk Assessment (ERA) has been provided. The results of the ERA show that there is no risk of increased environmental exposure with the use of this/these product(s).

*<You may need to present some results from the conclusion of the ERA assessment here>*

**III.6 Discussion on the non-clinical aspects**

***<Any meaningful discussion of the non-clinical studies can be presented here>***

The grant of (a) marketing authorisation(s) is recommended.

IV CLINICAL ASPECTS

**IV.1 Introduction**

The following clinical studies were submitted with this/these applications:

***<A list of studies should be provided>***

All studies were conducted in line with current Good Clinical Practice (GCP).

**IV. 2 Pharmacokinetics**

**Either**

No new pharmacokinetic data have been submitted for this/these application(s) and none were required.

**Or**

In support of the application(s), the following was/were submitted:

<PHARMACOKINETIC STUDY 1>

This study was a… *<A one-sentence description of the study should be included here, including whether it is open- or closed-label, randomised or non-randomised, how many treatments, how many periods, how many sequences, single- or multiple-dose, crossover or parallel study>* comparing the test product <STATE TEST PRODUCT> versus the reference product(s) <STATE REFERENCE PRODUCT(S)> in subjects/patients under fasted/fed conditions.

Subjects were administered…*<A one- or two-sentence description of the drug administration should be provided, including whether it is single or multiple dosing of test/reference products, and when these are taken in relation to meals>*. Blood samples were taken pre-dose and up to <X> hours post dose, with a washout period of <Y> days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

*<A summary table should be provided for each active variable measured, including Test and Reference calculations used to show the main conclusions of the study (such as bioequivalence with another product). More than one summary table may be required if there is more than one active variable being measured or more than one reference product used in comparison with the test product.>*.

<PHARMACOKINETIC STUDY 2>

*<In instances where more than one pharmacokinetic study was performed, each should be described as per above>*.

**IV.3 Pharmacodynamics**

**Either**

No new pharmacodynamic data have been submitted for this/these application(s) and none were required.

**Or**

In support of the application(s), the following was/were submitted:

<PHARMACODYNAMIC STUDY 1>

This study was a… <A one-sentence description of the study should be included here, including whether it is open- or closed-label, randomised or non-randomised, how many treatments, how many periods, how many sequences, single- or multiple-dose, crossover or parallel study> comparing the <STATE PARAMETER BEING TESTED> for the test product <STATE TEST PRODUCT(S)> versus the reference product(s) <STATE REFERENCE PRODUCT(S)> in subjects/patients under fasted/fed conditions.

Subjects/patients were administered…<A one- or two-sentence description of the drug administration should be provided, including whether it is single or multiple dosing of test/reference products, and when these are taken in relation to meals.> <Details should also be provided of the method of measurements and how frequently these were collected.>

A summary of the pharmacodynamic results for the test and reference products are presented below:

<A summary table should be provided for each pharmacodynamic variable assessed, including the data that is intended to show therapeutic equivalence between the test and reference products.>

<PHARMACODYNAMIC STUDY 2>

<In instances where more than one pharmacodynamic study was performed, each should be described as per above>.

**IV.4 Clinical efficacy**

**Either**

No new efficacy data have been submitted for this/these application(s) and none were required.

**Or**

In support of the application(s), the following was/were submitted:

<EFFICACY STUDY 1>

***<A suitable description of the study should be provided here, including the main objective(s) of the study, details of the study population (main inclusion/exclusion criteria), the methodology (duration of study, dosing, timepoints, etc), the main efficacy parameter(s)/endpoint(s) measured, any analysis of these parameter(s)/endpoint(s), the main results of the study and conclusion. This should be available in the clinical assessment report.>***

<EFFICACY STUDY 2>

<In instances where more than one efficacy study was performed, each should be described as per above>.

**IV.5 Clinical safety**

<An overview of the safety profile of the product, as assessed in the clinical assessment report should be presented>.

**IV.6 Risk Management Plan (RMP)**

**Either**

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

**Or**

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional < if applicable: pharmacovigilance> <and> < if applicable: risk minimisation> measures have been proposed:

<Insert table of risk minimisation and additional pharmacovigilance measures from part VI ‘II.B Summary of important risks’ of the final RMP in the case folder>.

This is acceptable.

**IV.7 Discussion on the clinical aspects**

**Either**

The grant of (a) marketing authorisation(s) is recommended for this/these application(s).

**Or**

<A review of the conclusions from the studies submitted should be presented here. This should be taken from the clinical assessment report>

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

<Or>

A text draft of the Patient Information Leaflet (PIL) was presented. A commitment to provide a mock-up and evidence of user consultation of the PIL to the MHRA prior to marketing was accepted.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product(s) is acceptable, and no new non-clinical or clinical safety concerns have been identified.

**Either:**

Clinical experience with <name of actives> is considered to have demonstrated the therapeutic value of the combination. The benefit/risk is, therefore, considered to be positive.

**Or**

The study(ies) submitted show that this/these fixed combination product(s) are as effective as the monocomponents given separately at the same dose level, and that there is no interaction between the two active substances.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Application type** | **Scope** | **Product information affected** | **Date of grant** | **Outcome** | **Assessment report attached**  **Y/N** |
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