UK Public Assessment Report

Aprodip 1.5 mg prolonged-release tablets

(indapamide)

UK Licence No: PL 20117/0221

Morningside Healthcare Ltd
LAY SUMMARY
Aprodip 1.5 mg prolonged-release tablets
(indapamide)

This is a summary of the public assessment report (PAR) for Aprodip 1.5 mg prolonged-release tablets (PL 20117/0221). It explains how Aprodip 1.5 mg prolonged-release tablets were assessed and their authorisation recommended as well as the conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Aprodip 1.5 mg prolonged-release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Aprodip 1.5 mg prolonged-release tablets and what are they used for?
Aprodip 1.5 mg prolonged-release tablets is a generic medicine. This means that this medicinal product is similar to a ‘reference medicine’ already authorised in the UK called Natrilix SR 1.5 mg tablets (Les Laboratoires Servier; PL 05815/0010).

Aprodip 1.5 mg prolonged-release tablets are intended to reduce high blood pressure (hypertension).

How are Aprodip 1.5 mg prolonged-release tablets used?
Aprodip 1.5 mg prolonged-release tablets are taken by mouth. The whole tablet should be swallowed with a drink of water with or without food.

The usual dose in adults and elderly is one tablet, once a day, taken in the morning.

Aprodip 1.5 mg prolonged-release tablets can only be obtained on prescription from a doctor.

For further information on how Aprodip 1.5 mg prolonged-release tablets are used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How do Aprodip 1.5 mg prolonged-release tablets work?
The active ingredient in Aprodip 1.5 mg prolonged-release tablets, indapamide, is a diuretics. This medicine works by increasing the amount of urine produced in the body.

How have Aprodip 1.5 mg prolonged-release tablets been studied?
Because Aprodip 1.5 mg prolonged-release tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Natrilix SR 1.5 mg tablets (Les Laboratoires Servier, France). The product used in the bioequivalence study was Fludex LP 1.5mg tablets (Les Laboratoires Servier, France), which is the same product as Natrilix SR 1.5 mg tablets, but is marketed under a different brand name. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Aprodip 1.5 mg prolonged-release tablets?
As Aprodip 1.5 mg prolonged-release tablets is a generic medicine of the reference medicine, Natrilix SR 1.5 mg tablets, its benefits and risks are taken as being the same as those of Natrilix SR 1.5 mg tablets.

Why are Aprodip 1.5 mg prolonged-release tablets approved?
It was concluded that, in accordance with EU requirements, Aprodip 1.5 mg prolonged-release tablets have been shown to have comparable quality and to be bioequivalent to Natrilix SR 1.5 mg tablets. Therefore, the view was that, as for Natrilix SR 1.5 mg tablets, the benefit outweighs the identified risk.
What measures are being taken to ensure the safe and effective use of Aprodip 1.5 mg prolonged-release tablets?
A satisfactory pharmacovigilance system has been provided to monitor the safety of this product.

Other information about Aprodip 1.5 mg prolonged-release tablets
A Marketing Authorisation was granted in the UK on 03 March 2016.

The full PAR for Aprodip 1.5 mg prolonged-release tablets follows this summary.

For more information about treatment with Aprodip 1.5 mg prolonged-release tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2016.
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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 Morningside Healthcare Ltd a Marketing Authorisation for the medicinal product Aprodip 1.5 mg prolonged-release tablets (PL 20117/0221). This is a prescription only medicine (POM) indicated for essential hypertension.

This application was submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant has cross-referred to Natrilix SR 1.5 mg tablets (PL 05815/0010), first authorised to Les Laboratoires Servier on 09 January 1996. The product used for the purpose of the bioequivalence studies is Fludex LP 1.5 mg tablets (Servier Laboratoires Limited, France PL 05815/0010).

Aprodip 1.5 mg prolonged-release tablets contain the active substance, indapamide. Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Three bioequivalence studies were submitted to support this application, comparing the test product Indapamide 1.5 mg sustained release tablets with the clinical reference product Fludex LP 1.5 mg tablets (Les Laboratoires Servier, France) in healthy adult subjects, under fasting, fed and fed steady state (multi-dose) conditions. The applicant has stated that the bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

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 manufacturing and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

A detailed description of the pharmacovigilance system has been provided with this application and this is satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Aprodip 1.5 mg prolonged-release tablets outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction
This product is a prolonged-release tablet and contains 1.5 mg indapamide, as the active ingredient. The excipients present are lactose monohydrate, starch, pregelatinised (maize starch), hypromellose, silica, colloidal anhydrous, magnesium stearate making up the tablet core, and film coat consists of hypromellose, macroglol 6000 and titanium dioxide (E171). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the Tablets is of vegetable origin.

The finished product is packaged in polyvinylchloride (PVC)/aluminium blisters containing 10, 14, 15, 20, 30, 50, 56, 60, 84, 90 and 100 tablets.

Not all pack sizes may be marketed.

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: Indapamide
Chemical name(s): - 3-(aminosulfonyl)-4-chloro-N-(2,3-dihydro-2-methyl-1H-indol-1-yl)benzamide
- 4-chloro-N-(2-methyl-1-indolinyl)-3-sulfamoylbzamide
- 4-Chloro-N-[(2R)-2-methyl-2,3-dihydro-1H-indol-1-yl]-3-sulfamoylbzamide (Ph. Eur.)
- N-(3-sulfamoyl-4-chlorobenzamido)-2-methylindoline

Structure:

Molecular formula: C_{16}H_{16}ClN_{3}O_{3}S
Molecular weight: 365.8 g/mol
Appearance: white or almost white powder.
Solubility: Indapamide is practically insoluble in water, soluble in ethanol (96%) and slightly soluble in ether.

Indapamide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, indapamide, 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, prolonged-release tablets containing 1.5 mg indapamide that are bioequivalent to the innovator product, Natrilix SR 1.5 mg tablets (Les Laboratoires Servier, France).

Comparative dissolution and impurity profiles have been presented for the proposed and reference products.

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. A validation report for commercial scale batches has been provided. The process validation data provided is satisfactory.

Finished Product Specification
The finished product specification is 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 of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 5 years with no special storage conditions is set.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of indapamide are well known. As indapamide is a widely used, well-known active substance, no new non-clinical data have been supplied and none are required for applications of this type. An overview based on the literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type.
III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed product is intended for generic substitution, this will not lead to an increased exposure to the environment. 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 product from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
The pharmacokinetic, pharmacodynamic, clinical efficacy and safety properties of indapamide are well known. With the exception of the bioequivalence data, no new clinical data have been submitted and none are required for applications of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted three bioequivalence studies under fasting, fed and fasting steady state (multi-dose) conditions.

Study 1
This is a two-period, two-sequence, cross over single dose bioequivalence study comparing the pharmacokinetics of the test product Indapamide 1.5 mg sustained release tablets with the reference product Fludex LP 1.5 mg tablets (Les Laboratoires Servier, France) in healthy adult subjects, under fasting conditions.

The blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 144.0 hours post dose, after each administration. The two dosing periods were separated by a wash-out period of 11 days.

Result
Geometric Least Square Mean, Ratios and 90% Confidence Interval for Indapamide

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<th>Parameter</th>
<th>Test value (test/reference)</th>
<th>Lower 90% CL</th>
<th>Upper 90% CL</th>
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<tr>
<td>AUC_{0-4}</td>
<td>108.989</td>
<td>97.778</td>
<td>121.485</td>
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<td>AUC_{0-inf}</td>
<td>107.616</td>
<td>97.667</td>
<td>118.580</td>
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<tr>
<td>C_{max}</td>
<td>100.049</td>
<td>89.891</td>
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Study 2
This is a two-period, two-sequence, cross over single dose bioequivalence study comparing the pharmacokinetics of the test product Indapamide 1.5 mg sustained release tablets with the reference product Fludex LP 1.5 mg tablets (Les Laboratoires Servier, France) in healthy adult subjects, under fed conditions.

The blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 144.0 hours post dose, after each administration. The two dosing periods were separated by a wash-out period of 10 days.

Geometric Least Square Mean, Ratios and 90% Confidence Interval for Indapamide

<table>
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<td>C_{max}</td>
<td>94.269</td>
<td>84.810</td>
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Study 3
This is a two-period, two-sequence, multiple-dose, cross over bioequivalence study comparing the pharmacokinetics of the test product Indapamide 1.5 mg sustained release tablets with the reference product Fludex LP 1.5 mg tablets (Les Laboratoires Servier, France) in healthy adult subjects, under fasting conditions.

The blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 144.0 hours post dose, after each administration. The two dosing periods were separated by a wash-out period of 8 days.

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Conclusion
The 90% confidence intervals for C\text{max}, C\text{min} and AUC were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Indapamide 1.5 mg sustained release tablets) and the reference formulation (Fludex LP 1.5 mg tablets) under fasting, fed and at steady state conditions.

IV.3 Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Pharmacovigilance System
A satisfactory pharmacovigilance system has been provided to monitor the safety of this product.

IV.7 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

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, as amended. The language used for the purpose of user testing the package information leaflet (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 AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with indapamide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

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

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