Public Assessment Report

Decentralised Procedure

TELMISARTAN DR REDDY’S 20 MG TABLETS
TELMISARTAN DR REDDY’S 40 MG TABLETS
TELMISARTAN DR REDDY’S 80 MG TABLETS
(telmisartan)

Procedure No: UK/H/5034/001-003/DC

UK Licence No: PL 08553/0478-80

Dr. Reddy’s Laboratories (UK) Limited
LAY SUMMARY

On 21 April 2013, Germany, Romania and the UK agreed to grant Marketing Authorisations to Dr Reddy’s Laboratories (UK) Limited for the medicinal products Telmisartan Dr Reddy’s 20 mg (Germany and UK only), 40 mg and 80 mg Tablets (PL 08553/0478-80; UK/H/5034/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, Marketing Authorisations were granted in the UK on 22 May 2013.

This is a prescription-only medicine (POM) containing the active ingredient telmisartan. It is used to treat essential hypertension (high blood pressure) in adults and to reduce cardiovascular events (i.e. heart attack or stroke) in adults who are at risk. This product belongs to a group of medicines called angiotensin II receptor antagonists. Angiotensin II is produced in the body and causes blood vessels to narrow, increasing blood pressure. Telmisartan blocks the effects of angiotensin II so that the blood vessels relax and the pressure is lowered.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Telmisartan Dr Reddy’s 20 mg, 40 mg and 80 mg Tablets outweigh the risks and Marketing Authorisations were granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure .................................................... Page 4
Module 2: Summary of Product Characteristics .................................................. Page 5
Module 3: Patient Information Leaflet ............................................................... Page 6
Module 4: Labelling .............................................................................................. Page 7
Module 5: Scientific discussion during initial assessment ................................. Page 9

I Introduction
II About the product
III Scientific overview and discussion
   III.1 Quality aspects
   III.2 Non-clinical aspects
   III.3 Clinical aspects
IV Overall conclusion and benefit-risk assessment

Module 6 Steps taken after initial procedure ..................................................... Page 16
## Module 1
### Information about initial procedure

| Product Name       | Telmisartan Dr Reddy’s 20mg tablets  
|                   | Telmisartan Dr Reddy’s 40mg tablets  
|                   | Telmisartan Dr Reddy’s 80mg tablets  
| Type of Application| Generic, Article 10(1)               
| Active Substances  | Telmisartan                           
| Form               | Tablets                               
| Strength           | 20 mg, 40 mg and 80 mg                
| MA Holder          | Dr Reddy’s Laboratories (UK) Ltd, 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, UK 
| Reference Member State (RMS) | UK                                  
| Concerned Member States (CMS) | UK/H/5034/001/DC: Germany  
|                    | UK/H/5034/002-3/DC: Germany and Romania 
| Procedure Number   | UK/H/5034/001-3/DC                   
| Timetable          | Day 210 – 21 April 2013              

Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

The following text is the approved label text for Dr Reddy’s 20 mg, 40 mg and 80 mg Tablets (PL 08553/0478-80; UK/H/5034/001-3/DC). No label mock-ups have been provided for these products. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT
   Telmisartan 20 mg Tablets
   Telmisartan 40 mg Tablets
   Telmisartan 80 mg Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)
   Each tablet contains 20 mg telmisartan.
   Each tablet contains 40 mg telmisartan.
   Each tablet contains 80 mg telmisartan.

3. LIST OF EXCIPIENTS
   N/a

4. PHARMACEUTICAL FORM AND CONTENTS
   28 tablets
   56 tablets
   98 tablets

   28 tablets
   56 tablets
   98 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
   For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
   Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
   N/a

8. EXPIRY DATE
   EXP

9. SPECIAL STORAGE CONDITIONS
   This medicinal product does not require any special storage conditions.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
    Dr. Reddy’s Laboratories (UK) Ltd., 6 Riverview Road, Beverley, HU17 0LD

12. MARKETING AUTHORISATION NUMBER(S)
    PL 08553/0478
    PL 08553/0479
    PL 08553/0480
13. BATCH NUMBER
BN
14. GENERAL CLASSIFICATION FOR SUPPLY
POM

15. INSTRUCTIONS ON USE
Take as directed by your doctor.

16. INFORMATION IN BRAILLE
Telmisartan 20 mg Tablets
Telmisartan 40 mg Tablets
Telmisartan 80 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

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<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
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<tr>
<td>Telmisartan 40 mg Tablets</td>
</tr>
<tr>
<td>Telmisartan 80 mg Tablets</td>
</tr>
</tbody>
</table>

| 2. NAME OF THE MARKETING AUTHORISATION HOLDER |
| Dr. Reddy’s Laboratories (UK) Ltd. |

| 3. EXPIRY DATE |
| EXP |

| 4. BATCH NUMBER |
| BN |

| 5. OTHER |
| n/a |
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Telmisartan Dr Reddy’s 20 mg, 40 mg and 80 mg Tablets (PL 08553/0478-80; UK/H/5034/001-3/DC) could be approved. The applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Romania (UK/H/5034/002-3/DC only) and Germany as Concerned Member States (CMS).

These products are prescription-only medicines (legal classification POM).

These applications were made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Micardis 20 mg, 40 mg and 80 mg Tablets (Boehringer Ingelheim International GmbH), which were initially granted Marketing Authorisations in the EU on 07 September 1999 (20 mg) and 11 December 1998 (40 mg and 80 mg). The reference product used in the bioequivalence study was Micardis 80 mg Tablets (Boehringer Ingelheim International GmbH).

Telmisartan Dr Reddy’s 20 mg, 40 mg and 80 mg Tablets are indicated for the treatment of essential hypertension in adults and for the reduction of cardiovascular morbidity in adults with manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage.

Telmisartan is a long-acting nonpeptide angiotensin II receptor (type AT1) antagonist. It lowers blood pressure by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland, thus inhibiting the vasoconstrictor and aldosterone-secreting effects of angiotensin II.

No non-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.

With the exception of the bioequivalence study, no new 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.

A bioequivalence study was performed, which compared the pharmacokinetics of the test product, Telmisartan Dr Reddy’s 80 mg Tablets to those of the reference product, Micardis 80 mg Tablets (Boehringer Ingelheim International GmbH, Germany). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of the procedure on 21 April 2013. After a subsequent national phase, licences were granted in the UK on 22 May 2013.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Telmisartan Dr Reddy’s 20mg tablets  
| Telmisartan Dr Reddy’s 40mg tablets  
| Telmisartan Dr Reddy’s 80mg tablets |
| Name(s) of the active substance(s) (INN) | Telmisartan |
| Pharmacotherapeutic classification  
(ATC code) | Angiotensin II Antagonists, plain  
(C09CA07) |
| Pharmaceutical form and strength(s) | Tablets  
20 mg, 40 mg and 80 mg |
| Reference numbers for the Decentralised Procedure | UK/H/5034/001-03/DC |
| Reference Member State | UK |
| Member States concerned | UK/H/5034/001/DC: Germany  
UK/H/5034/002-3/DC: Germany and Romania |
| Marketing Authorisation Number(s) | PL 08553/0078-80 |
| Name and address of the authorisation holder | Dr Reddy’s Laboratories (UK) Ltd,  
6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, UK |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance – Telmisartan

rINN:  Telmisartan
Chemical name:  4’-[[4-Methyl-6-(1-Methyl-1H-benzimidazol-2-yl)-2-propyl-1Hbenzimidazol-1-y1]methyl]biphenyl-2-carboxylic acid

Structure:

![Structure diagram]

Molecular formula:  C_{33}H_{30}N_{4}O_{2}
Molecular weight:  514.62
Appearance:  White to slightly yellowish coloured powder, which is sparingly soluble in methylene chloride

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

P.  Medicinal Product

Other Ingredients
Other ingredients consist of the pharmaceutical excipients, namely meglumine, sodium hydroxide, povidone K-30, polysorbate 80, mannitol and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to formulate globally acceptable, stable and bioequivalent products that could be considered generic medicinal products of the currently licensed products, Micards 20 mg, 40 mg and 80 mg Tablets (Boehringer Ingelheim International GmbH).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution profiles have been provided for the proposed products and their respective reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.
Process validation has been carried out on three pilot-scale batches of finished product. The results are satisfactory.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**
The finished product is packaged in Aluminium/Aluminium blister packs (OPA/Aluminium/polyvinylchloride-Aluminium) in pack sizes of 28, 56 or 98 tablets.

The Marketing Authorisation Holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

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.

**Stability of the product**
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 24 months, with no special storage conditions.

**Bioequivalence/bioavailability**
A bioequivalence study was performed, which compared the pharmacokinetics of the test product, Telmisartan Dr Reddy’s 80 mg Tablets to those of the reference product Micardis 80 mg Tablets (Boehringer Ingelheim International GmbH, Germany).

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.

A bridging report referring to the results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for the product Dr Reddy’s telmisartan/hydrochlorothiazide 40/12.5 mg, 80/12.5 mg and 80/25 mg tablets (UK/H/5035/01-3/DC) was provided. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) form**
The MAA forms are satisfactory from a pharmaceutical perspective.

**Quality Overall Summary (Expert report)**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
The grant of Marketing Authorisations is recommended.
III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of telmisartan are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As these products are intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence study:

A randomised, open label, balanced, two-treatment, three-sequence, three-period, single-dose, partial replicate, crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.

Treatments were as follows:
Test: Telmisartan Dr Reddy’s 80 mg Tablets (Dr. Reddy’s Laboratories Limited, India)
Reference: Micardis 80 mg Tablets (Boehringer Ingelheim International GmbH, Germany)

Volunteers were given each treatment after a 10 hour fast. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post-dose. Each regimen was separated by a 12-day washout period.

The pharmacokinetic results are presented in the tables below:

Table 1. Pharmacokinetic parameters (non-transformed values; Arithmetic mean ± SD)

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>442.9870 ± 239.6931</td>
<td>461.4297 ± 314.4026</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.hr/mL)</td>
<td>2360.7679 ± 1907.3234</td>
<td>2357.9259 ± 1898.6418</td>
</tr>
<tr>
<td>AUC_{0-INF} (ng.hr/mL)</td>
<td>2660.4937 ± 2084.6370</td>
<td>2589.9924 ± 1986.8723</td>
</tr>
<tr>
<td>AUC_{0-t} / AUC_{0-INF} (%)</td>
<td>89.778 ± 5.9219</td>
<td>89.585 ± 6.7304</td>
</tr>
<tr>
<td>t_{1/2} (hr)</td>
<td>17.1843 ± 7.0904</td>
<td>16.2726 ± 9.2642</td>
</tr>
<tr>
<td>t_{0.5} (hr^{-1})</td>
<td>0.0540 ± 0.0418</td>
<td>0.0554 ± 0.0381</td>
</tr>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t_{max} (hr)</td>
<td>1.000 (0.50 – 4.00)</td>
<td>1.000 (0.33 – 4.00)</td>
</tr>
</tbody>
</table>
Table 2. Pharmacokinetic parameters in steady-state (Log-transformed values; Geometric mean, 90% CI)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Geometric Least Square Means</th>
<th>Point Estimate (%)</th>
<th>90% Confidence Interval</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max}</td>
<td>Test (T) 368.8331</td>
<td>Reference 358.2302</td>
<td>102.96</td>
<td>90.65</td>
</tr>
<tr>
<td>AUC_{0-4}</td>
<td>1775.6087</td>
<td>1726.4076</td>
<td>102.85</td>
<td>97.71</td>
</tr>
</tbody>
</table>

*In-transformed values

Compared with the reference product, the 90% confidence intervals for the test product are within 80.00-125.00% for C_{max} and AUC. Telmisartan Dr Reddy’s 80 mg Tablets are therefore considered bioequivalent with Micardis 80 mg Tablets.

As the 20 mg and 40 mg strengths of the product meet the bio-waiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 80 mg strength can be extrapolated to the 20 mg and 40 mg tablets.

**Efficacy**
No new data on efficacy have been submitted and none are required for this type of application.

**Safety**
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

**SmPC, PIL and Labels**
The SmPC, PIL and labels are acceptable from a clinical perspective.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.
Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Telmisartan Dr Reddy’s 20 mg, 40 mg and 80 mg Tablets 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 applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s product, Telmisartan Dr Reddy’s 80 mg Tablets and the reference product, Micardis 80 mg Tablets. As the 20 mg and 40 mg strengths of the product meet the bio-waiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 80 mg strength can be extrapolated to the 20 mg and 40 mg tablets.

No new or unexpected safety concerns arose from this application.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with telmisartan is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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