Public Assessment Report

Decentralised Procedure

Dapsone 50 mg Tablets
Dapsone 100 mg Tablets

(Dapsone)

Procedure No: UK/H/6673/001-002/DC

UK Licence Number: PL 11311/0575-0576

Tillomed Laboratories Limited
Dapsone 50 mg Tablets
Dapsone 100 mg Tablets

This is a summary of the Public Assessment Report (PAR) for Dapsone 50 mg and Dapsone 100 mg Tablets (PL 11311/0575-0576; UK/H/6673/001-002/DC). It explains how Dapsone 50 mg and Dapsone 100 mg Tablets were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Dapsone 50 mg and Dapsone 100 mg Tablets.

These products will be referred to collectively as ‘Dapsone Tablets’ throughout the remainder of this public assessment report (PAR).

For practical information about using Dapsone Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dapsone Tablets and what are they used for?
Dapsone Tablets are a ‘generic medicine’. This means that Dapsone Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Dapsone 50 mg and 100 mg Tablets (PL 00142/6609R and PL 00142/6610R; Actavis UK Limited).

Dapsone Tablets can be used to treat:
- leprosy
- blistering skin disorders such as dermatitis herpetiformis (which is connected to gluten sensitivity)
- prevention of pneumonia in immunodeficient patients (in particular patients with AIDS).

How do Dapsone Tablets work?
Dapsone Tablets contain the active ingredient dapsone, which belongs to a group of medicines called antibacterials. Dapsone works by stopping the production of folic acid in certain bacteria, therefore preventing them from growing.

How are Dapsone Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

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

This medicine should be swallowed with water and can be divided into equal doses.

The recommended doses are:
- **Adults and adolescents (aged over 12 years)**
  - Multibacillary leprosy: 100 mg daily for at least 2 years
  - Paucibacillary leprosy: 100 mg daily for at least 6 months
  - Dermatitis herpetiformis: initially 50 mg daily, which may be gradually increased to 300 mg daily and then reduced back down to the usual maintenance dose of 25 mg-50 mg daily.
  - *Pneumocystis jiroveci* pneumonia: in combination with trimethoprim, 50-100 mg daily or 100 mg twice weekly or 200 mg once weekly.
- **Children 6-12 years**
  - Multibacillary leprosy: 50 mg daily for at least 2 years
- Paucibacillary leprosy: 50 mg daily for at least 6 months
- **Children aged less than 6 years**
  - The safety and efficacy of Dapsone in children aged less than 6 years has not been established.
- **Elderly**
  - If the patient has liver problems, their doctor may give them a lower dose of the medicine.

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

For further information on how Dapsone Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What benefits of Dapsone Tablets have been shown in studies?**
Because Dapsone Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Dapsone 50 mg and 100 mg Tablets (PL 00142/6609R and PL 00142/6610R; Actavis UK Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Dapsone Tablets?**
Because Dapsone Tablets are generic medicines and are bioequivalent to the reference medicines; Dapsone 50 mg and 100 mg Tablets (PL 00142/6609R and PL 00142/6610R; Actavis UK Limited), their benefits and possible side effects are taken as being the same as the reference medicines.

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

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

**Why are Dapsone Tablets approved?**
It was concluded that, in accordance with EU requirements, Dapsone Tablets have been shown to have comparable quality and to be bioequivalent to Dapsone 50 mg and 100 mg Tablets (PL 00142/6609R and PL 00142/6610R; Actavis UK Limited). The benefits are greater than the risks and therefore agency recommended that Dapsone Tablets be approved for use.

**What measures are being taken to ensure the safe and effective use of Dapsone Tablets?**
A risk management plan (RMP) has been developed to ensure that Dapsone Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Dapsone Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Dapsone Tablets**
Germany (DE) and the UK agreed to grant marketing authorisations on 11 March 2018. Following a subsequent national phase in the UK, a Marketing Authorisation was granted on 10 April 2018.

The full PAR for Dapsone Tablets follows this summary.
For more information about treatment with Dapsone Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in May 2018.
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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 Tillomed Laboratories Limited a marketing authorisation for the medicinal products Dapsone Tablets (PL 11311/0575-0576; UK/H/6673/001-002/DC). These products are a prescription-only medicine (POM).

Dapsone Tablets are indicated for the following infections:

- As part of a multidrug regimen in the treatment of all forms of leprosy
- Treatment of blistering dermatoses such as dermatitis herpetiformis
- Prophylaxis of Pneumocystis jirovecii pneumonia in immunodeficient subjects, especially AIDS patients.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Germany (DE) as a Concerned Member State (CMS). These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Dapsone 50 mg and 100 mg Tablets (PL 00142/6609R and PL 00142/6610R) which were granted to Actavis UK Limited on 17 November 1988.

Dapsone is a sulfone which is active against a wide range of bacteria. Dapsone’s mechanism of action is probably similar to that of the sulfonamides which involves inhibition of folic acid synthesis in susceptible organisms. It is usually considered to be bacteriostatic against M leprae although it may also possess weak bactericidal activity. It is also active against Pneumocystis jirovecii. As with sulfonamides, antibacterial activity is inhibited by p-aminobenzoic acid. In dermatitis herpetiformis there is local accumulation of polymorphonuclear leukocytes (PMNL). The role of these PMNL cells in the development of inflammation, especially by the respiratory burst of highly toxic oxygen compounds is known. These active substances released against the micro-organisms can cause considerable damage in various tissues such as dermatitis herpetiformis on the skin. Dapsone also inhibits the cytotoxic extremely active myeloperoxidase hydrogen superoxide-halogen compound and the respiratory burst. Further, an inhibition of the Arthus reaction, the reduction of the response of lymphocytes to phytohemagglutinin, inhibition of complement binding by the alternative route of its activation, inhibition of several lysosomal enzyme systems and inhibition of leukotriene B4 with its specific receptors has been described with dapsone. It also interacts with the reactive oxygen species and may have antioxidant action.

The mechanism of resistance of Mycobacterium leprae against dapsone is not known. It is believed that mutations in the folP1 gene which codes for the Dihydropteroate synthetase, are responsible for the dapsone resistance.

No new non-clinical studies were submitted, which is acceptable given that these applications were based on being generic medicinal products of reference products that have been in clinical use for over 10 years.

One bioequivalence study (A randomised, open label, balanced, two treatment, two period, two sequence, single dose, two-way crossover, truncated, bioequivalence study) was submitted to support these applications. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

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

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer
authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considered that these applications could be approved at the end of procedure on 11 March 2018. After a subsequent national phase, licences were granted in the UK on 10 April 2018.
II QUALITY ASPECTS

II.1 Introduction
The finished products are formulated as tablets containing 50 mg and 100 mg dapsone per tablet. Other ingredients consist of the pharmaceutical excipients maize starch, silica colloidal anhydrous, magnesium stearate and microcrystalline cellulose.

The finished products are packed in unit dose blister packs consisting of aluminium lidding material foil plain-paper/polyethylene terephthalate/aluminium and base film polyvinylchloride/polyvinylidene chloride. Both strengths are available in packs of 28 tablets.

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: Dapsone
Chemical name: 2-Butyl-3-[(2‘(1H-tetrazole-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4,4]non-1-en-4-one

Structure:

\[
\text{H}_2\text{N} \quad \begin{array}{c}
\text{S} \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{NH}_2 \\
\end{array}
\]

Molecular formula: \( \text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2\text{S} \)
Molecular weight: 248.3 g/mol
Appearance: White to off white crystalline, odourless, powder
Solubility: Insoluble in water, sparingly soluble in water, freely soluble in acetone and in dilute mineral acids.

Dapsone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by the 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 develop safe, efficacious, tablets containing 50 mg and 100 mg of Dapsone per tablet that are a generic version of the reference products Dapsone 50 mg and 100 mg Tablets (PL 00142/6609R and PL 00142/6610R; Actavis UK Limited). The development of the products has been described, the choice of excipients is justified, and their functions explained.

Comparative \textit{in vitro} dissolution profiles have been provided for the proposed and reference products. Similarity has been confirmed between Dapsone Tablets and the reference products Dapsone 50 mg and 100 mg Tablets (PL 00142/6609R and PL 00142/6610R; Actavis UK Limited).
All excipients comply with their respective European Pharmacopeia monographs. Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

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

These products do not contain or consist of genetically modified organisms (GMO).

**Manufacture of the product**
Satisfactory batch formulae have been provided for the manufacture of the products, together with an appropriate account of the manufacturing process. Process validation data on commercial scale batches have been provided. The results are satisfactory.

**Finished Product Specification**
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unit dose blisters. These medicinal products do not require any special storage conditions.

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

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamics, pharmacokinetic and toxicological properties of dapsone are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

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

**III.2 Pharmacology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.3 Pharmacokinetics**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.4 Toxicology**
All excipients used in the drug product are compendial and are commonly used pharmaceutical excipients in oral products. The drug product excipients are acceptable and there are no toxicological concerns with impurities.
III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Dapsone Tablets are 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 these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of dapsone are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

Based on the results of the bioequivalence study, Dapsone Tablets can be considered to be bioequivalent to the reference products, Dapsone 50 mg and 100 mg Tablets (PL 00142/6609R and PL 00142/6610R; Actavis UK Limited).

IV.2 Pharmacokinetics
In support of these applications, the following bioequivalence study was submitted:

STUDY
A randomised, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, truncated, bioequivalence study of the applicant’s test product, Dapsone 100 mg Tablets (Tillomed Laboratories Limited) versus the reference product Dapsone 100 mg Tablets (Actavis UK Limited) in healthy human adult subjects, under fasting conditions.

Subjects were administered a single oral dose (1 x 100 mg tablet) of the test or reference product following a fast of at least 10 hours. Blood samples were collected for plasma levels pre-dose and up to and including 72 hours after the drug administration in each period. The washout period between treatment phases was 14 days.

The main pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Geometric Least Square Mean (GLSM)</th>
<th>Reference product (B)</th>
<th>Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>27</td>
<td>1491.967</td>
<td>1631.739</td>
<td>91.43</td>
<td>(87.61, 95.42)</td>
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<tr>
<td>AUC0-72</td>
<td>27</td>
<td>48735.419</td>
<td>47636.059</td>
<td>102.31</td>
<td>(97.30,107.57)</td>
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</table>

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for dapsone lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product Dapsone 100 mg Tablets (Tillomed Laboratories Limited), is bioequivalent to the reference product Dapsone 100 mg Tablets (PL 00142/6610R; Actavis UK Limited).
As the 50 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 100 mg tablet strength can be extrapolated to the 50 mg strength tablets.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

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

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety.

In line with the reference product, the applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for these applications from a clinical viewpoint.

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

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

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dapsone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The MAH has submitted the following approved labelling for this medicine which is presented below:
Par Dapsone 50 mg and 100 mg Tablets

Each tablet contains 50 mg of dapsone
Oral use
Read the package leaflet before use
Keep out of the sight and reach of children
This medicinal product does not require any special storage conditions

Marketing Authorisation Holder:
Tibomed Laboratories Limited
220 Butterfield, Great Marshes,
Luton LU2 8DL, UK.
Code No.: MN6DR203/PQY49

Note: Specimen below

Braille:
Dapsone 50 mg
Tablets
Dapsone 50 mg Tablets

Each tablet contains 50 mg of dapsone

Oral use

Read the package leaflet before use

Keep out of the sight and reach of children.

This medicinal product does not require any special storage conditions.

POM

Marketing Authorisation Holder:
Tilcomont Laboratories Limited
220 Butetfield, Cowley Marshes,
London E3 8DL, UK

PL 113195975

Marketing Authorisation Holder:
Tilcomont Laboratories Limited
220 Butetfield, Cowley Marshes,
London E3 8DL, UK

Note: Specimen below

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<td>7.8020E+04</td>
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Dapsone 100 mg Tablets

Each tablet contains 100 mg of dapsone
Oral use
Read the package leaflet before use
Keep out of the sight and reach of children
This medicinal product does not require any special storage conditions

Marketing Authorisation Holder: PL113/11/05/76
Tillotson Laboratories Limited
220 Butterfield, Great Mortings,
Luton LU2 9DL, UK
Code No.: MHDRUGSPDP149

Note: Specimen below

LOT: XXXXX
EXP: MA/20XX

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Annex I
Table of content of the PAR update
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Scope</th>
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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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