TABLE OF CONTENTS

Lay Summary .................................................. Page 2
Scientific discussion .......................................... Page 3
Steps taken for assessment .................................. Page 12
Summary of Product Characteristics ..................... Page 13
Patient Information Leaflet .................................. Page 14
Labelling .......................................................... Page 15
PRAVASTATIN SODIUM 10 MG, 20 MG, 30 MG AND 40 MG TABLETS

PL 11311/0507-10

LAY SUMMARY

On 15th February 2013 the MHRA granted Marketing Authorisations (licences) for the medicinal products Pravastatin sodium 10 mg, 20 mg, 30 mg and 40 mg Tablets (PL 11311/0507-10). These medicines are only available on prescription from your doctor.

Pravastatin belongs to a group of medicines called statins (HMG-CoA reductase inhibitors). It works by reducing the level of ‘bad’ cholesterol and fats (triglycerides) in your blood and raising the levels of ‘good’ cholesterol.

Pravastatin is used for the following:

- To treat high levels of cholesterol (primary hypercholesterolaemia) and other fats (mixed dyslipidaemia) in the blood, if these cannot be lowered by diet and exercise alone
- To reduce the risk of illness and death from heart disease in people with moderate to high cholesterol levels and at high risk of having a heart attack or stroke (primary prevention).
- To reduce the risk of further illness and death from heart disease in people who have already had a heart attack or unstable angina (chest pain) and have normal or raised cholesterol levels (secondary prevention)
- To reduce lipid levels in people who have had an organ transplant and are taking medication to stop the body rejecting the transplant

Having too much cholesterol in your blood can lead to coronary heart disease. It can clog blood vessels, leading to hardening of the arteries (atherosclerosis). Hardened arteries are less able to carry blood to the heart and around the body. This can lead to chest pain (angina) and heart attacks. Pravastatin can both prevent hardening of the arteries and slow it down.

If you take Pravastatin, your doctor will recommend other steps as part of your treatment, such as a low fat diet, exercise and weight reduction. Ask your doctor or pharmacist if you would like advice about any of the above factors.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pravastatin sodium 10 mg, 20 mg, 30mg and 40 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
PRAVASTATIN SODIUM 10 MG, 20 MG, 30 MG AND 40 MG TABLETS
PL 11311/0507-10

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 6
Non-clinical assessment Page 9
Clinical assessment Page 10
Overall conclusions and risk benefit assessment Page 11
INTRODUCTION

The MHRA granted Marketing Authorisations for medicinal products Pravastatin sodium 10 mg, 20 mg, 30 mg and 40 mg Tablets (PL 11311/0507-10) to Tillomed Laboratories Limited on 15th February 2013. These are prescription-only medicines (POM) used for the following indications:

Hypercholesterolemia
Treatment of primary hypercholesterolemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Primary prevention
Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia and at high risk of a first cardiovascular event, as an adjunct to diet (see section 5.1 Pharmacodynamic Properties).

Secondary prevention
Reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors (see section 5.1 Pharmacodynamic Properties).

Post transplantation
Reduction of post transplantation hyperlipidaemia in patients receiving immunosuppressive therapy following solid organ transplantation (see sections 4.2 Posology and method of administration, 4.5 Interaction with other medicinal products and 5.1 Pharmacodynamic Properties).

These applications were submitted as simple abridged applications according to Article 10c of Directive 2001/83/EC, as amended. These products are cross-referring to Pravastatin sodium 10 mg, 20 mg, 30 mg and 40 mg Tablets (PL 11311/0495-0498), first authorized to Roger Oakes Ltd on 7th February 2011. These applications then underwent a change of ownership procedure to the Marketing Authorisation holder to Tillomed laboratories Ltd on 23rd May 2011.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.

Pravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, the enzyme catalysing the early rate-limiting step in cholesterol biosynthesis, and produces its lipid-lowering effect in two ways. Firstly, with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL-cholesterol. Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL cholesterol, the LDL-cholesterol precursor.
A pharmacovigilance system has been provided with these applications and is satisfactory. Suitable justification for non-submission of an Environmental Risk Assessment (ERA) has been provided for these products.
**PHARMACEUTICAL ASSESSMENT**

**LICENCE NO:** PL 11311/0507-10  
**PROPRIETARY NAME:** Pravastatin sodium 10, 20, 30 and 40 mg Tablets  
**COMPANY NAME:** Tillomed Laboratories Limited  
**E.C. ARTICLE:** Article 10c of Directive 2001/83/EC  
**LEGAL STATUS:** POM

### 1 INTRODUCTION

These are simple, informed consent applications for Pravastatin sodium 10 mg, 20 mg, 30 and 40 mg Tablets, submitted under Article 10c of Directive 2001/83/EC. The applications cross-refer to Pravastatin sodium 10 mg, 20 mg, 30 mg and 40 mg Tablets (PL 11311/0495-0498), approved on 7th February 2011 to Roger Oakes Ltd. These applications then underwent change of ownership procedures to the Marketing Authorisation holder Tillomed laboratories Ltd on 23rd May 2011. The current applications are considered valid.

### 2 MARKETING AUTHORISATION APPLICATION (MAA)

#### 2.1 Name(s)

The proposed names of the products are Pravastatin sodium 10 mg, 20 mg, 30 mg and 40 mg Tablets. The products have been named in line with current requirements.

#### 2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product is a tablet for oral use and contains 10 mg, 20 mg, 30 mg and 40 mg of the active ingredient pravastatin sodium.

The tablets are packed in;
- Blister (Aluminium/OPA/Auminium/Polyvinylchloride)
- Blister (Aluminium/Polyvinylchloride/COC/Polyvinlydichloride)
- Polyethylene tablet container and polypropylene cap with desiccant (silica gel) insert.

The pack sizes for the blisters are 7, 10, 14, 20, 28, 30, 50, 56, 60, 98, 100x1 and 100 tablets.

And for the tablet container pack sizes of 28, 30, 98, 100 and 250 tablets are available.

Specification and Certificate of Analysis for all packaging components used have been provided and are satisfactory. The packaging and pack sizes are the same as those for the reference products.

The proposed shelf-lives are 3 years for Blister (Al/OPA/Al/PVC) with storage conditions ‘Do not store above 30°C’ and ‘Store in the original package’ and 3 years for the tablet container with storage condition ‘Keep the tablet container tightly closed’ and 1 year for Blister (Al/PVC/COC/PVdC) with storage conditions ‘Do not store above 25°C’ and ‘Store in the original package’ have been set.
The shelf-lives and storage conditions are identical to those for the reference products and are satisfactory.

2.3 Legal status
These products are prescription-only medicines (POM).

2.4 Marketing Authorisation Holder/Contact Persons/Company
The proposed Marketing Authorisation holder is Tillomed Laboratories Ltd, 3 Howard Road, Eaton Socon, St. Neots, Cambridgeshire PE19 8ET, UK

The Qualified Person (QP) responsible for pharmacovigilance is stated and a Curriculum Vitae (CV) is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specifications
The proposed finished product and shelf-life specifications are in line with the details registered for the reference products.

2.9 Drug substance specification
The proposed drug substance specification conforms to the current European Pharmacopoeia monograph for pravastatin sodium, and is in line with those for the reference products.

An European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability for the manufacturer of pravastatin sodium has been provided. The active substance manufacturer is the same as that for the cross-reference products.

2.10 TSE Compliance
No materials of human or animal origin have been used in the manufacture of this product. The applicant has confirmed that the magnesium stearate used in the tablet is of vegetable origin. This is consistent with the reference products.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formula utilising the same process as the reference products Pravastatin sodium 10 mg, 20 mg, 30 mg and 40 mg Tablets (PL 11311/0495-0498).
3 EXPERT REPORT
The applicant cross-refers to the data for cross-reference products Pravastatin sodium 10 mg, 20 mg, 30 mg and 40 mg Tablets (PL 11311/0495-0498), to which it claims to be identical. This is acceptable. The applicant has included detailed expert reports of the applications. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearance of the products is identical to those of the reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The proposed SmPCs are consistent with the details registered for the reference products.

6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING
User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Simvastatin 5 mg, 10 mg, 20 mg and 40 mg Film-coated Tablets (Winthrop Pharmaceuticals via BGMA). A critical analysis demonstrated that the key messages for safe and effective use for all leaflets were similar. The justification of the rationale for bridging is accepted.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and sufficient space for a standard UK pharmacy dispensing label.

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

7. CONCLUSIONS
The data submitted with the applications are acceptable. The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the reference products and, as such, have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to the previously granted applications for Pravastatin sodium 10 mg, 20 mg, 30 mg and 40 mg Tablets (PL 11311/0495-0498), granted to Roger Oakes Ltd on 7th February 2011. These applications then underwent change of ownership procedures to the Marketing Authorisation holder Tillomed laboratories Ltd on 23rd May 2011.

Pharmaceutical, non-clinical and clinical expert statements have been provided, together with CVs showing that the experts are appropriately qualified. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference products and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the reference products. Extensive clinical experience with pravastatin sodium is considered to have demonstrated the therapeutic values of the compounds. The risk benefit is, therefore, considered to be positive.
PRAVASTATIN SODIUM 10 MG, 20 MG, 30 MG AND 40 MG TABLETS

PL 11311/0507-10

STEPS TAKEN FOR ASSESSMENT

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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 16&lt;sup&gt;th&lt;/sup&gt; March 2012</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications are valid on 14&lt;sup&gt;th&lt;/sup&gt; July 2012</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 10&lt;sup&gt;th&lt;/sup&gt; August 2012, 26&lt;sup&gt;th&lt;/sup&gt; October 2012 and 26&lt;sup&gt;th&lt;/sup&gt; November 2012</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on 1&lt;sup&gt;st&lt;/sup&gt; October 2012, 30&lt;sup&gt;th&lt;/sup&gt; October 2012 and 27&lt;sup&gt;th&lt;/sup&gt; November 2012</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 15&lt;sup&gt;th&lt;/sup&gt; February 2013</td>
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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
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Pravastatin sodium 30 mg Tablets
PL Holder: Tillomed Laboratories Ltd.
PL 11311/0506

Pravastatin sodium 30 mg Tablets
PL Holder: Tillomed Laboratories Ltd.
PL 11311/0509

Pravastatin sodium 30 mg Tablets
PL Holder: Tillomed Laboratories Ltd.
PL 11311/0509

Pravastatin sodium 40 mg Tablets
PL Holder: Tillomed Laboratories Ltd.
PL 11311/0509

Product licence holder:
Tillomed Laboratories Limited,
3 Howard Road, Eaton Socon,
St. Neots, Cambridgeshire,
PE19 8ET, United Kingdom
PL 11311/0510