UK Public Assessment Report

Sukkarto SR 500 mg and 1000 mg prolonged release tablets

(metformin hydrochloride)

UK licence numbers: PL 20117/0110-0111

Morningside Healthcare Limited
Lay Summary
Sukkarto SR 500 mg prolonged release tablets
Sukkarto SR 1000 mg prolonged release tablets
(metformin hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Sukkarto SR 500 mg and 1000 mg prolonged release tablets (PL 20117/0110-0111). Sukkarto SR 500 mg and 1000 mg prolonged release tablets will be referred to as Sukkarto SR tablets throughout this report, for ease of reading. It explains how Sukkarto SR tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Sukkarto SR tablets.

For practical information about using Sukkarto SR tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Sukkarto SR tablets and what are they used for?
Sukkarto 500 mg and 1000 mg SR tablets are the same as Metabet SR 500 mg and 1000 mg prolonged release tablets, which are already authorised (PL 20117/0173 and PL 20117/0184, respectively). The company that makes Metabet SR 500 mg and 1000 mg prolonged release tablets has used its scientific data as the basis for the grant of identical licences for Sukkarto SR 500 mg and 1000 mg tablets (informed consent).

Sukkarto SR tablets are used for the treatment of Type 2 (non-insulin dependent) diabetes mellitus particularly in overweight patients, where diet and exercise changes alone have not been sufficient to control it.

How do Sukkarto SR tablets work?
Sukkarto SR tablets contain the active substance metformin hydrochloride, which belongs to a group of medicines called “biguanides”. Biguanides are used in the treatment of diabetes.

Insulin is a hormone that enables body tissues to take glucose from the blood and use it for energy or fat storage for future use. People with Type 2 diabetes do not make enough insulin in their pancreas or their body does not respond properly to the insulin it does make. This causes a build-up of glucose in the blood that can cause a number of serious long-term problems. Sukkarto SR tablets make the body more sensitive to insulin and help the body to use glucose in a normal way. Sukkarto SR tablets are specially made to release the active substance, metformin hydrochloride, slowly into the body. This is different to other types of tablet that contain metformin hydrochloride.

How are Sukkarto prolonged release tablets used?
Sukkarto SR tablets should be swallowed whole with a glass of water. These tablets must NOT be chewed.

Always take Sukkarto SR tablets as directed by the prescribing doctor.

In adults the usual starting dose is one 500 mg tablet daily with an evening meal. After two weeks the prescribing doctor may increase the dose to a maximum of
2000 mg per day. In some cases the doctor may recommend that the patient takes the tablet twice a day.

If the patient is taking Sukkarto SR tablets with insulin, the usual dose is one 500 mg tablet once a day, while the insulin dosage is adjusted on the basis of blood sugar measurements.

In the elderly the starting dose will be determined after tests have been carried out on the patient’s kidney function.

Sukkarto SR tablets are NOT recommended for use in children and adolescents below 18 years.

Please read Section 3 of the package leaflet for further information.

Sukkarto SR tablets can only be obtained with a prescription.

**What benefits of Sukkarto SR tablets have been shown in studies?**
Sukkarto SR tablets are considered identical to the previously authorised Metabet SR 500 mg and 1000 mg prolonged release tablets, with the same benefits and risks. No new studies are provided for Sukkarto SR tablets but reference is made to the studies for Metabet SR 500 mg and 1000 mg prolonged release tablets.

**What are the possible side effects from Sukkarto SR tablets?**
The most common side effects with Sukkarto SR tablets (which may affect more than 1 in 10 people) are gastrointestinal disorders, such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

The common side effect with Sukkarto SR tablets (which may affect up to 1 in 10 people) is taste disturbance.

For the full list of all side effects reported with Sukkarto SR tablets, see section 4 of the package leaflet.

For further information about side effects that may occur with using Sukkarto SR tablets, please refer to the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency website.

**Why are Sukkarto SR tablets approved?**
The MHRA decided that the benefits of Sukkarto SR tablets are greater than the risks and recommended that these products be approved for use.

**What measures are being taken to ensure the safe and effective use of Sukkarto SR tablets?**
Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.
Other information about Sukkarto SR tablets
Marketing Authorisations were granted in the UK to Morningside Healthcare Limited on 12 July 2013.

The full PAR for Sukkarto SR tablets follows this summary.

For more information about taking Sukkarto SR tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2015.
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I Introduction
The MHRA granted Marketing Authorisations for medicinal products Sukkarto SR 500 mg and 1000 mg prolonged release tablets (PL 20117/0110-11) to Morningside Healthcare Ltd on 12th July 2013. These are prescription-only medicines (POM) used for the treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Sukkarto SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

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 Metabet SR 500 mg and 1000 mg prolonged release tablets (PL 20117/0173 and PL 20117/0184), authorized to Morningside Healthcare Limited on 16th June 2010 and 11th February 2011, respectively.

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.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:
(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;
(3) delay of intestinal glucose absorption.

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.
II  Quality aspects

II.1  Introduction
These are simple, informed consent applications for Sukkarto SR 500 mg and 1000 mg prolonged release tablets, submitted under Article 10c of Directive 2001/83/EC, as amended. The applications cross-refer to Metabet SR 500 mg and 1000 mg prolonged release tablets (PL 20117/0173 and PL 20117/0184), approved on 16th June 2010 and 11th February 2011 to Morningside Healthcare Limited. The current applications are considered valid.

The applicant cross-refers to the data for cross-reference products Metabet SR 500 mg and 1000 mg prolonged release tablets (PL 20117/0173 and PL 20117/0184), 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.

The product is a tablet for oral use and contains 500 mg and 1000 mg metformin hydrochloride. The proposed compositions are consistent with the details registered for the reference products. The appearance of the products is identical to those of the reference products.

The tablets are packed in polyvinyl chloride/polyvinylidichloride/Aluminium blister. The pack sizes are 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 100 and 112 film-coated tablets.

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.

II.2  Drug Substance
The proposed drug substance specification conforms to the current European Pharmacopoeia monograph for metformin hydrochloride, and is in-line with those for the reference products.

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

II.3  Medicinal Product
Pharmaceutical development
No materials of human or animal origin have been used in the manufacture of these products. The applicant has confirmed that the magnesium stearate used in the tablet is of vegetable origin. This is consistent with the reference products.

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 Metabet SR 500 mg and 1000 mg prolonged release tablets (PL 20117/0173 and PL 20117/0184).

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

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

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

**Stability of the product**
The proposed shelf-life is 3 years with no special storage conditions.

The shelf-life and storage condition are identical to those for the reference products and are satisfactory.

**II.4 Discussion on chemical and pharmaceutical aspects**
The data submitted with the applications are acceptable. The grant of Marketing Authorisations is recommended.

**III Non-clinical aspects**
No new non-clinical data have been supplied with these applications and none are required for applications of this type.

**IV Clinical aspects**
No new clinical data have been supplied with these applications and none are required for applications of this type.

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

**Risk Management Plan (RMP)**
These applications cross-refer to Metabet SR 500 mg and 1000 mg prolonged release tablets (PL 20117/0173 and PL 20117/0184). The applications for the Marketing Authorisations for Metabet SR 500 mg and 1000 mg prolonged release tablets were submitted, and approved, before implementation of the Pharmacovigilance legislation on 21 July 2012 and, therefore, preceded the mandatory requirement of an RMP for a new Marketing Authorisation. A suitable justification for not submitting a Risk Management Plan was provided with these applications and was considered satisfactory.
Discussion on the clinical aspects
The data submitted with the applications are acceptable. The grant of Marketing Authorisations is recommended.

V  User consultation
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 Metformin 500 mg and 850 mg Tablets. 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.

VI  Overall conclusion, benefit/risk assessment and recommendation

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 Metabet SR 500 mg and 1000 mg prolonged release tablets (PL 20117/0173 and PL 20117/0184), granted to Morningside Healthcare Limited on 16th June 2010 and 11th February 2011, respectively.

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.

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.
**Benefit/risk assessment**

The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. The applicant’s products are identical to the reference products. Extensive clinical experience with metformin hydrochloride is considered to have demonstrated the therapeutic values of the compounds. The risk benefit is therefore considered to be positive.

The Summaries of Product Characteristics (SmPCs), package leaflet text and labelling are satisfactory, in line with current guidelines and consistent with the cross-reference products. In accordance with Directive 2012/84/EU, as amended, the current approved UK versions of the SmPCs and package leaflet text for these products are available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labelling text is listed below:
Each prolonged release tablet contains metformin hydrochloride 1000 mg corresponding to 750 mg metformin base.

**DOSEAGE:** To be taken as directed by the doctor. The tablets should be swallowed whole.

For oral use.

Read the package leaflet before use.

**KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.**
Annex - Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To register new bioequivalence studies for Sukkarto SR 1000 mg prolonged release tablets, (National Type II Variation).</td>
<td>N</td>
<td>27 August 2015</td>
<td>07 October 2015</td>
<td>Approval</td>
<td>Y – Annex 1</td>
</tr>
</tbody>
</table>
Annex 1

Our Reference: PL 20117/0111 - 0010
Product: PL 20117/0111 Sukkarto SR Prolonged Release Tablets 1000mg
Marketing Authorisation Holder: MORNINGSIDE HEALTHCARE LIMITED
Active Ingredient(s): METFORMIN HYDROCHLORIDE.

Type of Procedure: National
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable):

Reason:
To register new bioequivalence studies.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 166224 and covers the following submissions PL 20117/0184 – 0022 (Bolamyn SR 1000 mg prolonged release tablets, Metabet SR 1000mg prolonged release tablets).

Supporting Evidence
The European Medicines Agency (EMA) has recommended to suspend a number of medicines for which authorisation in the European Union (EU) was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India via Article 31 referral - EMEA/H/A-31/1408 dated 21/05/2015.

The current Marketing Authorisations (MAs) PL 20117/0184 and PL 20117/0111 were granted on the basis of bioequivalence (BE) studies carried out at GVK Biosciences in Hyderabad, India. Therefore, the MA holder has submitted two new bioequivalence studies for these products to replace those of GVK and maintain the MAs in the UK.

Evaluation
Study 1
A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, bioequivalence study of Metformin Hydrochloride 1000 mg Prolonged Release Tablets (Test product A) with Glucophage SR (Metformin Hydrochloride) 1000 mg Prolonged Release Tablets (Reference product B) in healthy human adult male and/or female subjects under fasting conditions.

After overnight fasting for at least 8 hours, one prolonged release tablet of Metformin Hydrochloride 1000 mg [Test Product (A) or Reference Product (B)] was administered orally to each subject in sitting posture, with 150 mL of 20% w/v aqueous glucose solution at room temperature, in each study period, as per the randomization schedule generated using statistical analysis software. A washout period of seven days was maintained between the 2 phases of the study.
Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 36 hours post-dose.

The main pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Summary of Bioequivalence Parameters of Metformin</th>
<th>Parameter</th>
<th>N</th>
<th>Least Square Mean (LSM) Test product (A)</th>
<th>Reference product (B)</th>
<th>LSM Ratio</th>
<th>90% CI for LSMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>56</td>
<td>1349.984</td>
<td>1178.572</td>
<td>114.54</td>
<td>(109.08, 120.28)</td>
<td></td>
</tr>
<tr>
<td>AUC_{0-\infty} (ng h/mL)</td>
<td>56</td>
<td>10560.408</td>
<td>9694.388</td>
<td>108.93</td>
<td>(101.71, 116.67)</td>
<td></td>
</tr>
</tbody>
</table>

Overall, the design and conduct of the bioequivalence study was appropriate. There were no serious or clinically significant protocol deviations and no major safety concerns. No pre-dose levels of metformin were detected in the first or second period of the study. There were no subjects with first scheduled post-dose time point as C_{max}. There were no observations with extrapolated AUC_{0-\infty} more than 20%.

Based on the above results bioequivalence of the test formulation with the reference product under fasting conditions was demonstrated, as for the primary pharmacokinetic parameters the 90% CI of all ratios were within the 80.00%-125.00% range in line with CHMP Guideline on the investigation of bioequivalence (CHMP/EWP/QWP/1401/98 Rev.1/Corr**).

**Study 2**

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, bioequivalence study of Metformin Hydrochloride 1000 mg Prolonged Release Tablets (Test product A) with Glucophage® SR (Metformin Hydrochloride) 1000 mg Prolonged Release Tablets (Reference product B) in healthy human adult male and/or female subjects under fed conditions.

The design was similar to the fasting Study 1. However, in this case the subjects were given a high-fat, high-calorie breakfast 30 minutes prior to scheduled time of dosing.

Blood sampling and handling was as per Study 1 (above).

The main pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Summary of Bioequivalence Parameters of Metformin</th>
<th>Parameter</th>
<th>N</th>
<th>Least Square Mean (LSM) Test product (A)</th>
<th>Reference product (B)</th>
<th>LSM Ratio</th>
<th>90% CI for LSMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>48</td>
<td>1002.188</td>
<td>970.299</td>
<td>103.29</td>
<td>(98.74, 108.04)</td>
<td></td>
</tr>
<tr>
<td>AUC_{0-\infty} (ng h/mL)</td>
<td>48</td>
<td>13189.425</td>
<td>13035.941</td>
<td>101.18</td>
<td>(97.26, 105.25)</td>
<td></td>
</tr>
</tbody>
</table>

As with Study 1 the general design and conduct of this biostudy was appropriate and there were no critical protocol deviations. No pre-dose levels of metformin were detected in the first or second period of the study. There were no subjects with first scheduled post-dose time point as C_{max} and no observations with extrapolated AUC_{0-\infty} >20%.
Based on the above results bioequivalence of the test formulation with the reference product under fed conditions was demonstrated, as for the primary pharmacokinetic parameters the 90% CI of all ratios were within the 80.00%-125.00% range in line with CHMP Guideline on the investigation of bioequivalence (CHMP/EWP/QWP/1401/98 Rev.1/Corr**).

**Dissolution data**
In accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** the results of *in vitro* dissolution tests with three different buffers and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study, were reported.

**Conclusion**
The submitted biostudies are generally acceptable and support the bioequivalence between the test formulations and the respective originator strengths under the examined conditions. The applicant satisfactorily addressed points that were raised.

**Decision:** Approved
**Date:** 07 October 2015