Public Assessment Report

Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets

(Irbesartan and hydrochlorothiazide)

PL 42930/0008-0010

Wilcare Pharma Limited
Lay Summary
Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets
(Irbesartan and hydrochlorothiazide)

This is a summary of the Public Assessment Report (PAR) for Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets (PL 42930/0008-0010). These medicinal products will be referred to as Irbesartan/Hydrochlorothiazide Tablets in this summary, for ease of reading.

This summary explains how Irbesartan/Hydrochlorothiazide 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 these products.

For practical information about using Irbesartan/Hydrochlorothiazide Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Irbesartan/Hydrochlorothiazide Tablets and what are they used for?
These medicines are the same as Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets (PL 34771/0088-0090), which are already authorised. The company that makes Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets (PL 34771/0088-0090), Macleods Pharma UK Limited, has agreed that its scientific data can be used as a basis for the grant of identical licences for Irbesartan/Hydrochlorothiazide Tablets (PL 42930/0008-0010).

Irbesartan/Hydrochlorothiazide Tablets are used to treat high blood pressure, when treatment with Irbesartan or hydrochlorothiazide alone did not provide adequate control of the blood pressure.

How do Irbesartan/Hydrochlorothiazide Tablets work?
Irbesartan/Hydrochlorothiazide Tablets is a combination of two active substances, irbesartan and hydrochlorothiazide. Irbesartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body that binds to receptors in blood vessels causing them to tighten. This results in an increase in blood pressure. Irbesartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax and the blood pressure to lower.

Hydrochlorothiazide is one of a group of medicines (called thiazide diuretics) that causes increased urine output and so causes a lowering of blood pressure.

How are Irbesartan/Hydrochlorothiazide Tablets used?
Irbesartan/Hydrochlorothiazide Tablets are taken by mouth. The whole tablet should be swallowed with a glass of water. These medicinal products can be taken at any time of the day (at about the same time each day) with or without food.

The usual dose of Irbesartan/Hydrochlorothiazide Tablets is one or two tablets a day.
These products will usually be prescribed by a doctor when the previous treatment did not reduce the blood pressure enough.

Irbesartan/Hydrochlorothiazide Tablets should not be given to children under 18 years of age.

Irbesartan/Hydrochlorothiazide Tablets can only be obtained with a prescription from a doctor.

For further information on how Irbesartan/Hydrochlorothiazide Tablets are used, please see the Summaries of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Irbesartan/Hydrochlorothiazide Tablets have been shown in studies?
As Irbesartan/Hydrochlorothiazide Tablets (PL 42930/0008-0010) are considered identical to Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets (PL 34771/0088-0090), their benefits and risks are taken as being the same as those for Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets (PL 34771/0088-0090).

What are the possible side effects from Irbesartan/Hydrochlorothiazide Tablets?
Like all medicines, Irbesartan/Hydrochlorothiazide Tablets can cause side effects, although not everybody gets them.

The most common side effects with Irbesartan/Hydrochlorothiazide Tablets which may affect up to 1 in 10 people are nausea/vomiting, abnormal urination, fatigue, dizziness (including when getting up from a lying or sitting position) and blood tests may show raised levels of an enzyme that measures the muscle and heart function (creatine kinase) or raised levels of substances that measure kidney function (blood urea nitrogen, creatinine).

For the full list of all side effects reported with Irbesartan/Hydrochlorothiazide Tablets, see section 4 of the package leaflet.

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

Why are Irbesartan/Hydrochlorothiazide Tablets approved?
No new or unexpected safety concerns arose from these applications. It was, therefore, considered that the benefits of Irbesartan/Hydrochlorothiazide Tablets outweigh the risks, and the grant of Marketing Authorisations was recommended.

What measures are being taken to ensure the safe and effective use of Irbesartan/Hydrochlorothiazide Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Irbesartan/Hydrochlorothiazide Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Irbesartan/Hydrochlorothiazide Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.
Other information about Irbesartan/Hydrochlorothiazide Tablets
Marketing Authorisations for Irbesartan/Hydrochlorothiazide Tablets were granted in the UK on 18th June 2015.

For more information about taking Irbesartan/Hydrochlorothiazide Tablets, read the PIL, or contact your doctor or pharmacist.

The full PAR for Irbesartan/Hydrochlorothiazide Tablets follows this summary.

This summary was last updated in July 2015.
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I  Introduction
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Wilcare Pharma Limited Marketing Authorisations for the medicinal products Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets (PL 42930/0008-0010) on 18th June 2015. These products are prescription only medicines (POM) indicated for the treatment of essential hypertension.

This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone.

These applications were submitted as abridged simple applications, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets, which were authorised to Macleods Pharma UK Limited (PL 34771/0088-0090) on 1st May 2012.

Irbesartan/Hydrochlorothiazide Tablets is a combination of an angiotensin-II receptor antagonist, irbesartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Irbesartan is a potent, orally active, selective angiotensin-II receptor (AT$_1$ subtype) antagonist. It is expected to block all actions of angiotensin-II mediated by the AT$_1$ receptor, regardless of the source or route of synthesis of angiotensin-II. The selective antagonism of the angiotensin-II (AT$_1$) receptors results in increases in plasma renin levels and angiotensin-II levels, and a decrease in plasma aldosterone concentration. Serum potassium levels are not significantly affected by irbesartan alone at the recommended doses in patients without risk of electrolyte imbalance. Irbesartan does not inhibit ACE (kininase-II), an enzyme which generates angiotensin-II and also degrades bradykinin into inactive metabolites. Irbesartan does not require metabolic activation for its activity.

Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of irbesartan tends to reverse the potassium loss associated with these diuretics. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

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.
The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.
II Quality aspects

II.1 Introduction
These are simple, informed consent applications for Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets, submitted under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg tablets, which were authorised to Macleods Pharma UK Limited (PL 34771/0088-0090) on 1st May 2012. The current applications are considered valid.

II.2 Drug Substances
Drug substance specifications
The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

II.3 Medicinal Product
Names
The proposed product names for these applications are Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets. The products have been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack size
Each film-coat tablet contains 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg of irbesartan/hydrochlorothiazide as active ingredients. The route of administration is oral.

The tablets are packed in polyvinylidene chloride (PVdC) coated white opaque polyvinylchloride (PVC)/polyethylene (PE) film/aluminium foil blisters containing 28 tablets.

The proposed shelf-life is 36 months with no special storage conditions.

The proposed packaging and shelf-life are consistent with the details registered for the cross-reference products.

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

Marketing Authorisation Holder/Contact Persons/Company
Wilcare Pharma Limited, Building 6 Unit 14, Croxley, Green Business Park, Watford, England WD18 8YH.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory Curriculum Vitae (CV) has been provided.

Manufacturer
The proposed manufacturing site is consistent with that registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.
Qualitative and quantitative composition
The proposed compositions are identical to those of the reference products and are acceptable.

Manufacturing process
The proposed manufacturing processes are identical to those of the reference products and are acceptable.

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

TSE Compliance
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.

Bioequivalence
No bioequivalence data are required to support these simple abridged applications as the proposed products are manufactured to the same formula utilising the same process as the cross-reference products, Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets (PL 34771/0088-0090).

Expert Report
The applicant cross-references the data for Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets (PL 34771/0088-0090) to which these applications are claimed to be identical. This is acceptable.

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

III Non-clinical aspects
Introduction
As these are abridged simple applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Environmental Risk Assessment (ERA)
A suitable justification has been provided for not submitting an environmental risk assessment. As the applications are identical versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.
IV Clinical aspects

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
The applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Measures</th>
<th>Risk Minimization</th>
<th>Additional Minimization Measures</th>
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</thead>
<tbody>
<tr>
<td>Important Identified Risks</td>
<td></td>
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<tr>
<td>Hypersensitivity and severe skin reactions</td>
<td>The risks (1) associated with the use of the drug product in patients with history of allergic reactions, and (2) of hypersensitivity and severe skin reactions associated with the use of the drug product are described in the SPC Sections 4.3, 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
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<tr>
<td>Hepatic impairment</td>
<td>The risks (1) associated with the use of the drug product in patients with hepatic impairment, and (2) of hepatic impairment associated with the use of the drug product are described in the SPC Sections 4.2, 4.3, 4.4, 4.8 and 5.2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td>The risks (1) associated with the use of the drug product in patients with renal impairment (2) of renal impairment associated with the use of the drug product, and (3) of renal impairment associated with the concomitant use of the drug</td>
<td>None</td>
<td>product</td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Routine Risk Minimization Measures</td>
<td>Additional Risk Minimization Measures</td>
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<td>with other medicinal products are described in the SPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9 and 5.2, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
<td></td>
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</tr>
<tr>
<td>Electrolyte imbalances</td>
<td>The risks (1) of electrolyte imbalances associated with the use of the drug product, and (2) of electrolyte imbalances associated with the concomitant use of the drug product with other medicinal products are described in the SPC Sections 4.3, 4.4, 4.5, 4.8 and 4.9, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
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<tr>
<td>Hypotension</td>
<td>The risks of hypotension (1) associated with the use of the drug product (2) associated with the use of the drug product in volume-depleted patients and in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy and (3) associated with the concomitant use of the drug product with other medicinal products are described in the SPC Sections 4.3, 4.4, 4.5, 4.8 and 4.9, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester of pregnancy</td>
<td>The risks associated with the use of the drug product in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester of pregnancy are described in the SPC Sections 4.3, 4.4 and 4.6, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in patients with primary aldosteronism</td>
<td>The risk associated with the use of the drug product in patients with primary aldosteronism is described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
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</tr>
<tr>
<td>Concomitant use with lithium</td>
<td>The risk associated with the concomitant use of the drug product with lithium is described in the SPC Sections 4.4 and 4.5, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Routine Measures</td>
<td>Risk Minimization</td>
<td>Additional Risk Minimization Measures</td>
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<td>minimise this risk.</td>
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<tr>
<td><strong>Important Potential Risks</strong></td>
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<tr>
<td>Exacerbation or activation of systemic lupus erythematosus</td>
<td>The risk of exacerbation or activation of SLE associated with the use of the drug product is described in the SPC Sections 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
<td></td>
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<tr>
<td>Impaired glucose tolerance</td>
<td>The risk of impaired glucose tolerance associated with the use of the drug product, is described in the SPC Sections 4.4, 4.5 and 4.8, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
<td></td>
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<tr>
<td>Increased cholesterol and triglyceride levels</td>
<td>The risk of increased cholesterol and triglyceride levels associated with the use of the drug product, is described in the SPC Sections 4.4, 4.5 and 4.8, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
<td></td>
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<tr>
<td>Acute myopia and secondary acute angle closure glaucoma</td>
<td>The risks of acute myopia and secondary acute angle-closure glaucoma associated with the use of the drug product are described in the SPC Sections 4.4 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>The risks (1) associated with the use of the drug product in patients with hyperuricaemia, and (2) of hyperuricaemia associated with the use of the drug product are described in the SPC Sections 4.4, 4.5 and 4.8, and appropriate advice is provided to the prescriber to minimise these risks.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in 1st trimester of pregnancy</td>
<td>The risk associated with the use of the drug product in 1st trimester of pregnancy is described in the SPC Sections 4.4 and 4.6, and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Missing Information</strong></td>
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</tr>
<tr>
<td>Safety Concern</td>
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<td>Additional Risk Minimization Measures</td>
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<tr>
<td>Use in children and adolescents</td>
<td>The SPC Section 4.2 states that there is no information available regarding safety and efficacy of the drug product in children and adolescents, and thus, its use is not recommended in this population group.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in lactating women</td>
<td>The SPC Section 4.6 states that there is no information available regarding the use of the drug product in lactating women, and thus, its use is not recommended in this population group.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in patients with recent kidney transplantation</td>
<td>The SPC Section 4.4 states that there is no experience regarding the administration of the drug product in patients with recent kidney transplantation. Thus, its use is not recommended in this population group.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Use in patients with severe hepatic impairment</td>
<td>The SPC Sections 4.2, 4.3 and 5.2 state that studies have not been performed in patients with severe hepatic impairment, and thus, its use is not recommended in this population group.</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

The applicant proposes only routine risk minimisation measures, which are detailed in the SmPCs. These are considered sufficient. No additional risk minimisation measures are considered necessary.

The grant of Marketing Authorisations is recommended.

V User consultation
A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to the leaflet for Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated Tablets (PL 34771/0088-0090). The bridging report submitted by the applicant is acceptable.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant’s products are identical to the reference products. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics, Patient Information Leaflet & Labels
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

The currently approved labelling is provided below:
UKPAR Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg Film-coated tablets

PL 42930/0008-0010
UKPAR Irbesartan/Hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg
Film-coated tablets

PL 42930/0008-0010
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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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