Dutasteride Regiomedica 0.5 mg capsules, soft (dutasteride)

Date: 2 July 2014

This module reflects the scientific discussion for the approval of Dutasteride Regiomedica 0.5 mg capsules, soft. The procedure was finalised on 30 December 2013. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 9-11.
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dutasteride Regiomedica 0.5 mg capsules, soft from Regiomedica GmbH.

The product is indicated for:
- treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).
- Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Avodart 0.5 mg, soft capsules (NL License RVG 28317) which has been registered in the Netherlands by GlaxoSmithKline since 16 December 2002 through mutual recognition procedure SE/H/0304/001.

The concerned member states (CMS) involved in this application were Bulgaria and Poland.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Dutasteride Regiomedica 0.5 mg is a light brown, oblong soft-gelatin capsule without printing, containing a clear, slightly yellow to pale amber, oily liquid.

The capsules are packed in PVC/PVDC/Aluminium blisters.

The excipients are:
- **Capsule contents** - glycerol monocaprylocaprate, butylhydroxytoluene (E321)
- **Capsule shell** - gelatin, glycerol, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172)

II.2 Drug Substance

The active substance is dutasteride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to pale yellow, slightly hygroscopic powder, which is insoluble in water, soluble in methanol and ethanol. The molecule contains seven chiral centres. Dutasteride is produced as a single enantiomer with 5-alpha, 17-beta absolute configuration. The seven chiral centres are found at carbons C5, C8, C9, C10, C13, C14 and C17. The optical purity of dutasteride is being controlled. Dutasteride exhibits polymorphism. The manufacturer consistently produces the anhydrous crystalline form I.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

**Manufacturing process**
The substance is synthesised in eight steps. A class 1 metal catalyst is used in the process, as well as class 2 and 3 solvents. The material has been adequately characterized and adequate specifications have been adopted for the starting material and reagents.
Quality control of drug substance
The drug substance specification has been established in-house, based on the specification of the ASMF-holder, and is in line with general requirements of the Ph.Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for six full-scale batches stored at 25°C/60% RH (three batches up to 36 months, one up to 24 months, one up to 18 months and one up to 12 months) and 40°C/75% RH (three batches up to 6 months). No out of specifications have been observed. A re-test period of 36 months can be granted. No storage restrictions are necessary.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were performed to obtain a stable product and in which the drug substance was present in dissolved form. The pharmaceutical development of the product has been adequately performed and included the development of the dissolution method. The Dutasteride Regiomedica 0.5 mg capsules (test product) was compared to the French innovator product Avodart® 0.5 mg capsules with regard to dissolution behaviour, assay and impurity profiles. The dissolution results show the capsule contents are not released into the dissolution media for both test and reference when the dissolution media is either pH 1.2, 4.5 or 6.8. The results show that Dutasteride Regiomedica 0.5 mg has a similar dissolution profile to Avodart® 0.5 mg capsules when testing is performed in 0.1 M hydrochloric acid. The pharmaceutical development has been sufficiently described.

Manufacturing process
The manufacturing process consists of preparation of the capsule fill mass and the gelatin mass, which are then used for encapsulation and drying. The capsules are subsequently packaged into blisters. The manufacturing process is considered non-standard and has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with the Ph.Eur. requirements or Directive 2008/128/EC & Regulation 231/2012 (colourants). These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, dimensions, identification (dutasteride, butylhydroxytoluene and colourants), average mass of capsule content, assay (dutasteride and butylhydroxytoluene), uniformity of dosage units, related substances, dissolution and microbial purity. The shelf-life limits are identical to the release limits except for butylhydroxytoluene amount. This is acceptable, based on the provided stability data. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC/Aluminium blisters. The results were within limits. Photostability testing showed that the product is not sensitive to light. The shelf-life of 30 months when stored below 30 °C can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM for the gelatin have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.
II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dutasteride Regiomedica 0.5 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments were made:

- The MAH will perform comparative dissolution profile testing on the first three production batches.
- The MAH will continue testing on the three commercial scale batches included in the stability studies up to the shelf-life, according to the protocol.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dutasteride Regiomedica is 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Avodart 0.5 mg, soft capsules which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dutasteride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Dutasteride Regiomedica 0.5 mg (Regiomedica GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Avodart 0.5 mg capsules (GSK, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 18-48 years. Each subject received a single dose (0.5 mg) of one of the 2 dutasteride formulations. The tablet was orally
administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 42 days.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 32, 48, 56 and 72 hours after administration of the products.

A single-dose, crossover study under fasting conditions to assess bioequivalence for dutasteride is considered adequate. Dutasteride can be taken with or without food, according to the SmPC.

**Analytical/statistical methods**
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. Dutasteride has a very long elimination half-life (about 65h) and therefore and in accordance with the guideline, AUC\(_{0-72h}\) was taken as main variable for the extent of absorption.

**Results**
Two subjects dropped out, one withdrew for personal reasons and one for protocol violation. Thirty-eight subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \(t_{max}\) (median, range)) of dutasteride under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-72}) ng.h/ml</th>
<th>AUC(_{0-\infty}) ng.h/ml</th>
<th>(C_{max}) ng/ml</th>
<th>(t_{max}) h</th>
<th>(t_{1/2}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>38.7 ± 18.2</td>
<td>66.4 ± 39.0</td>
<td>2.87 ± 1.16</td>
<td>1.25</td>
<td>66 ± 29</td>
</tr>
<tr>
<td>Reference</td>
<td>37.5 ± 17.9</td>
<td>65.3 ± 39.2</td>
<td>3.03 ± 1.24</td>
<td>1.25</td>
<td>64 ± 25</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.02 (0.98 - 1.07)</td>
<td>1.03 (0.97 - 1.10)</td>
<td>0.95 (0.88 - 1.04)</td>
<td>--</td>
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</tr>
<tr>
<td>CV (%)</td>
<td>36.6</td>
<td>45.4</td>
<td>38.8</td>
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</tr>
</tbody>
</table>

*AUC\(_{0-\infty}\)* area under the plasma concentration-time curve from time zero to infinity
*AUC\(_{0-4}\)* area under the plasma concentration-time curve from time zero to \(t\) hours
\(C_{max}\) maximum plasma concentration
\(t_{max}\) time for maximum concentration
\(t_{1/2}\) half-life

\*ln-transformed values

**Conclusion on bioequivalence study**
The 90% confidence intervals calculated for AUC\(_{0-72h}\), AUC\(_{0-\infty}\) and \(C_{max}\) are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study Dutasteride Regiomedica 0.5 mg is considered bioequivalent with Avodart 0.5 mg capsules.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**IV.3 Risk Management Plan**
The MAH has submitted a risk management plan, 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 Dutasteride Regiomedica.
Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sexual adverse events of altered [decreased] libido, impotence, ejaculation disorders may persist after drug discontinuation</td>
</tr>
<tr>
<td>• Breast disorders</td>
</tr>
<tr>
<td>• Allergic reactions, including rash, pruritus, urticaria, localized oedema, and angioedema</td>
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<tr>
<td>• Cardiac failure</td>
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<tr>
<td>• Depressed Mood</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cardiovascular events other than cardiac failure</td>
</tr>
<tr>
<td>• Male breast cancer</td>
</tr>
<tr>
<td>• High-grade prostate cancer</td>
</tr>
<tr>
<td>• Interference with formation of external male genitalia in the foetus</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Important missing information</th>
</tr>
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<tr>
<td>• Safety in men with severe hepatic impairment</td>
</tr>
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</table>

At the moment no additional pharmacovigilance activity is warranted. Routine pharmacovigilance is sufficient.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Avodart 0.5 mg capsules. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The medicinal product is intended for the treatment of benign prostatic hyperplasia, which affects only men, so only male participants were interviewed. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

It was concluded that the PL is intelligibly written. Both the writing style and the clear presentation contribute to this assessment. This is primarily reflected by the fact that information is generally found quickly. 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

Dutasteride Regiomedica 0.5 mg capsules, soft has a proven chemical-pharmaceutical quality and is a generic form of Avodart 0.5 mg, soft capsules. Avodart is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.
There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for product with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 December 2013.
<table>
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<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/Non approval</th>
<th>Assessment report attached</th>
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Summary Public Assessment Report

Generics

Dutasteride Regiomedica 0.5 mg capsules, soft (dutasteride)

NL/H/2861/001/DC

Date: 2 July 2014
Summary Public Assessment Report

Generics

Dutasteride Regiomedica 0.5 mg capsules, soft

Active substance: dutasteride

This is a summary of the public assessment report (PAR) for Dutasteride Regiomedica 0.5 mg capsules, soft. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Dutasteride Regiomedica.

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

What is Dutasteride Regiomedica 0.5 mg and what is it used for?
Dutasteride Regiomedica is a ‘generic medicine’. This means that it is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Avodart 0.5 mg soft capsules.

This medicine is used to treat men with an enlarged prostate (benign prostatic hyperplasia). This is a non-cancerous growth of the prostate gland, caused by producing too much of a hormone called dihydrotestosterone. As the prostate grows, it can lead to urinary problems, such as difficulty in passing urine and a need to go to the toilet frequently. It can also cause the flow of the urine to be slower and less forceful.

How is this medicine used?
The medicine can only be obtained with a prescription. The recommended dose is one capsule (0.5 mg) taken once a day. The capsules should be swallowed whole with water, and must not be chewed or opened. Contact with the contents of the capsules may cause soreness to the mouth or throat. Dutasteride is a long term treatment. Some men notice an early improvement in their symptoms. However, others may need to take the medicine for 6 months or more before it begins to have an effect. The patient should continue taking this medicine for as long as the doctor tells him to.

How does this medicine work?
This medicine contains the active ingredient dutasteride. It belongs to a group of medicines called 5-alpha reductase inhibitors. This medicine lowers the production of dihydrotestosterone, the hormone that causes prostate enlargement. It helps to shrink the prostate and relieve the symptoms. This reduces the risk of a complete block of the urine flow (acute urinary retention).

How has this medicine been studied?
Because Dutasteride Regiomedica is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Avodart. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of this medicine?
Because Dutasteride Regiomedica is a generic medicine and is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as the reference medicine.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, Dutasteride Regiomedica has been shown to have comparable quality and to be bioequivalent to Avodart. Therefore, the view was that, as for Avodart, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Dutasteride Regiomedica, including the appropriate precautions to be followed by healthcare professionals and patients.
Other information about this medicine
The marketing authorisation for Dutasteride Regiomedica 0.5 mg capsules, soft was granted in the Netherlands on 20 January 2014.

The full PAR for Dutasteride Regiomedica can be found on the website http://mri.medagencies.org/Human. For more information about treatment with this medicine, read the package leaflet (http://mri.medagencies.org/download/NL_H_2861_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in July 2014.