Public Assessment Report

Decentralised Procedure

Febuxostat Warren 80 and 120 mg film-coated tablets  
(febuxostat)

UK/H/6418/001-002/DC

UK licence no: PL 42831/0037 - 0038

WARREN GENERICS s.r.o.
LAY SUMMARY

Febuxostat Warren 80 and 120 mg film-coated tablets
(febuxostat)

This is a summary of the Public Assessment Report (PAR) for Febuxostat Warren 80 and 120 mg film-coated tablets (PL 42831/0037 - 0038; UK/H/6418/001-002/DC). It explains how Febuxostat Warren 80 and 120 mg film-coated 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 these products. These products will be referred to as Febuxostat film-coated tablets throughout the remainder of this summary.

For practical information about using Febuxostat film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Febuxostat film-coated tablets and what are they used for?
Febuxostat film-coated tablets are ‘generic medicines’. This means that Febuxostat film-coated tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Adenuric 80 mg and 120 mg film-coated tablets.

Febuxostat film-coated tablets contain the active substance febuxostat and are used to treat gout, which is associated with an excess of a chemical called uric acid (urate) in the body. In some people, the amount of uric acid builds up in the blood and may become too high to remain soluble. When this happens, urate crystals may form in and around the joints and kidneys. These crystals can cause sudden, severe pain, redness, warmth and swelling in a joint (known as a gout attack). Left untreated, larger deposits called tophi may form in and around joints. These tophi may cause joint and bone damage.

Febuxostat is for adults.

How do Febuxostat film-coated tablets work?
Febuxostat works by reducing uric acid levels. Keeping uric acid levels low by taking Febuxostat once every day stops crystals building up, and over time it reduces symptoms. Keeping uric acid levels sufficiently low for a long enough period can also shrink tophi.

How are Febuxostat film-coated tablets used?
The pharmaceutical form of Febuxostat film-coated tablets are tablets and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as his/her doctor has advised. The patient should check with his/her doctor or pharmacist if unsure.

The usual dose is one tablet daily. The back of the blister pack is marked with the days of the week to help the patient confirm that a dose has been taken each day. The tablets should be taken by mouth and can be taken with or without food.

Gout
Febuxostat is available as either an 80 mg tablet or a 120 mg tablet. The patient’s doctor will have prescribed the strength most suitable for patient. The patient should continue to take Febuxostat every day even when he or she is not experiencing gout flare or attack.
Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Febuxostat film-coated tablets have been shown in studies?**
Febuxostat Warren 80 and 120 mg film-coated tablets are generic medicines, studies in patients have been limited to tests to determine that these medicines are bioequivalent to the reference medicines, Adenuric 80 mg and 120 mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Febuxostat film-coated tablets?**
Because Febuxostat Warren 80 and 120 mg film-coated tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are taken as being the same as the reference medicines.

For the full list of all side effects reported with Febuxostat film-coated tablets, see Section 4 of the package leaflet available on the MHRA website.

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

**Why are Febuxostat film-coated tablets approved?**
It was concluded that, in accordance with EU requirements, Febuxostat film-coated tablets has been shown to have comparable quality and to be bioequivalent to Adenuric 80 mg and 120 mg film-coated tablets. Therefore, the MHRA decided that, for Febuxostat film-coated tablets, the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Febuxostat film-coated tablets?**
A Risk Management Plan (RMP) has been developed to ensure that Febuxostat film-coated tablets is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for this product, 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 and healthcare professionals will be monitored and reviewed continuously, as well.

**Other information about Febuxostat film-coated tablets**
On 11 December 2017 (day 208 of the procedure) Germany, and the UK agreed to grant Marketing Authorisations for Febuxostat film-coated tablets. Following a subsequent national phase, Marketing Authorisations were granted on 10 January 2018 in the UK.

The full PAR for Febuxostat film-coated tablets follows this summary.

For more information about treatment with Febuxostat film-coated tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in February 2018.
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I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the applications for Febuxostat Warren 80 and 120 mg film-coated tablets (PL 42831/0037 - 0038; UK/H/6418/001-002/DC) could be approved.

These are decentralised abridged applications submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the reference products, Adenuric 80 mg and 120 mg film-coated tablets, which were granted Marketing Authorisations to Menarini International Operations Luxembourg S.A. on 21 April 2008 following a centralised procedure.

Febuxostat Warren 80 and 120 mg film-coated tablets are ‘prescription only medicines’ (legal status “POM”) containing the active substance febuxostat. These products are indicated in adults for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Febuxostat is a non-purine, selective inhibitor of xanthine oxidase.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

One bioequivalence study (conducted under fasting conditions) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines. With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application, and these are satisfactory.

The United Kingdom acted as RMS and Germany was the CMS.

All Member States agreed to grant Market Authorisations for the Febuxostat Warren 80 and 120 mg film-coated tablets on 11 December 2017 (day 208 of the procedure). Following a subsequent national phase, the UK granted a Market Authorisation (PL 42831/0037 - 0038) for these products on 10 January 2018.
II QUALITY ASPECTS

II.1 Introduction
Febuxostat Warren 80 mg film-coated tablets are pale yellow to yellow coloured, capsule shaped, biconvex, film coated tablets debossed with ‘80’ on one side and are plain on other side. Each tablet contains 80 mg of febuxostat.

Febuxostat Warren 120 mg film-coated tablets have the same appearance as the 80 mg product, but are debossed with ‘120’ on one side and are plain on other side. Each tablet contains 120 mg of febuxostat.

The other ingredients in Febuxostat Warren 80 and 120 mg film-coated tablets consist of the pharmaceutical excipients:

Tablet core: lactose monohydrate, microcrystalline cellulose, magnesium stearate, hydroxypropylcellulose, croscarmellose sodium, silica colloidal anhydrous

Tablet coating: Opadry II Yellow 85F42129 containing: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172)

The finished product is packaged in an aclar / polyvinyl chloride / aluminium blister which is paced in a carton box available in pack sizes of 1, 14, 28, 30 and 84 film-coated tablets.

Not all pack sizes may be marketed, however, the marketing authorisation holder has agreed to provide mock-ups of any pack size to the relevant regulatory authorities before marketing.

All primary product packaging complies with the current requirements. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 DRUG SUBSTANCES

Febuxostat

Chemical Name: 2-(3-cyano-4-isobutoxyphenyl)-4-methyl-1,3- thiazole-5-carboxylic acid

Structure:

Molecular Formula: C₁₆H₁₆N₂O₅S
Molecular Mass: 316.38

Appearance: White to off white crystalline powder
Solubility: Freely soluble in Dimethyl formamide, soluble in Tetrahydrofuran, sparingly soluble in Acetone and Ethanol.

Febuxostat is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data that comply with the proposed specification are provided.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to formulate products which could be considered generic medicinal products of the reference medicinal products, Adenuric 80 mg and 120 mg film-coated tablets (Menarini International Operations Luxembourg S.A.). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, except for Opadry-II Yellow 85F42129 which is controlled to an in-house specification.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).
Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale.

Finished Product Specification
The finished product specification is acceptable. Test methods have been described that have been adequately validated. Batch data that comply with the release specification have been provided. In-house working standards are used, which are compared to European Pharmacopoeia references, where available. Representative Certificates of Analysis have been provided.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened product. This medicinal product does not require any special storage conditions.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Febuxostat Warren 80 and 120 mg film-coated tablets.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance febuxostat are well-known. No new non-clinical data have been submitted for these applications and none are required. 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
No new pharmacology data were submitted and none are required for applications of this type.

III.3 Pharmacokinetics
No new pharmacokinetic data were submitted and none are required for applications of this type.

III.4 Toxicology
No new toxicology data were submitted and none are required for applications of this type.

III.5 Environmental Risk Assessment
Since these products will be used as a substitute for other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk
Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.

III.6 Discussion on non-clinical aspects
It is recommended that Marketing Authorisations are granted for Febuxostat Warren 80 and 120 mg film-coated tablets.

IV CLINICAL ASPECTS
IV.1 Introduction
No new clinical studies have been performed and none are required for applications of this type. A comprehensive review of the published literature has been provided by the applicant.

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

An open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over, single oral dose bioequivalence study in healthy male volunteers under fasting conditions.

The subjects fasted overnight for 10 hours. A single 120 mg dose of Febuxostat 120 mg film-coated tablets (WARREN GENERICS s.r.o) or Adenuric 120 mg film-coated tablets (Menarini International Operations Luxembourg S.A) was administered with 240 mL of water according to the randomisation schedule.

Blood samples were collected pre-dose and up to 48 hours post-dose. The washout period was 7 days.

The summary of pharmacokinetic results is found in the table below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-4} ng*h/ml</th>
<th>AUC_{0-\infty} ng*h/ml</th>
<th>C_{\text{max}} ng/ml</th>
<th>t_{\text{max}} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>21611.9500 (±5597.1191)</td>
<td>21876.8218 (±5642.51765)</td>
<td>5970.1587 (±2040.51378)</td>
<td>1.25 (0.50-5.00)</td>
</tr>
<tr>
<td>Reference</td>
<td>20777.7538 (±5614.45542)</td>
<td>21041.9899 (±5640.51110)</td>
<td>5867.1376 (±2387.96065)</td>
<td>1.25 (0.50-5.00)</td>
</tr>
</tbody>
</table>

AUC_{0-4} Area under the plasma concentration curve from administration to last observed concentration at time t.

AUC_{0-72h} can be reported instead of AUC_{0-\infty} in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.

AUC_{0-\infty} Area under the plasma concentration curve extrapolated to infinite time.

AUC_{0-72h} does not need to be reported when AUC_{0-\infty} is reported instead of AUC_{0-72h}.

C_{\text{max}} Maximum plasma concentration

t_{\text{max}} Time until C_{\text{max}} is reached

The 90% confidence intervals of the test/reference ratio for AUC and C_{\text{max}} values for febuxostat 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**). Based on the data provided, the applicant’s test product, Febuxostat 120 mg film coated tablets can be considered bioequivalent to the reference product, Adenuric 120 mg film-coated tablets (Menarini International Operations Luxembourg S.A).
As these products meet the biowaiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study with the 120 mg tablet strength can be extrapolated to the 80 mg tablet strength.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none are required for applications of this type.

**IV.4 Clinical Efficacy**

No new data on efficacy have been submitted and none are required for applications of this type.

**IV.5 Clinical Safety**

No new data on clinical safety have been submitted and none are required for applications of this type.

**IV.6 Risk Management Plan (RMP)**

The marketing authorisation holder has submitted an 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 Febuxostat Warren 80 and 120 mg film-coated tablets.

A summary of safety concerns, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
</tr>
<tr>
<td>- Serious skin / hypersensitivity reactions</td>
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<tr>
<td>- Rhabdomyolysis</td>
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<tr>
<td>- Drug-drug interaction with azathioprine or mercaptopurine</td>
</tr>
<tr>
<td><strong>Important potential risks</strong></td>
</tr>
<tr>
<td>- Cardiovascular events</td>
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<tr>
<td>- Hepatic events</td>
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<tr>
<td>- Renal events</td>
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<tr>
<td>- Haematological / Bleeding events</td>
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<tr>
<td>- Thyroid events</td>
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<tr>
<td>- Off label use in the paediatric population (TSL specific)</td>
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<tr>
<td><strong>Missing information</strong></td>
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<tr>
<td>- Children and adolescents</td>
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<tr>
<td>- Subjects in whom the rate of serum urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome)</td>
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<tr>
<td>- Organ transplantation</td>
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<tr>
<td>- Severe hepatic impairment</td>
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<tr>
<td>- Pregnancy and lactation</td>
</tr>
<tr>
<td>- Limited experience in: female patients, elderly patients, severe renal impairment, moderate hepatic impairment.</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.7 Discussion of the clinical aspects**

It is recommended that Marketing Authorisations are granted for Febuxostat Warren 80 and 120 mg film-coated tablets.
V USER CONSULTATION
A user consultation with target patient groups on the package leaflet has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with febuxostat is considered to have demonstrated the therapeutic value of the compound. The products are considered to be bioequivalent to the reference products and their benefits and risks are considered similar. The benefit/risk balance is, therefore, considered to be positive.

PRODUCT LITERATURE
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.
Febuxostat 120 mg film-coated tablets

Each film-coated tablet contains 120 mg of febuxostat. Also contains lactose (as monohydrate). See the package leaflet for further information. Oral use.

WARREN GENERICS s.r.o. U Státní tvrze 285/21
196 00 Prague 9 Czech Republic

Use as directed by your doctor.
Keep out of the sight and reach of children.
Read the package leaflet before use. Medicinal product subject to medical prescription.

Barcode
Febuxostat 120 mg film-coated tablets

Each film-coated tablet contains 120 mg of febuxostat. Also contains lactose (as monohydrate). See the package leaflet for further information. Oral use. Use as directed by your doctor.

POM

Place dispensary label here

Barcode
Febuxostat Warren 80 and 120 mg film-coated tablets

UK/H/6418/001-002/DC
<table>
<thead>
<tr>
<th>Dosage</th>
<th>Pack Size</th>
<th>Brand Name</th>
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<tr>
<td>80 mg</td>
<td>3000 tablets</td>
<td>Febuxostat Warren 80</td>
</tr>
<tr>
<td>120 mg</td>
<td>3000 tablets</td>
<td>Febuxostat Warren 120</td>
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</tbody>
</table>

*UK/H/6418/001*
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)

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<thead>
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<th>Scope</th>
<th>Procedure number</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>
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