EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/123663/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Febuxostat Krka

International non-proprietary name: febuxostat

Procedure No. EMEA/H/C/004773/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
MS	Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control test
IR	Infrared
KF	Karl Fischer titration
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification / Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
ND	Not detected
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
PET/Al/PET/ LDPE	Polyethylene terephthalate/Aluminium/Polyethylene terephthalate/Low density polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
QC	Quality Control
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
TLC	Thin layer chromatography
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant KRKA, d.d., Novo mesto submitted on 23 April 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Febuxostat Krka, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 March 2017.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10(2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

Febuxostat Krka 80 mg/Febuxostat Krka 120 mg is indicated 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 Krka 120 mg is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

Febuxostat Krka is indicated in adults.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Adenuric instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is: Adenuric

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strengths, pharmaceutical form: Adenuric, 80 mg, 120 mg, film-coated tablets
- Marketing authorisation holder: Menarini International Operations Luxembourg S.A.
- Date of authorisation: 21-04-2008
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/447/001-024

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strengths, pharmaceutical form: Adenuric, 80 mg, 120 mg film-coated tablets
- Marketing authorisation holder: Menarini International Operations Luxembourg S.A.
- Date of authorisation: 21-04-2008
- Marketing authorisation granted by:

  - Union
- Marketing authorisation number: EU/1/08/447/001-024

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Adenuric, 120 mg, film-coated tablets
- Marketing authorisation holder: Menarini International Operations Luxembourg S.A.
- Date of authorisation: 21-04-2008
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation numbers: EU/1/08/447/003-004, 009-012, 019-024
- Bioavailability study number: 17-571 (Sponsor study-code)

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

The application was received by the EMA on	23 April 2018
The procedure started on	24 May 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	13 August 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	28 August 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 September 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 October 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	19 November 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to	29 November 2018

CHMP during the meeting on	
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	13 December 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	03 January 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 January 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	24 January 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Febuxostat Krka on	31 January 2019

2. Scientific discussion

2.1. Introduction

This is a marketing authorisation application of a generic febuxostat product. The indications sought for Febuxostat KrKa are the same as those of reference product Adenuric:

Febuxostat Krka 80 mg is only indicated 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 Krka 120 mg is indicated:

- 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).

- for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

Febuxostat Krka is indicated in adults.

Posology

Gout:

The recommended oral dose of Febuxostat Krka is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, Febuxostat Krka 120 mg once daily may be considered.

Febuxostat Krka works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dL (357 µmol/L).

Gout flare prophylaxis of at least 6 months is recommended.

Tumor Lysis Syndrome:

The recommended oral dose of Febuxostat Krka is 120 mg once daily without regard to food.

Febuxostat Krka should be started two days before the beginning of cytotoxic therapy and continued for a minimum of 7 days; however treatment may be prolonged up to 9 days according to chemotherapy duration as per clinical judgment.

Elderly

No dose adjustment is required in the elderly.

Renal impairment

The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min).

No dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment

The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).

Gout:

The recommended dose in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment.

Tumour Lysis Syndrome:

In the pivotal Phase III trial (FLORENCE) only subjects with severe hepatic insufficiency were excluded from trial participation. No dose adjustment was required for enrolled patients on the basis of hepatic function.

Paediatric population

The safety and efficacy of Febuxostat Krka in children below the age of 18 years have not been established.

No data are available.

Pharmacodynamic and pharmacokinetic properties of febuxostat

Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the above transformations are catalyzed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an in vitro inhibition Ki value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

The efficacy of febuxostat was demonstrated in three Phase 3 pivotal studies.

Pharmacokinetic properties

In healthy subjects, maximum plasma concentrations (Cmax) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when

doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life (t1/2) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with febuxostat 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

Absorption

Febuxostat is rapidly (tmax of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, Cmax is approximately 2.8-3.2 µg/mL, and 5.0-5.3 µg/mL, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in Cmax and a 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, febuxostat may be taken without regard to food.

Distribution

The apparent steady state volume of distribution (Vss/F) of febuxostat ranges from 29 to 75 L after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

Biotransformation

Febuxostat is extensively metabolized by conjugation via uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation via the cytochrome P450 (CYP) system. Four pharmacologically active hydroxyl metabolites have been identified, of which three occur in plasma of humans. In vitro studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of 14C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the active substance (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the faeces as the unchanged febuxostat (12%), the acyl glucuronide of the active substance (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

Renal impairment

Following multiple doses of 80 mg of febuxostat in patients with mild, moderate or severe renal impairment, the Cmax of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 µg·h/mL in the normal renal function group to 13.2 µg.h/mL in the severe renal dysfunction group. The Cmax and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment

Following multiple doses of 80 mg of febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the Cmax and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Age

There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of febuxostat in elderly as compared to younger healthy subjects.

Gender

Following multiple oral doses of febuxostat, the Cmax and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected Cmax and AUC were similar between the genders. No dose adjustment is needed based on gender.

Aspects on the development programme

To support the marketing authorisation application, the Applicant has submitted a bioequivalence study conducted with the 120 mg strength. The reference product is Adenuric 120 mg film-coated tablets.

A biowaiver was requested for the additional strength 80 mg.

The applicant did not receive CHMP or national Scientific Advice pertinent to the development programme.

The finished product febuxostat film-coated tablets is presented in the form of immediate release film coated tablets for oral administration and is available in 2 strengths, defined by the quantity of drug substance febuxostat, i.e. 80 mg and 120 mg.

Drug substance febuxostat in the medicinal product is in an anhydrous crystalline polymorphic form.

Febuxostat film-coated tablets 80 mg and 120 mg have been developed and manufactured by Krka, d.d., Novo mesto, Slovenia.

The applicant has applied for the following pack sizes: 14, 28, 56, and 84 film-coated tablets. All pack sizes are consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 80 mg or 120 mg of febuxostat as active substance.

Other ingredients are:

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

Film coating: poly(vinyl alcohol), macrogol 3350, titanium dioxide (E171), talc, red iron oxide (E172) (80 mg), yellow iron oxide (E172) (120 mg).

The product is available in PVC/PVDC/PVC//Al blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of febuxostat is 2-(3-cyano-4-isobutyloxyphenyl)-4-methylthiazole-5-carboxylic acid corresponding to the molecular formula $C_{16}H_{16}N_2O_3S$. It has a relative molecular mass of 316.37 g/mol and the following structure:

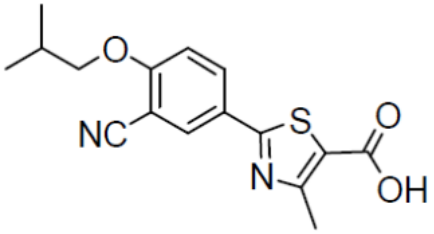

Figure 1: Active substance structure

The chemical structure of febuxostat was elucidated by a combination of elemental analysis and the following spectroscopic methods: infrared (IR), Raman, nuclear magnetic resonance (NMR), mass spectrometry (MS) and UV. The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD) and melting point.

The active substance is a white crystalline powder, with needle to thin plate shaped particles, slightly hygroscopic, soluble at room temperature in acetone, sparingly soluble in ethyl acetate and 1-octanol, slightly soluble in ethanol and methanol and insoluble in water. Febuxostat is insoluble in aqueous buffers with pH at 1.0 and 4.5 and slightly soluble in aqueous buffer with pH 7.5 at 37°C.

Febuxostat possesses no optical isomers. Polymorphism has been observed for febuxostat. It is known to exist in different crystalline forms and in an amorphous form. All the known crystalline forms (hydrate, solvate or anhydrous) were described with literature sources and with their solvent of crystallization. It has been demonstrated that the manufacturer consistently produces an anhydrous crystalline form of febuxostat, which is obtained by the defined process parameters and solvent system used. The polymorphic form is controlled in the active substance specification by an XRPD method.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. Febuxostat is synthesized in two main stages (five chemical synthetic steps) using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities, including potential genotoxic impurities, were well discussed with regards to their origin and characterised. An appropriate control strategy for impurities has been proposed. The active substance is packaged in four-layer bags constructed of PET/Al/PET/LDPE, which complies with the EC directive 2002/72/EC and EC 10/2011 as amended, and placed into carton drums.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC), impurities (HPLC), assay (HPLC), water (KF), sulphated ash (Ph. Eur.), FBX oxime acid impurity (HPLC), residual solvents (GC), polymorphic form (XRPD), particle size (laser diffraction) and microbiological quality (Ph.Eur.).

Impurities are controlled according to ICH Q3A and appropriate specifications have been set. Test for heavy metals is omitted from specification in line with ICH Q3D. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (n=3 production scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. The active substance is photostable.

The following parameters were tested: appearance, identification, water content, impurities, assay and polymorph content. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

Results from forced degradation studies under stressed (acidic, basic, oxidation, light and heat conditions) were also provided as part of the HPLC assay and impurities analytical method validation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months when stored in the proposed container at a temperature below 25ºC.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Febuxostat 80 mg film-coated tablets are presented as off pink, oval, biconvex, film-coated tablets scored on one side. Tablet dimension: approximately 16 mm × 8 mm.

Febuxostat 120 mg film-coated tablets are presented as brownish yellow, slightly biconvex, capsule shaped film-coated tablets scored on both sides. Tablet dimension: approximately 19 mm × 8 mm.

The score lines are to facilitate breaking for ease of swallowing and not to divide into equal doses.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

This application for Febuxostat 80 mg and 120 mg film-coated tablets is a generic application, made according to Article 10(1) of Directive 2001/83/EC, claiming bioequivalence to the reference medicinal product Adenuric 80 mg and 120 mg film-coated tablets (MAH: Menarini International Operations Luxembourg S.A). The reference medicinal product was first authorised in the EU in April 2008.

The aim of the formulation development programme was to design bioequivalent, effective and safe generic alternative to the reference medicinal product of specified quality and a simple and reproducible technological procedure to consistently deliver the intended performance of the medicinal product. The pharmaceutical development followed a traditional approach.

The main difference between the reference product and proposed formulation is the form of active substance febuxostat in finished product; both forms of febuxostat are anhydrous forms. To avoid patent infringement a different polymorphic form of the active substance was used in the formulation.

A comparison of the final Febuxostat film-coated tablets (Krka) and reference product Adenuric film coated tablets (Menarini, source: SmPC, www.ema.europa.eu) compositions is provided in Table 1.

Table 1 Comparison of test and reference product compositions

Febuxostat film coated tablets (Krka)	Adenuric film coated tablets (Menarini)
Core	
Febuxostat	Febuxostat
Lactose monohydrate	Lactose monohydrate
Microcrystalline cellulose	Microcrystalline cellulose
Hydroxypropylcellulose	Hydroxypropylcellulose
Croscarmellose sodium	Croscarmellose sodium
Silica, colloidal hydrated	Silica, colloidal hydrated
Magnesium stearate	Magnesium stearate
Film coating	
Coating mixture: - Poly(vinyl alcohol) - Macrogol 3350 - Titanium dioxide (E171) - Talc	Coating mixture: - Poly(vinyl alcohol) - Macrogol 3350 - Titanium dioxide (E171) - Talc - Iron oxide, yellow (E172) (both strengths, 80 mg and 120 mg)
Iron oxide, yellow (E172) (only in 120 mg strength)	
Iron oxide, red (E172) (only in 80 mg strength)	

In the proposed formulation, the active substance is presented in an anhydrous crystalline polymorphic form. Batch analysis data and XRPD testing confirm that the polymorphic form of febuxostat remains unchanged during manufacturing process and on stability testing. Based on the provided data, omission of determination of polymorphic form of active substance in finished product specification is justified.

Febuxostat is a BCS Class 2 (high permeability, low solubility) active substance according to the Biopharmaceutics Classification System (BCS). As particle size could potentially influence the solubility and consequently, dissolution and bioavailability of febuxostat from the finished product the influence of particle size of febuxostat on dissolution profiles was evaluated. On the basis of these results it was concluded that there is no influence of particle size of febuxostat on the manufacturing process or performance of the finished product, product. An appropriate active substance specification, based on the particle size distribution of febuxostat used to manufacture the bio-batch of test product used in the bioequivalence study, has been set.

During the development of the formulation, physical characteristics of excipients, granules, compression mixtures and tablet cores were studied in order to evaluate the influence on the manufacturing process and performance of the finished product. The selected formulation was carefully studied during the production of small scale batches to determine the technological parameters and requirements. Scale-up to pilot scale was carried out. The influence of the hardness on the dissolution profile was investigated. Further scale up to production scale batches was conducted. These batches were used in in-vivo bioequivalence study and for ICH stability testing which were produced by the same manufacturing process using the same type of equipment.

The higher strength, Febuxostat 120 mg film-coated tablets formulation was proven to be bioequivalent to the reference medicinal product Adenuric 120 mg film-coated tablets in *in vivo* bioequivalence study under fasting condition () in accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). The study was conducted in compliance with current GCP and GLP standards.

The applicant requested a biowaiver for Febuxostat 80 mg film-coated tablets based on the proven bioequivalence of the Febuxostat 120mg film coated tablets and the fulfilment of the following requirements of the Guideline of Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1):

- The different test products are manufactured by the same manufacturing process;
- The qualitative composition of the different strengths is the same;
- The composition of the strengths are quantitatively proportional, the ratio between the amount of each excipient to the amount of active substance is the same for all strengths;
- Febuxostat demonstrates linear pharmacokinetics.
- The two strengths demonstrated similar dissolution profiles under all tested conditions across the physiological pH range.

The development of the QC dissolution test method was guided by the recommendations of relevant chapters 2.9.3 (*Dissolution test for solid dosage forms*) and 5.17.1 (*Recommendations on dissolution testing*) of the European Pharmacopoeia and relevant sections of EMA guideline CPMP/EWP/QWP/1401/98Rev.1/Corr**. In compliance with the above guidance, the basic criteria which governed the choice of the dissolution method (apparatus, medium, volume, stirring rate) was the discriminatory power of the method, reflecting *in vivo* conditions, fulfilment of 'sink conditions', complete release of the drug substance within a specified time and appropriate robustness for routine QC testing. The discriminatory power of the dissolution method was investigated by performing dissolution testing of batches with changes in the composition and the manufacturing process of Febuxostat 120 mg film-coated tablets. In response to questions raised during the procedure the applicant performed additional investigations and development work and updated the method. The final selected dissolution method for QC testing was shown to be discriminatory.

The primary packaging is PVC/PVDC/PVC/Al blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: mixing and homogenizing, granulation (fluid bed granulation) and drying, sieving, blending, compression, coating and packaging. The process is considered to be a standard manufacturing process.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Proposed holding times have been justified and validated. Major steps of the manufacturing process have been validated by a number of studies at minimum production scale. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. A further three batches will be validated at maximum production scale prior to commercialisation in line with the submitted validation scheme

Product specification

The finished product release specifications shown in Table 3 include appropriate tests for this kind of dosage form; appearance, uniformity of dosage units (Ph. Eur., water (Ph. Eur.), identification (HPLC, TLC), related substances (HPLC), assay (HPLC), dissolution (Ph. Eur.), microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three production scale batches of each strength of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. These batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for in line with the proposed shelf-life specifications. The analytical procedures used are stability indicating. No significant changes have been observed.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. A bulk stability study was performed on one batch per strength at long term and accelerated conditions which supports the claimed holding time for bulk product.

Based on available stability data, the proposed shelf-life of 24 months, without any special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose monohydrate used in the formulation is of animal origin and is TSE/BSE free and that magnesium stearate used in the formulation is of vegetable origin and is TSE/BSE free.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment studies were submitted. During the assessment, the applicant was requested to present data to substantiate the claim that an increase in environmental exposure of the active substance would not be expected. The applicant has provided an updated ERA showing the febuxostat consumption data for EU countries in the last four years, to support the notion that the marketing authorization of this additional generic product will not significantly change the increase of environmental burden, since the demand for a compound on the market would stay approximately the same regardless of the number of products available on the market. The overall consumption data for febuxostat in the European countries demonstrate that the concentration of febuxostat entering the surface waters via excretion of the treated patients exceeds the phase II trigger value of 0.01 µg/L, therefore an ERA phase II is required.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of febuxostat to the environment.

The applicant commits to perform the following studies as follow-up measures: ERA phase II studies by the end of year 2021.

2.3.3. Discussion on non-clinical aspects

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Pharmacodynamic, pharmacokinetic and toxicological properties of febuxostat are well known. As febuxostat is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

As the overall consumption data for febuxostat in the European countries demonstrate that the concentration of febuxostat entering the surface waters via excretion of the treated patients exceeds the phase II trigger value of 0.01 µg/L the applicant commits to perform ERA phase II studies by the end of year 2021.

2.3.4. Conclusion on the non-clinical aspects

The non-clinical aspects are considered adequate to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing febuxostat. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) in its current version, is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Exemption

The applicant has performed and submitted one bioequivalence study using the highest strength (120mg) and has requested a biowaiver for the lower strength 80mg based on the proven bioequivalence of the febuxostat 120mg film-coated tablets and the fulfilment of the following requirements of the Guideline of Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1):

- Both strengths of Febuxostat KrKa film-coated tablets (80 mg and 120 mg) are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.
- The qualitative composition of the two strengths is the same.
- The composition of the strengths are quantitatively proportional, the ratio between the amount of each excipient to the amount of active substance is the same for all strengths.
- Appropriate dissolution data was submitted by the applicant.

Considering the linearity in the pharmacokinetics of febuxostat, the CHMP concluded that it was sufficient to establish bioequivalence with only one strength.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

2.4.2. Pharmacokinetics

Study 17-571 (BEF-470-17) – Comparative, Randomised, Single dose, 2-way crossover bioavailability study of febuxostat 120mg tablet formulation tablets in healthy volunteers under fasting conditions

Methods

Study design

This was a randomised, laboratory blinded, two-way, single centre, balanced, single dose, crossover comparative oral bioavailability study to establish comparative bioequivalence of Febuxostat 120mg film coated tablets and Adenuric 120mg film coated tablets (Febuxostat, MAH: Menanrini International Luxembourg) in 50 healthy, adult male and female human subjects under fasting conditions.

The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety of the subjects.

Based on the randomised schedule and following an overnight fast of at least 10 hours in both periods each volunteer received a single oral dose of Febuxostat 120mg film coated tablets in period I and either one tablet of the reference or test product in period II.

Test and reference products

Febuxostat 120mg film coated tablets manufactured by Krka d.d. Novo Mesto Slovenia and Adenuric 120mg film coated tablets manufactured by Menanrini-Von Heyden .

Table 2 Test and reference product information

Product characteristics	Test product	Reference product
Name	Febuxostat 120 mg film-coated tablets	Adenuric® 120 mg film-coated tablets (febuxostat)
Strength	febuxostat 120 mg	febuxostat 120 mg
Dosage form	film-coated tablets	film-coated tablets
Manufacturer	Krka, d.d., Novo mesto, Slovenia, EU	Menarini-Von Heyden GmbH, Germany, EU
Measured content(s) (% of label claim)	febuxostat 101.3 %	febuxostat 103.0 %
Commercial Batch Size	Specified in the Module 3 of the dossier in chapter 3.2.P.3.2 Batch Formula	
Expiry date (Retest date)	Retest date: 7 February 2018	Expiry date: October 2019
Member State where the reference product is purchased from:		Germany, EU
This product was used in the following trials:	KRKA study code:17-571; CRO's study code: BEF-470-17	KRKA study code:17-571; CRO's study code: BEF-470-17

Population(s) studied

Main inclusion criteria: Healthy male and female subjects ≥ 18 and ≤ 55 years of age, with Body Mass Index within 18.5-30 kg/m2, Caucasian race, non-smokers.

Subjects were in good health as determined by the medical history, complete physical examination (including vital signs), electrocardiogram (ECG) and clinical laboratory tests (hematology, biochemical profile, urinalysis), including negative serum pregnancy test (for female subjects), negative Human Immunodeficiency Virus (HIV), Hepatitis B and Hepatitis C tests at screening and negative urine screen for drugs of abuse, alcohol test, cotinine test and serum pregnancy test (for female subjects) at check-in of each period.

Fifty (50) healthy adult human male and female subjects were enrolled as per the protocol whilst 47 subjects completed both study periods.

- One female subject was withdrawn from the study by the investigator in period 1 due to adverse events (nausea, vomiting and headache). Her febuxostat plasma concentration data up to the withdrawal are reported in the Bioanalytical report assessed by the CHMP.
- Two male subjects withdrew themselves, from the study by not attending the Check-in Period 2 due to private reasons. At that time subjects were contacted via telephone and stated, that they are feeling well and decided not to attend end-of-study clinical laboratory tests. Due to self-withdrawal, their plasma samples were not subjected to the bioanalysis of febuxostat.

Analytical methods

Analysis of febuxostat was performed using test method ASP/17-571(FSS). This HPLC/MS/MS method involved the extraction of febuxostat and the respective internal standards from human plasma.

Storage period of study samples

Dosing started on the 28 November 2017 and the bioanalysis was performed between 11 December 2017 to 20 December 2017.

The long-term stability of febuxostat in human plasma covers 63 days at -20°C.

Two thousand five hundred and fifty nine (2569) samples were expected according to the protocol however 2515 blood samples were received (54 missing samples). The missing samples have been adequately justified by the Applicant (drop outs and missed blood draws). Twenty three (23) samples were re-assayed and the reason for their repeats was documented and adequately presented.

Bioanalytical report

The bioanalytical report was submitted with 20% of the subject chromatograms presented as well as the method SOPs. A certificate of analysis for the internal standards and the reference standards of febuxostat have been provided and are deemed acceptable.

Incurred Sample Reanalysis

One hundred and seventy six (176) samples for Febuxostat were identified for incurred sample reanalysis. 95.5% are the percentage of samples for all three API's where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

Validation of the test method

The method has been validated (VR/FSS-4P/01 (R01)) and revised twice.

The following parameters were addressed: Specificity and selectivity, Linearity including calibration curve, limit of quantification including accuracy and precision, precision (intra and inter day), accuracy (intra and inter day), recovery of the analyte and internal standard, matrix effect (accuracy and precision in human plasma, haemolysed human plasma, lipaemic human plasma), reinjection reproducibility, dilution integrity including accuracy and precision, freeze thaw stability (4 cycles), auto sampler storage stability, bench top stability, extraction procedure stability, storage stability at -80°C, long stability in biological matrix at -20°C, short term stability in the biological matrix at +5°C and at sample processing temperature, short term and long term stock and working solutions stability (of analyte and internal standard methanol) at -20°C and at +5°C respectively.

Each parameter has been assessed and the limits are justified. They were deemed acceptable by the CHMP.

Assay specificity in the presence of the following concomitantly administered compounds was assessed: Acetaminophen (12000.00ng/mL) and Ibuprofen (32000.00 ng/mL). No significant interference was observed.

The influence of metabolites of Febuxostat (Febuxostat Acyl-ß-D-glucuronide) was also observed.

In summary, the CHMP was of the opinion that the analytical methods used were acceptable and appropriate. The chromatograms presented are acceptable and the re-analysed samples have been adequately justified. The calibration curves are appropriate and the stability testing supports the conditions the samples were exposed to during collection and testing. The applicant has also provided

all the validation reports and relevant supportive data together with certificates of analysis for the analyte standard and internal standards used in the analytical method validation. The relevant SOPs have been provided and deemed valid. The Incurred sample reanalysis was provided as well as information on the partial revalidation of the method. These are deemed acceptable. Co-administered drug effect was also carried out as part of validation and no significant interference was observed.

The method was audited on 22 February 2018 and the outcome was satisfactory.

Pharmacokinetic variables

- Primary parameters: Cmax and AUC0-72,
- Secondary parameters: AUC0-∞, Tmax, residual area, λZ and T1/2.
- Bioequivalence criteria: The 90% confidence intervals of the relative mean AUC 0-t, and Cmax of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

The CHMP was of the opinion that the pharmacokinetic variables are adequate for the study.

Statistical methods

Analysis of variance (ANOVA) was performed on the ln-transformed AUCt, AUCi and Cmax parameters for febuxostat. Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals was calculated for the Test to Reference ratios of least-squares means for parameters AUCt, AUCi and Cmax using ln-transformed data.

Criteria for Bioequivalence:

Statistical inference of febuxostat was based on a bioequivalence approach using the following standards:

Bioequivalence was concluded if the 90% geometric confidence intervals of the ratio (Test/Reference) of least-squares means derived from analyses on the ln-transformed PK parameters AUCt and Cmax for febuxostat were within 80.00% – 125.00% range.

Descriptive statistics were also done for all pharmacokinetic parameters.

ANOVA model:

Fixed factors: sequence, period, treatment, subject (nested within sequence)

Safety: Descriptive statistics.

The CHMP was of the opinion that appropriate variables were measured. The statistical methodology is endorsed.

The sampling schedule provides adequate estimation of Cmax. Statistical data and a graphical representation to cover the plasma concentration time curve long enough to provide an estimate of the extent of absorption, have been provided.

Results

Table 3 Pharmacokinetic parameters for Febuxostat 120mg n=47 (non-transformed values)

Pharmacokinetic parameter	[2]Arithmetic Means (±SD)	
	Test product	Reference Product
$AUC_{(0-t)}$ (h*ng/mL)	14303.22 (±4751.57)	14660.95 (±5466.63)
$AUC_{(0-\infty)}$ (h*ng/mL)	14740.22 (±5033.30)	15088.12 (±5650.88)
Cmax (ng/mL)	5529.33 (±1867.05)	5211.92 (±1983.83)
Tmax[1] (h)	1.00 (0.33, 4.67)	1.00 (0.33, 4.67)

[1]Median (Min, Max)
[2]Arithmetic Means (±SD)

Table 4 Statistical analysis for Febuxostat 120mg n=47 (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	98.57%	95.74% - 101.48%	8.4%
Cmax	106.87%	98.13% - 116.39%	25.0%

[1]Estimated from the Residual Mean Squares.

The CHMP was of the opinion that the 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters AUC0-t and Cmax were within 80-125% acceptance range for febuxostat. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **). Bioequivalence with the parent compound Febuxostat has been shown.

Safety data

A total of 8 post-dose adverse events were reported by 4 (8%) of the 50 subjects who received at least one dose of the study medication (safety population). Two cases of “headache” was reported by 4.1% (n=2) of the 49 subjects who received treatment A and by 4.2% (n=2) of the 48 subjects who received treatment B. Two cases of “nausea” and two cases of ”vomiting” were reported by 4.1% (n=2) of the 49 subjects who received treatment A.

The severity of 6 (six) registered AEs was graded as “moderate”, and the severity of 2 (two) registered AEs was graded as “mild”. The two cases of “headache” were graded as “mild” and two cases were graded as “moderate“, two cases of “nausea” and two cases of “vomiting” were graded as “moderate”.

The relationship with the study medication of all adverse events was judged as “possible”.

AE resolved completely by the end of the study and the subjects recovered without a treatment.

No severe adverse events, serious adverse events or deaths occurred during the study.

Upon conclusion of the clinical portion of the study, the results from the subjects who completed end of study procedures, including laboratory tests and vital signs measurements confirmed the absence of significant changes in the subject’s state of health. No new safety concerns related to administered formulations were raised during the conduct of this study.

Table 5 Adverse events

Period of the Study	Last treatment received	Adverse Event	Intensity	Expected /serious	Onset date/ time	End date/ time	Action taken*	Relation-ship to study drug
II	B	Headache	mild	YES/NO	06.12.2017 16^{15} h	06.12.2017 19^{00} h	None	possible
I	A	Headache	moderate	YES/NO	29.11.2017 11^{45} h	29.11.2017 17^{30} h	Drug treatment	possible
I	A	Nausea	moderate	YES/NO	29.11.2017 11^{45} h	29.11.2017 17^{30} h	Drug treatment	possible
I	A	Vomiting	moderate	YES/NO	29.11.2017 14^{20} h	29.11.2017 14^{23} h	Drug treatment	possible
I	B	Headache	mild	YES/NO	29.11.2017 17^{00} h	29.11.2017 22^{45} h	None	possible
I	A	Headache	moderate	YES/NO	29.11.2017 15^{00} h	29.11.2017 23^{00} h	Drug treatment	possible
I	A	Nausea	moderate	YES/NO	29.11.2017 15^{00} h	29.11.2017 23^{00} h	None	possible
I	A	Vomiting	moderate	YES/NO	29.11.2017 20^{10} h	29.11.2017 20^{12} h	None	possible

*The drugs used for management of adverse events that occurred during the study are displayed in a table in Section 9.4.7 (Prior and Concomitant Therapy).

The CHMP commented that there were no other screening or post-study laboratory results outside of normal range that were deemed clinically significant by the Investigator.

The two treatments were well tolerated by the subjects (in both periods) enrolled in the study. The adverse events mentioned above are all included in the SmPC and there are no new concerns arising from this study. The two products had similar safety profiles.

Conclusions

Based on the presented bioequivalence study the test formulation Febuxostat 120mg film coated tablets of Krka d.d. Slovenia is considered bioequivalent with the reference Adenuric 120mg film coated tablets.

The results of study 17-571 with Febuxostat 120mg formulation can be extrapolated to the 80mg, according to conditions in the relevant Guideline.

The two treatments were well tolerated by the subjects (in both periods) enrolled in the study. The adverse events mentioned above are all included in the SmPC and there are no new concerns arising from this study. The two products had similar safety profiles.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameters AUC0-t and Cmax were within 80-125% acceptance range for Febuxostat.

This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **).

The results of study 17-571 with Febuxostat 120mg formulation can be extrapolated to the other 80mg strength, according to conditions in the relevant Guidelines.

The two treatments were well tolerated by the subjects (in both periods) enrolled in the study. The adverse events mentioned above are all included in the SmPC and there are no new concerns arising from this study. The two products had similar safety profiles.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence study the test formulation Febuxostat 120mg film coated tablets of Krka d.d. Slovenia is considered bioequivalent with the reference Adenuric 120mg film coated tablets.

The results of study 17-571 with Febuxostat 120mg formulation can be extrapolated to the other 80mg strength, according to conditions in the relevant Guideline.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	Serious skin / hypersensitivity reactions
	Rhabdomyolysis
	Drug-drug interaction with azathioprine or mercaptopurine
Important potential risks	Cardiovascular events
	Hepatic events
	Renal events
	Neuropsychiatric events
	Haematological / Bleeding events
	Thyroid events
	Off label use in the paediatric population (TLS specific)
Missing information	Children and adolescents
	Subjects in whom the rate of serum urate formation is greatly increased (e.g Lesch-Nyhan syndrome)
	Organ transplantation
	Severe hepatic impairment
	Pregnancy and lactation
	Limited experience in: severe renal impairment, moderate hepatic impairment
	Interaction with standard therapy of haematological malignancies (TLS specific)
	Off label use in patients with solid tumors (TLS specific)

Pharmacovigilance plan

Not applicable, there are no studies in the pharmacovigilance plan.

Risk minimisation measures

Not applicable, there are no additional risk minimisation measures in the risk management plan and routine risk minimisation is aligned with the originator.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Product information

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.

3. Benefit-risk balance

This application concerns a generic version of febuxostat Film-coated tablet. The reference product Adenuric is indicated for "*Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis)*" and for the "*prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS)*". "*ADENURIC is indicated in adults*." No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a Comparative, Randomised, Single dose, 2-way crossover bioavailability study of febuxostat 120mg tablet formulation tablets in healthy volunteers under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Febuxostat KrKa met the protocol-defined criteria for bioequivalence when compared with the reference product Adenuric. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Febuxostat Krka is favourable in the following indication:

"Febuxostat Krka is indicated 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 Krka is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

Febuxostat Krka is indicated in adults."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.