21 April 2017
EMA/368110/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Febuxostat Mylan

International non-proprietary name: febuxostat

Procedure No. EMEA/H/C/004374/0000

Note

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 26 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Febuxostat Mylan, 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 28 January 2016.

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 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 indication:

Febuxostat Mylan 80 mg
Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Febuxostat Mylan 120 mg
Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).
Prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

Febuxostat Mylan 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:

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

- Product name, strength, pharmaceutical form: Adenuric 80 mg; 120 mg Film-coated tablet
- Marketing authorisation holder: Menarini International Operations Luxembourg S.A.
- Date of authorisation: 21.04.2008
- Marketing authorisation granted by:
  - Community

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

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

- Product name, strength, pharmaceutical form: Adenuric 80 mg; 120 mg Film-coated tablet
- Marketing authorisation holder: Menarini International Operations Luxembourg S.A.
- Date of authorisation: 21.04.2008
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/08/447/001-024

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

- Product name, strength, pharmaceutical form: Adenuric 120 mg Film-coated tablet
- Marketing authorisation holder: Menarini International Operations Luxembourg S.A.
- Date of authorisation: 21.04.2008
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/08/447/003
- Bioavailability study number(s): C15224

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.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Juris Pokrotnieks

- The application was received by the EMA on 26 April 2016.

- The procedure started on 19 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 August 2016.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 19 August 2016.
- During the meeting on 2 September 2016 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 December 2016.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2017.
- During the PRAC meeting on 9 February 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 March 2017.
- During the meeting on 21 April 2017, 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 Mylan.

2. Scientific discussion

2.1. Introduction

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

Febuxostat Mylan 80 mg film-coated tablets are 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).

Febuxostat Mylan 120 mg film-coated tablets are 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) 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).

Febuxostat Mylan is indicated only for adults.

Posology

Gout: The recommended oral dose of Febuxostat Mylan 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 Mylan 120 mg once daily may be considered.

Febuxostat Mylan 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 Mylan is 120 mg once daily without regard to food.

Febuxostat Mylan 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 the efficacy of febuxostat in children aged 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.

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.

According to the Biopharmaceutics Classification System febuxostat is classified as a Class 2 compound (low solubility, high permeability).

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.

2.2. Quality aspects

2.2.1. Introduction

Febuxostat Mylan is presented as film coated tablets containing 80 mg or 120 mg of febuxostat as the active substance.

Other ingredients of the tablet core are lactose, microcrystalline cellulose, magnesium stearate, hydroxypropylcellulose, croscarmellose sodium, colloidal hydrated silica, colloidal anhydrous silica, crospovidone and talc. The film coating is composed of hypromellose, titanium dioxide (E171) , ethylcellulose, iron oxide yellow (E172), triacetin and iron oxide black (E172).

The product is available either in (PVC/OPA/Alu)/Alu with embedded desiccant or in HDPE bottles with polypropylene (PP) screw cap closure with desiccant 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-(2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic 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:

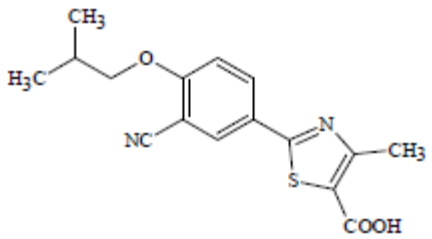

Figure 1. Structure of febuxostat.

The structure of the active substance was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, UV spectroscopy, IR spectroscopy, elemental analysis and powder XRD.

Febuxostat appears as a white or off white, slightly hygroscopic crystalline powder, freely soluble in dimethyl formamide, soluble in dimethyl sulphoxide and sparingly soluble in ethanol. In aqueous buffer media with pH below 6 it is insoluble; and its solubility is 2 mg /ml at pH 8.

Febuxostat does not exhibit isomerism as it does not contain chiral centre but it exhibits polymorphism. The active substance (AS) manufacturer consistently produces febuxostat Form K, which is confirmed by XRD data and which is controlled by XRD method at release and during stability studies.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance (AS) has been provided in the restricted part of the ASMF and it was considered satisfactory.

Febuxostat is synthesized in seven main chemical steps and crystallisation followed by micronisation. The starting materials, which have been redefined during the evaluation, are well-defined and controlled by acceptable specifications. The synthesis is performed in two sites. The first site performs the two first steps of the synthetic process and the second the last five. A satisfactory description of the synthesis and the micronisation step has been provided. Two proposed batch sizes have been defined.

Four intermediates are isolated and their specifications were presented and considered acceptable. Critical steps and critical process parameters have been identified. Adequate in-process controls are applied during the synthesis. 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 genotoxic impurities were well discussed with regards to their origin and characterised. The carry-over of reagents, solvents, intermediates and impurities from the redefined starting materials to febuxostat active substance

along with updated discussion on evaluation of genotoxic impurities was also provided and is considered satisfactory.

Febuxostat is packed in a LDPE bag under nitrogen atmosphere, inserted in a triple laminated aluminium bag along with two silica gel and one molecular sieve sachets and sealed under vacuumised nitrogen. These bags are further packed in HDPE drum. The polythene bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended. The specification of the LDPE bag as well as CoAs were presented.

Specification

The active substance specification includes appropriate tests and limits for appearance (visual), solubility (visual), identity (IR, HPLC), polymorphism (XRD), sulfated ash (Ph. Eur.), loss on drying (Ph. Eur.), heavy metals (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC), and particle size (laser diffraction).

Four compounds involved in the synthesis of the active substance were identified that have structural alerts and have been assessed according to ICH M7 and are sufficiently controlled. Satisfactory information regarding the potential carry over of these impurities has been presented. According to the TTC concept, and taking the maximum daily dose of 120 mg/day of febuxostat active substance into consideration, the permissible level of genotoxic impurity is 12.5 ppm. The absence of the above mentioned impurities in the final active substance has been demonstrated as all of these compounds were found below LOD which is far below 30% of TTC. Therefore it was concluded that absence of genotoxic impurities in final AS has been sufficiently demonstrated.

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 from six production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on six production scale batches of active substance from the proposed manufacturer stored in the intended commercial packaging for up to 48 months under long term conditions (25 °C ± 2 °C / 60 % RH ± 5% RH) and for up to 6 months under accelerated conditions (40 °C ± 2 °C /75 % RH ± 5% RH) was provided according to the ICH guidelines.
Samples were tested for description, identification, polymorphic form, loss on drying, related substances and assay. The analytical methods used were the same as for release and were stability indicating.
No significant changes to any of the measured parameters were observed under either storage condition and all remained within specification. The stability of the polymorph was also verified by analysing accelerated (40±2°C, 75±5% RH) and long term (25±2°C, 60±5% RH) stability samples of the aforementioned validation batches. Febuxostat Form K was found to be stable and consistent with the initial pattern upon storage. Based on the presented data a change of polymorphic form during the proposed retest period is considered highly unlikely.

Photostability testing following the ICH guideline Q1B was performed as part of initial forced degradation study on one commercial scale batch. The results showed that the AS is not sensitive to light.

Stress testing in solution (thermal, acidic, basic, oxidative, heat) and in solid state (light, UV, heat) was also performed on one commercial scale batch. Samples were tested for description, identification, specific optical rotation, loss on drying, assay and related substances. No degradation was observed under the conditions tested, except under base hydrolysis where significant degradation occurred. The degradation pathways and the stability indicating power of the assay and related substance methods have been demonstrated.

The stability results justify the proposed retest period of 48 months in the proposed container without special storage conditions.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as yellow, capsule shaped, biconvex tablets, debossed with “M” on one side of the tablet and “FX3” (80 mg tablets) or “FX4” (120 mg tablets) on other side, intended for oral administration.

The aim of the pharmaceutical development work was to develop an immediate release product with a robust formulation, adequate chemical stability, and an efficient, simple and reproducible manufacturing process, which performs similarly *in vivo* to the reference product.

The following physico-chemical properties of febuxostat have been studied: particle size distribution, apparent density, tapped density, compressibility index and Hausner ratio. The solubility studies showed that active substance exhibits pH dependent solubility; insoluble in water, 0.1 N HCl and pH 4.5 acetate buffer and showing higher solubility in pH 6.8 phosphate buffer and pH 7.5 phosphate buffer (>0.44 mg/ml).

The excipients for product development studies were chosen based on the innovator product details, literature search and on AS-excipients compatibility study. The prototype product development was initiated with dose proportional composition for both strengths. In order to evaluate the effect of different excipient concentrations on manufacturability several trials were conducted before concluding the final composition.

All excipients used in the proposed formulation are conventional pharmaceutical ingredients and comply with their respective Ph.Eur. monograph. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The compatibility studies of the AS and various excipients showed no changes in appearance and content of total impurities, therefore, it was concluded that febuxostat is compatible with all excipients intended to use in the product development.

Since the formulation of reference product available in different EU member states is identical, as it is approved through centralized procedure, two different batches of Adenuric 120mg film coated tablets were evaluated for physical and chemical properties. They both showed similar physical and chemical characteristics. In order to assess pharmaceutical equivalence, test and reference products were compared with regard to their quality characteristics (related substances) and *in vitro* performance (dissolution profiles). Both test and reference product exhibited similar impurity profiles.

The choice of the proposed dissolution method has been sufficiently described and justified. In order to assess the discriminatory power of the selected dissolution method, dissolution studies on different batches

with slightly modified composition and manufacturing process were performed. From the results it can be concluded that the selected dissolution method is discriminatory in nature with respect to the studied formulation and process changes.

Comparative dissolution profiles of Febuxostat Mylan 80 mg and 120 mg-film-coated tablets (test formulation) and EU reference product Adenuric 80 mg and 120 mg film-coated tablets were generated in different dissolution media i.e. pH 6.8 Phosphate buffer (release media), 0.1N HCl and pH 4.5 Acetate buffer covering the pH range of pH 1.2 - pH 6.8.

From the above results it was apparent that more than 85% of the labelled amount of the AS was released within 15 minutes from both the test and reference formulations in pH 6.8 phosphate buffer and in the QC release medium. Release of the reference product in 0.1 N HCl and pH 4.5 acetate buffer was faster than the test, but incomplete release was observed for both the test product and reference product.

The differences in the dissolution profiles were justified, as required by the guideline on the Investigation of Bioequivalence, based on the solubility study of febuxostat and the potential impact of even slight differences in the manufacturing process or formulation on the overall solubility. Since Febuxostat Mylan 120 mg film-coated tablet was found to be bioequivalent to reference product Adenuric 120 mg tablet, the difference in drug release profile in 0.1N HCl and pH 4.5 acetate buffer between test product and reference product is not expected to have any effect on the *in vivo* performance of the test product.

Dry granulation technique was chosen for manufacturing process of the drug product because direct compression process was not considered suitable due to the very poor flow characteristics of active substance. Premix blending was optimised with regard to the resulting blend uniformity. The roller compaction process parameters were studied to ensure manufacturability and regarding the potential impact on the release and degradation of the AS. Studies regarding the milling process focused on identifying the screen size and milling speed which would yield the desired particle size distribution of granules. Finally the impact of different tablet hardness values on physical characteristics and dissolution profile was evaluated and acceptable ranges were set. In addition a detailed risk assessment of process variables was included in the dossier. It has also been demonstrated that polymorphic form K is stable during manufacturing process and storage of finished product.

A comparative bioequivalence study was performed between Febuxostat Mylan 120 mg film coated tablets and Adenuric 120 mg film coated tablets. There is no difference in the formulation used in the clinical study and the formulation intended for commercialisation in Europe. It has been also confirmed that the same manufacturing process has been followed in the manufacturing of Febuxostat Mylan 120 mg film-coated tablets used in the bioequivalence study, manufacturing process validation study and stability studies.

A biowaiver has been requested for the 80 mg strength which has been accepted since the conditions for strength biowaiver (80 mg strength) according to the Guideline CPMP/EWP/ QWP/1401/98 Rev. 1 are fulfilled. The dissolution profiles have been compared between the test product used in the bioequivalence study (Febuxostat 120 mg film-coated tablets) against the test product (Febuxostat 80 mg film coated tablets) and found similar. In addition the applicant has committed that comparative dissolution profile testing will be undertaken on the first three production scale batches of the largest batch size.

The primary packaging of Febuxostat Mylan film coated tablets is Alu/OPA/ PVC/desiccant)/Alu blister pack, or white opaque high density polyethylene (HDPE) bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad and a desiccant (silica gel). The primary packaging material complies with EU Regulations No.10/2011 and No.1935/2004/EC. The provided stability results indicate that the proposed packaging materials are suitable for the storage of the finished product.

Manufacture of the product and process controls

The manufacturing process can be considered as a standard process which comprises the following main steps: sifting, blending, roller compaction, milling and sifting, final blending, compression of tablets, film-coating and packaging. Two batch sizes for each strength are proposed as commercial batch sizes.

Critical steps of the manufacturing process were defined: blending, compression, film-coating and packaging. The IPC performed per each respective manufacturing step were described and are considered acceptable.

Holding time studies were successfully finalized for common blend, tablet cores and film coated tablets.

The manufacturing process validation was completed on three batches of each strength at the lower proposed commercial batch size. All batches fully met the quality control specifications. Furthermore the applicant committed that validation of the packaging process of Febuxostat 80 mg and 120 mg film-coated tablets in the proposed blister packs and HDPE bottle packs will be performed as per the provided process validation protocols. The results of routine and extended in-process control (IPC) testing have demonstrated that the manufacturing process is robust and consistently yields a product capable of meeting the pre-defined quality characteristics.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (UV, IR), identification of colourants (chemical), loss on drying (Ph. Eur.), uniformity of dosage units by content uniformity (Ph. Eur.), dissolution (UV), assay (HPLC), related substances (HPLC), residual solvents (GC) and microbiological test (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data on three commercial scale batches (lower proposed batch size) were presented. All batches are representative of the commercial formula and manufacturing process. All batches met the commercial specification limits.

Stability of the product

Stability data from three commercial scale batches for each strength stored under long term conditions for up to 12 months (25 °C / 60% RH) and for up to six months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packagings proposed for marketing.

Samples were tested for description, assay, dissolution, related substances, loss on drying and microbiological test. Samples were tested at each time point for all parameters except for microbiological purity. The methods used were the same as for release testing and are stability indicating. There was no significant change in any of characteristics tested at any time point and no trends were observed.

A photostability study has been performed on one commercial scale batch of Febuxostat 120 mg film-coated tablets according to ICH Q1B Guideline. The following parameters were tested: description, assay, dissolution, loss on drying and related substances. The obtained stability results indicated that there are no

out of specification results and thus, it can be concluded that Febuxostat film-coated tablets are not photosensitive.

In-use stability studies were conducted on two batches of Febuxostat 80 mg film-coated tablets in line with requirements of NfG on In–use stability testing of human medicinal products (CPMP/QWP/2934/99). Samples were analysed in accordance with shelf-life specification, tested parameters were description, assay, related substances, dissolution, loss on drying and microbiological purity. The results support the proposed in-use stability of 180 days after first opening of bottles.

Based on the provided stability data, the proposed shelf life of 2 years stored in the original package, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

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 for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should conduct the comparative dissolution profiles testing on the first three production scale batches of the largest batch size against the test product used in the bioequivalence study (Febuxostat 120 mg film-coated tablets).

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 was submitted. This was justified by the applicant as the introduction of Febuxostat Mylan manufactured by Mylan S.A.S is considered unlikely to result in any significant increase in the combined sales volumes for all febuxostat containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased. The CHMP agreed with this justification.

2.3.3. Discussion on non-clinical aspects

The range of non-clinical data presented in the dossier is typical for generic application and include no new studies. Only well-known excipients are included in Febuxostat Mylan 80 mg film-coated tablets and Febuxostat 120 mg film-coated tablets.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

The proposed impurity limits in the concerned product are within the qualification thresholds given in ICH guidelines. No safety issues are expected based on the impurity profile of this medicinal product.

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.

The applicant has provided a statement to the effect that clinical trials conducted outside the community

were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant applied for marketing authorization for two different strengths of febuxostat containing film-coated tablets – 80 and 120 mg. Bioequivalence was demonstrated for the highest strength (i.e. 120 mg). In vivo bioequivalence study waiver is sought for the lower strength of 80 mg based on the consideration of the general biowaiver criteria as specified in the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1.

Febuxostat 80 mg and 120 mg have the same quantitative and qualitative composition in active substance and the same pharmaceutical form than the reference product. Its bioequivalence with the reference medicinal product has been proven by means of a bioequivalence study between Febuxostat 120 mg film-coated tablets formulations (Test) manufactured by Mylan Laboratories Limited and the reference product Adenuric 120 mg film - coated tablets of Menarini international Operations Luxembourg, S.A. The bioequivalence of the other of the strength was asked to be a waived based on the following general requirements:

- Both strengths of Febuxostat Mylan film-coated tablets (80 mg and 120 mg) are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.
- The excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected.
- The qualitative composition of both strengths is the same. Both the strengths are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same for both the strengths.
- Both strengths exhibit similar *in-vitro* performance. So the dissolution profiles can be considered similar.
- The absorption kinetics of Febuxostat is linear within the therapeutic dose range.

Linearity in the pharmacokinetics of febuxostat is justified.

Dissolution profiles

The dissolution profiles of test and reference products is similar in release media (pH 6.8 phosphate buffer; paddle apparatus), incomplete release of active substance is observed in 0.1 N HC and pH 4.5 acetate buffer for both products. The Applicant has demonstrated discriminatory power of the updated dissolution method and similarity of dissolution profiles for the bio-batch of the test product and batch of additional strength of test product at all three media.

Clinical studies

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

2.4.2. Pharmacokinetics

Study C15224: A randomized, open-label, balanced, two-treatment, two-period, two-sequence,

single-dose, crossover oral bioequivalence study of Febuxostat tablets 120 mg of Mylan Laboratories Limited, India with Adenuric® (Febuxostat) 120 mg film coated tablets of Menarini international O.L.S.A1, Avenue de la Gare, L-1611 Luxembourg in normal healthy adult human subjects under fasting conditions

Methods

Study design

The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence (TR and RT), single oral dose, crossover, bioequivalence study in healthy, adult, human subjects under fasting conditions, with a screening period of 21 days prior to the dosing in first period.

All subjects underwent a screening procedure 21 days prior to the dosing in first period comprising of complete medical history, physical examination with vital signs, 12 – lead ECG, clinical chemistry, haematology, urine analysis and serology.

Forty four subjects in period-1, forty three subjects in period-2 were administered with Investigational products (i.e. either test product or reference product). The washout period was 9 days between each consecutive dosing period.

The order of receiving test product (T) and reference product (R) for each subject during each period of the study was be determined according to a randomization schedule.

As this was an open labelled study, hence the subjects and the investigators were not blinded towards the identity of the test and reference products. Analyst had no access to the randomization schedule.

During the study the tolerability of the products after oral ingestion was assessed by following up all adverse events. The safety variables were adverse events, physical examination with vital signs, clinical chemistry, haematology and urine analysis.

Test and reference products

Test Product	
Name and strength	Febuxostat tablets 120 mg
Formulation	tablets
Manufactured by	Mylan Laboratories Limited, Plot No. 11, 12 & 13, Indore SEZ, Pharma Zone, Phase – II Sector – III, Pithampur – 454775, Dist – Dhar (M.P.) India.
Batch No.	2009932
Batch size	120 000

Commercial Batch size	1 000 000
Manufacturing date	August 2015
Expiry date	July 2017
Storage conditions	Do not store above 25 ^{o}C, store in original container

Reference product	
Name and strength	Adenuric (Febuxostat) 120 mg film-coated tablets
Formulation	tablets
Manufacturing authorization holder	Menarini international O.L.S.A1, Avenue de la Gare, L-1611 Luxembourg.
Lot No.	48510
Expiry date	October 2017
Member State where the reference product is purchased from:	UK
Storage conditions	Do not store above 25 ^{o}C, store in original container

Certificates of analysis have been provided for both test and reference products.

Febuxostat Mylan 120 mg manufactured by Mylan Laboratories Limited (Unit 11), India has been compared to Adenuric (Febuxostat) 120 mg film coated tablets.

Population studied

A total of 46 subjects including two additional subjects were enrolled and checked in for the study. Two additional subjects were enrolled in the study to compensate any dropout/withdrawn prior to dosing in period - 1. After completion of the dosing activity of 44 subjects, stand by subjects were checked–out from the clinical facility without being dosed in period - 1.

Subjects participated in the study were healthy non-smoking male adults, aged between 21 and 43 years of age (both inclusive); having BMI between 19.0 and 29.7 kg/ m2 (both inclusive). All subjects were of Asian origin.

Hence, as per the protocol, forty-four (44) subjects were dosed in Period-I of the study.

In overall, forty three (43) subjects completed the study and there was one subject withdrawn from the study:

- Subject No. 28 did not report on the clinical facility for period–2 check–in, hence withdrawn from the study.

Subject No. 28 due to the missing PK data for Period 2 was excluded from PK analysis. 43 subjects were included in PK and statistical analysis

Analytical methods

The analytical method for the determination of Febuxostat concentration was validated and was considered as acceptable. The study sample analysis was performed using the same anticoagulant as for the validation.

Pharmacokinetic variables

The primary pharmacokinetic variables were C_{max} and AUC_{0-t}. The secondary pharmacokinetic variables were AUC_{0-inf}, t_{max}, $t_{1/2}$, $K_{el,}$ $(AUC_{0-t}/AUC_{0-inf})*100$.

These pharmacokinetic parameters were calculated for Febuxostat of test product and reference product by using non-compartmental model of WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA).

The selected pharmacokinetic parameters and model used are acceptable.

Statistical methods

For pharmacokinetic and statistical analysis actual time of collection from the scheduled time was used for estimation of pharmacokinetic parameters, which was computed using non-compartmental model of WinNonlin Professional Software version 5.3 (Pharsight Corporation, USA) for Febuxostat.

The ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-inf of Febuxostat were subjected to Analysis of Variance (ANOVA). Statistical comparison of the pharmacokinetic parameters of the two formulations was carried out by using SAS statistical software version 9.2 to assess the bioequivalence of test product and reference product.

Determination of sample size

Based on the sponsor's in-house estimate the maximum intra-subject variability observed among primary pharmacokinetic parameters found to be approximately 29%. The following estimates were considered for the computation of sample size:

T/R ratio = 95-105%

Intra-Subject C.V (%) approximately 29%

Significance Level = 5%

Power ≥ 80%

Bioequivalence Limits = 80 – 125%

Based on the above estimate, a sample size of 38 subjects were sufficient to establish bioequivalence between formulations with adequate power. However, considering the drop-outs, a sample size of 44 subjects was considered for the study.

Bioequivalence of the test product with that of the reference product under fasting conditions was concluded if the 90% confidence intervals of geometric least square mean ratio of the test and reference product falls within the acceptance range of 80.00 % – 125.00% for ln-transformed Cmax and AUC0-t for Febuxostat.

Results

Table 1 - Pharmacokinetic parameters for febuxostat (non-transformed values)

Pharmacokinetic parameter	**Test**	**Reference**
	arithmetic mean ±SD	**arithmetic mean ±SD**
AUC_{0-t} (ng.hr/mL)	25024.548 ± 5854.6553	26177.339 ± 6548.1685
$AUC_{0-\infty}$ (ng.hr/mL)	25470.875 ± 5893.3974	26627.064 ± 6572.7699
C_{max} (ng/mL)	7456.028 ± 2172.6213	7497.577 ± 2431.1037
T_{max}* (hr)	1.50 (0.50 - 4.50)	1.25 (0.33 - 4.50)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max}* time for maximum concentration (* median, range)		

Table 2 - Statistical analysis for febuxostat (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%**
AUC_{0-t} (ng.hr/mL)	95.88	92.42-99.47	10.1
$AUC_{0-\infty}$ (ng.hr/mL)	95.94	92.54-99.46	10.0
C_{max} (ng/mL)	100.16	92.33-108.65	22.7

Safety data

One AE (during post study safety evaluation) was reported by subject No. 33 during the study. This AE [increased SGOT (AST) level] was mild in intensity and possibly related to the study drug. On repeated

follow-up AE was considered to be resolved completely [SGOT (AST) was found to be within the acceptable limits].

There were no deaths, significant or serious adverse events during the conduct of this study. Both of the products were similarly well tolerated.

None of the subjects had experienced adverse events during their in-house stay in both the study periods, so no concomitant medication was given.

Conclusions

Based on the presented bioequivalence study Febuxostat 120 mg film – coated tablets of Mylan Laboratories Limited is considered bioequivalent with Adenuric 120 mg film - coated tablets.

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

To support this marketing authorisation application, one bioequivalence study conducted with the 120 mg strength was submitted. The reference product is Adenuric 120 mg film-coated tablets. A biowaiver is requested for the additional strength 80 mg.

The results presented herein show that the criteria used to assess bioequivalence between the Test and Reference formulations were all fulfilled.

The Test Product (T) (Febuxostat Mylan 120 mg film-coated tablets, when compared with the Reference Product (R) (Adenuric 120 mg film-coated tablets of Menarini international O.L.S.A, Luxembourg) meets the bioequivalence criteria in terms of rate and extent of absorption after administration of single dose as set in the protocol.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), ANOVA model is acceptable for analysis of logarithmically transformed pharmacokinetic parameters Cmax and AUC. Determination of sample size with consideration of drop-outs and withdrawals is acceptable. The bioequivalence criteria are set according to the regulation.

Overall, medicinal products tested were generally safe and well tolerated by the subjects included in this study.

2.4.6. Conclusions on clinical aspects

The composition of the test product is qualitatively and quantitatively the same as the reference product. The choice of the 120 mg strength for the bioequivalence study is considered adequate, the test product

Febuxostat Mylan 120 mg film-coated tablets has shown bioequivalence to the reference product Adenuric 120 mg film- coated tablets.

Since the 80 mg strength of Febuxostat Mylan film-coated tablets fulfils all requirements to waive bioequivalence studies for additional strengths as mentioned in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 Corr **), the bioequivalence study results of Febuxostat Mylan 120 mg film-coated tablets can be extended to Febuxostat Mylan 80 mg film-coated tablets and a biowaiver for this additional strength is acceptable.

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

The clinical aspects of the Summary of Product Characteristics (SmPC) are in line with the SmPC of the reference product.

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 populations (TLS specific)
Missing information	-Children and adolescents -Subjects in whom the rate of serum urate formation is greatly increased (eg. malignant disease and its treatment, Lesch-Nyhan syndrome -Organ transplantation -Severe hepatic impairment -Pregnancy and lactation

Summary of safety concerns	
	-Limited experience in: female patients, elderly patients, 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

No additional pharmacovigilance activities are needed for this product.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Serious skin/ hypersensitivity reactions	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern Section 2 and 4 of PL contain adequate information on this safety concern	None
Important identified risks: Rhabdomyolysis	Section 4.8 of the SPC contain adequate information on this safety concern Section 4 of PL contain adequate information on this safety concern	None
Important identified risks: Drug-drug interaction with azathioprine or mercaptopurine	Section 4.4 and 4.5 of the SPC contain adequate information on this safety concern Section 2 of PL contain adequate information on this safety concern	None
Important potential risks: Cardiovascular events	Section 4.4 and 4.8 of the SPC contain adequate information on this safety concern	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 2 and 4 of PL contain adequate information on this safety concern	
Important potential risks: Hepatic events	Section 4.4, 4.8 and 5.1 of the SPC contain adequate information on this safety concern Section 2 and 4 of PL contain adequate information on this safety concern	None
Important potential risks: Renal events	Section 4.8 of the SPC contain adequate information on this safety concern Section 2 and 4 of PL contain adequate information on this safety concern	None
Important potential risks: Neuropsychiatric events	Section 4.8 of the SPC contain adequate information on this safety concern Section 4 of PL contain adequate information on this safety concern	None
Important potential risks: Haematological/Bleeding events	Section 4.8 of the SPC contain adequate information on this safety concern Section 4 of PL contain adequate information on this safety concern	None
Important potential risks: Thyroid events	Section 4.4, 4.8 and 5.1 of the SPC contain adequate information on this safety concern Section 2 and 4 of PL contain adequate information on this safety concern	None
Important potential risks: Off label use in the paediatric	Section 4.1 of the SPC contain adequate information on this	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
population (TLS specific)	safety concern	
Missing information: Children and adolescents	Section 4.2 of the SPC contains information on the lack of experience in children below the age of 18 years. Section 2 of PIL addresses this lack of information in children below the age of 18 years.	None
Missing information: Subjects in whom the rate of serum urate formation is greatly increased (eg, malignant disease and its treatment, Lesch-Nyhan syndrome)	Section 4.4 of the SPC contains information on the lack of experience in this sub population. Section 2 of PIL advices patient to talk to doctor before taking febuxostat if they are being treated for high uric acid levels as a result of Lesch-Nyhan syndrome.	None
Missing information: Organ transplantation	Section 4.4 of the SPC contains information on the lack of experience in organ transplant recipients.	None
Missing information: Severe hepatic impairment	Section 4.2 of the SPC contains information on the lack of experience in patients with severe hepatic impairment.	None
Missing information: Pregnancy and lactation	Section 4.6 of the SPC contains data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. It is unknown whether febuxostat is excreted in human breast milk. Section 2 of PIL contains it is not	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	known if febuxostat may harm your unborn child or may pass into human breast milk.	
Missing information: Limited experience in: female patients, elderly patients, severe renal impairment, moderate hepatic impairment	Section 4.2 of the SPC contains limited information in patients with moderate hepatic impairment and efficacy and safety have not been fully evaluated in patients with severe renal impairment.	None
Missing information: Interaction with standard therapy of haematological malignancies (TLS specific)	Section 4.5 of the SPC contains information on lack of drug interaction studies of febuxostat with cytotoxic chemotherapy	None
Missing information: Off label use in patients with solid tumors (TLS specific)	Section 4.1 of the SPC contains information on lack of use of febuxostat in TLS related to solid tumors.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.6. PSUR submission

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.

2.7. Pharmacovigilance

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.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Adenuric. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of febuxostat film coated tablet. The reference product Adenuric 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) 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).]. 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 an open label, balanced, randomized, two-treatment, two-period, two-sequence (TR and RT), single oral dose, crossover design. 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 Mylan met the protocol-defined criteria for bioequivalence when compared with Adenuric. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞ and Cmax were all contained within the protocol-defined acceptance range of [range, 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 Mylan is favourable in the following indication:

Febuxostat Mylan 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 Mylan (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 Mylan 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 (See Annex I: Summary of Product Characteristics, section 4.2).

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.