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Public Assessment Report

Name of the Product:

Denofix

80 mg, 120 mg film-coated tablets

(febuxostat)

Procedure number: HU/H/0530/001-002/DC

Marketing authorisation holder:

Zaklady Farmaceutyczne POLPHARMA SA

Date: 02 January 2019

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Denofix 80 mg, 120 mg film-coated tablets. The holder of the marketing authorisation is Zaklady Farmaceutyczne POLPHARMA SA.

The active substance is febuxostat. Each film-coated tablet contains 80 mg or 120 mg febuxostat (as febuxostat hemihydrate).

The other ingredients are:

- *tablet core:* lactose monohydrate, cellulose, microcrystalline (E460), hydroxy-propylcellulose (E463), croscarmellose sodium, silica, colloidal anhydrous (E551), magnesium stearate (E470b);

- *film-coating:* poly(vinyl alcohol) (E1203), talc (E553b), titanium dioxide (E171), macrogol 3350 (E1521), methacrylic acid - ethyl acrylate copolymer (1:1) (Type A), iron oxide yellow (E172), sodium hydrogen carbonate (E500(ii)).

The Denofix 80 mg film-coated tablets are pale yellow to yellow, film-coated, capsule shaped tablets, engraved with “80” on one side and plain on the other, with dimensions 16.5 mm x 7.0 mm ± 5%.

The Denofix 120 mg film-coated tablets are pale yellow to yellow, film-coated, capsule shaped tablets, engraved with “120” on one side and plain on the other, with dimensions
18.5 mm x 9.0 mm ± 5%.

The film-coated tablets are packed in Aluminium-OPA/Alu/PVC or Aluminium-PVC/PE/PVDC blisters.

The Denofix film-coated tablets (further on: Denofix) contain the active substance febuxostat and are used to treat gout, which is associated with an excess of a chemical called uric acid (urate) in the body. In some people, the amount of uric acid builds up in the blood and may become too high to remain soluble. When this happens, urate crystals may form in and around the joints and kidneys. These crystals can cause sudden, severe

pain, redness, warmth and swelling in a joint (known as a gout attack). Left untreated, larger deposits called tophi may form in and around joints. These tophi may cause joint and bone damage.

Denofix works by reducing uric acid levels. Keeping uric acid levels low by taking Denofix once every day stops crystals building up, and over time it reduces symptoms. Keeping uric acid levels sufficiently low for a long enough period can also shrink tophi.

Denofix 120 mg film-coated tablets are also used to treat and prevent high blood levels of uric acid that may occur when the patient starts to receive chemotherapy for blood cancers. When chemotherapy is given, cancer cells are destroyed and uric acid levels increase in the blood accordingly, unless the formation of uric acid is prevented.

Denofix is for adults.

What patients need to know before taking Denofix?

Those who are allergic to febuxostat or any of the other ingredients of this medicine should not take Denofix.

Warnings and precautions

Patients should consult their doctor before taking Denofix if they
- have or have had heart failure or heart problems,
- have or have had renal disease and/or serious allergic reaction to allopurinol (a medication used for the treatment of gut),
- have or have had liver disease or liver function test abnormalities,
- are being treated for high uric acid levels as a result of Lesch-Nyhan syndrome (a rare inherited condition in which there is too much uric acid in the blood),
- have thyroid problems.

Patients who experience allergic reactions to Denofix should stop taking this medicine. Possible symptoms of allergic reactions might be:
- rash including severe forms (e.g. blisters, nodules, itchy-, exfoliative rash), itchiness,

- swelling of limbs or face,
- difficulties in breathing,
- fever with enlarged lymph nodes,
- but also serious life threatening allergic conditions with cardiac and circulatory arrest.

The doctor might decide to permanently stop treatment with Denofix.

There have been rare reports of potentially life-threatening skin rashes (Stevens-Johnson Syndrome) with the use of febuxostat, appearing initially as reddish target-like spots or circular patches often with central blister on the trunk. It may also include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). The rash may progress to widespread blistering or peeling of the skin. Patients who have developed Stevens-Johnson Syndrome with the use of febuxostat, must not be re- started on Denofix at any time. Those who develop a rash or these skin symptoms, seek immediate advice from a doctor and tell that you are taking this medicine.

Those who are having a gout attack at the moment (a sudden onset of severe pain, tenderness, redness, warmth and swelling in a joint), wait for the gout attack to subside before first starting treatment with Denofix.

For some people, gout attacks may flare up when starting certain medicines that control uric acid levels. Not everyone gets flares, but patients could get a flare-up even if taking Denofix, and especially during the first weeks or months of treatment. It is important to keep taking Denofix even if having a flare, as Denofix is still working to lower uric acid. Over time, gout flares will occur less often and be less painful if the patient keeps taking Denofix every day.

The doctor will often prescribe other medicines, if they are needed, to help prevent or treat the symptoms of flares (such as pain and swelling in a joint).

In patients with very high urate levels (e.g. those undergoing cancer chemotherapy), treatment with uric acid-lowering medicines could lead to the build-up of xanthine in the urinary tract, with possible stones, even though this has not been observed in patients being treated with febuxostat for Tumour Lysis Syndrome.

The doctor may ask the patient to have blood tests to check that the liver is working normally.

Children and adolescents

This medicine should not be given to children under the age of 18 because the safety and efficacy have not been established.

Other medicines and Denofix

Patients should tell their doctor if taking, have recently taken or might take any other medicines.
It is especially important if they are taking medicines containing any of the following substances as they may interact with Denofix and the doctor may wish to consider necessary measures:

- mercaptopurine (used to treat cancer),
- azathioprine (used to reduce immune response),
- theophylline (used to treat asthma).

Pregnancy and breast-feeding

It is not known if Denofix may harm an unborn child. Therefore, Denofix should not be used during pregnancy. It is also not known if Denofix may pass into human breast milk. Denofix should not be used by those who are breast feeding, or are planning to breastfeed.

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, consult their doctor for advice before taking this medicine.

Driving and using machines

Patients should be aware that they may experience dizziness, sleepiness, blurred vision and numbness or tingling sensation during treatment and should not drive or operate machines if affected.

Denofix contains lactose and sodium

Denofix contains lactose (a type of sugar). Those who have been told by their doctor that they have an intolerance to some sugars, contact the doctor before taking this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

How to take Denofix

The recommended dose is one tablet daily. The back of the blister pack is marked with the days of the week to help the patient check that he/she have taken a dose each day.

The tablets should be taken with or without food.

Gout: Denofix is available as either an 80 mg tablet or a 120 mg tablet. Your doctor will prescribe the strength most suitable for the patient.

Taking Denofix should be continued every day even when not experiencing gout flare or attack.

Prevention and treatment of high uric acid levels in patients undergoing cancer chemotherapy: Denofix is available as a 120 mg tablet. Patients should start taking this tablet two days before chemotherapy and continue its use according to the doctor's advice. Usually the treatment is short-term.

What to do if take more Denofix has been taken than it should have been?

In the event of an accidental overdose the doctor should be consulted what to do, or the nearest accident and emergency department contacted.

What to do if taking Denofix has been forgotten?

If a dose has been missed, it should be taken as soon as remembering it unless it is almost time for the next dose, in which case the forgotten dose should be missed out and the next dose at the normal time taken. Double dose to make up for a forgotten dose should never be taken.

May patients stop taking Denofix?

Patient should not stop taking Denofix without the advice of the doctor even if feeling better. If taking Denofix is stopped, the uric acid levels may begin to rise and the symptoms may worsen due to the formation of new crystals of urate in and around the joints and kidneys.

Possible side effects

Like all medicines, Denofix can cause side effects, although not everybody experiences them.

Patients must stop taking this medicine and contact their doctor immediately or go to an emergency department nearby if the following rare (may affect up to 1 in 1,000 people) side effects occur, because a serious allergic reaction might follow:
- anaphylactic reactions, drug hypersensitivity (see also section "Warnings and precautions");
- potentially life-threatening skin rashes characterized by formation of blisters and shedding of the skin and inner surfaces of body cavities, e.g. mouth and genitals, painful ulcers in the mouth and/or genital areas, accompanied by fever, sore throat and fatigue (Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis), or by enlarged lymph nodes, liver enlargement, hepatitis (up to liver failure), raising of the white-cells count in the blood (drug reaction with eosinophilia and systemic symptoms-DRESS);
- generalised skin rashes.

Common side effects (may affect up to 1 in 10 people):
- abnormal liver test results,
- diarrhoea,
- headache,
- rash (including various types of rash, please see below under "uncommon" and "rare" sections),
- nausea,
- increase in gout symptoms,
- localised swelling due to retention of fluids in tissues (oedema).

Other side effects which are not mentioned above are listed below.

Uncommon side effects (may affect up to 1 in 100 people):
- decreased appetite, change in blood sugar levels (diabetes) of which a symptom may be excessive thirst, increased blood fat levels, weight increase;
- loss of sex drive;
- difficulty in sleeping, sleepiness;
- dizziness, numbness, tingling, reduced or altered sensation (hypoesthesia, hemiparesis or paraesthesia), altered sense of taste, diminished sense of smell (hyposmia);
- abnormal ECG heart tracing, irregular or rapid heartbeats, feeling your heart beat (palpitation);
- hot flushes or flushing (e.g. redness of the face or neck), increased blood pressure, bleeding (haemorrhage, seen only in patients taking chemotherapy for blood disorders);
- cough, shortness of breath, chest discomfort or pain, inflammation of nasal passage and/or throat (upper respiratory tract infection), bronchitis;
- dry mouth, abdominal pain/discomfort or wind, heartburn/indigestion, constipation, more frequent passing of stools, vomiting, stomach discomfort;
- itching, hives, skin inflammation, skin discoloration, small red or purple spot on the skin, small, flat red spots on the skin, flat, red area on the skin that is covered with small confluent bumps, rash, areas of redness and spots on the skin, other type of skin conditions;
- muscle cramp, muscle weakness, pain/ache in muscles/joints, bursitis or arthritis (inflammation of joints usually accompanied by pain, swelling and/or stiffness), pain in extremity, back pain, muscle spasm;
- blood in the urine, abnormal frequent urination, abnormal urine tests (increased level of proteins in the urine), a reduction in the ability of the kidneys to function properly;
- fatigue, chest pain, chest discomfort;
- stones in the gallbladder or in bile ducts (cholelithiasis);
- increase in blood thyroid stimulating hormone (TSH) level;
- changes in blood chemistry or amount of blood cells or platelets (abnormal blood test results);
- kidney stones;
- erectile difficulties.

Rare side effects (may affect up to 1 in 1,000 people):

- muscle damage, a condition which on rare occasions can be serious. It may cause muscle problems and particularly, if at the same time, the patient feels unwell or have a high temperature it may be caused by an abnormal muscle breakdown. The doctor must be contacted immediately if experiencing muscle pain, tenderness or weakness;
- severe swelling of the deeper layers of the skin, especially around the lips, eyes, genitals, hands, feet or tongue, with possible sudden difficult breathing;
- high fever in combination with measles-like skin rash, enlarged lymph nodes, liver enlargement, hepatitis (up to liver failure), raising of the white-cells count in the blood (leukocytosis, with or without eosinophilia);
- reddening of the skin (erythema), rash in various types (e.g. itchy, with white spots, with blisters, with blisters containing pus, with shedding of the skin, measles-like rash), widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis (Stevens-Johnson Syndrome/Toxic epidermal necrolysis);
- nervousness;
- feeling thirsty;
- ringing in the ears;
- blurred vision, change in vision;
- hair loss;
- mouth ulceration;
- inflammation of the pancreas: common symptoms are abdominal pain, nausea and vomiting;
- increased sweating;
- weight decrease, increased appetite, uncontrolled loss of appetite (anorexia);
- muscle and/or joint stiffness;
- abnormally low blood cell counts (white or red blood cells or platelets);
- urgent need to urinate;
- changes or decrease in urine amount due to inflammation in the kidneys (tubulointerstitial nephritis);
- inflammation of the liver (hepatitis);
- yellowing of the skin (jaundice);
- liver damage;
- increased level of creatine phosphokinase in blood (an indicator of muscle damage).

How to store Denofix

This medicinal product does not require any special storage conditions but it must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Denofix 80 mg, 120 mg film-coated tablets. The procedure was finalised at 16 July 2018. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member States concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS Poland) concerned the generic version of febuxostat 80 mg and 120 mg film-coated tablets (Denofix, in the CMS Dnoff tablets).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary.

The applicant has adequately demonstrated bioequivalence between the product and reference products. The originator and reference products are Adenuric 80 mg and 120 mg film-coated tablets by Menarini International Operations Luxembourg S.A., authorised for marketing since April 2008 in the European Economic Area.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Denofix 80 mg, 120 mg film-coated tablets (Zaklady Farmaceutyczne POLPHARMA SA.)

Denofix 80 and 120 mg film-coated tablets are indicated for the treatment of chronic hyperuricemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Moreover, febuxostat 120 mg film-coated tablets are also indicated for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of Tumour Lysis Syndrome.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

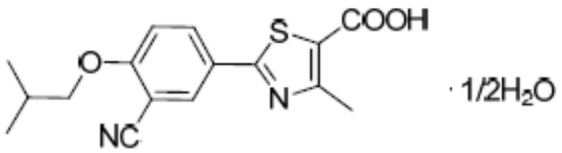
Zaklady Farmaceutyczne POLPHARMA SA has applied for marketing authorisation via Decentralised Procedure for products Denofix 80 mg and 120 mg film-coated tablets according to Article 10(1) of consolidated Directive 2001/83/EC (i.e. generic application).

The reference products are Adenuric® 80 mg and 120 mg film-coated tablets (containing 80 mg or 120 mg febuxostat as active ingredient, respectively) which were the original products of Menarini International Operations Luxembourg S.A.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorisation dossier. The Quality Overall Summary is adequate.

INN name: febuxostat hemihydrate.
Chemical name: 2-(3-Cyano-4-isobutyloxyphenyl)-4-methylthiazole-5-carboxylic acid, hemi hydrate
Structure:



The active substance is white to off-white crystalline powder, freely soluble in dimethyl sulfoxide, soluble in acetone, slightly soluble in ethanol, practically insoluble in water. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by FT-IR, NMR, MS, TGA, DSC, XRDP and by UV spectroscopy. The impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Febuxostat is not official in the European Pharmacopoeia (Ph. Eur.) Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, solubility, identification by IR and HPLC, water content, sulphated ash, heavy metals, related substances, assay, residual solvents and polymorphic content.
Testing methods not described in details in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The drug substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of is acceptable with no special storage condition.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop film-coated tablets containing febuxostat as drug substance in 80 and 120 mg doses pharmaceutically equivalent and bioequivalent to the reference medicinal product of Menarini.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

80 mg: pale yellow to yellow, film-coated, capsule shaped tablets, engraved with “80” on one side and plain on the other, with dimensions 16.5 mm x 7.0 mm ±5%.

120 mg: pale yellow to yellow, film-coated, capsule shaped tablets, engraved with “120” on one side and plain on the other, with dimensions 18.5 mm x 9.0 mm ±5%.

The excipients used in the finished product for the core are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, anhydrous collidal silica and magnesium stearate. The coating contains the following excipients: poly(vinil alcohol), talc, titanium dioxide (E171), macrogol, methacrylic acid-ethylacetate copolymer, yellow iron oxide (E172) and sodium hydrogen carbonate. All excipients used comply with their respective Ph. Eur. monograph except iron oxide (USP/NF). Compliance of the product with the general monograph of the Ph. Eur. on *the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Council of Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is Aluminium-OPA/Alu/PVC or Aluminium-PVC/PE/PVDC blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years with no special storage conditions is approved.

The Summary of Product Characteristics, Package Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From quality aspects the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of febuxostat are well known. As febuxostat is a widely used, well-known active substance, no further studies are required and the applicant has provided none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient.

III.2 Pharmacology

Febuxostat is a potent xanthine oxidase inhibitor that was approved for the treatment of chronic hyperuricemia and gout. It is of a different chemical class than allopurinol and a more selective inhibitor of enzyme activity.

In both *in vitro* and *in vivo* animal studies, febuxostat inhibited XO more potently than allopurinol. Animal studies have demonstrated that the potency of febuxostat is 10–30 times that of allopurinol. In one study in chimpanzees (which resemble humans in lacking uricase and having higher purine metabolite levels and urate excretion rates), both allopurinol and febuxostat (each 5 mg/kg/day orally), decreased serum urate levels after 24, 48, and 72 hours of administration. However, febuxostat was more effective than allopurinol at lowering uric acid. Allopurinol decreased serum urate concentration by 28% (24 h), 42% (48 h), and 45% (72 h), as compared with the respective values for febuxostat of 56%, 70%, and 74%

III.3 Pharmacokinetics

Febuxostat was rapidly absorbed from the gastrointestinal tract following oral administration of [14C] febuxostat to mice (tmax 0.5-2 h), rats and dogs (tmax 0.25-0.5 hours). Plasma total radioactivity AUC values were generally 6-7-fold higher in mice and rats than those in dogs given an

equivalent dose. Febuxostat AUC values were nearly 9 times higher in rats than in dogs. The terminal half-life of febuxostat generally ranged from 2-4 hours in mice and appeared to be slightly longer in rats and dogs.

Absorption was decreased 36-48% in rats and 55% in dogs when febuxostat was administered with food.

In vitro and *ex vivo* plasma protein binding studies with [14C] febuxostat showed that the drug is highly bound in rat plasma (≥98.8%).

The studies showed that febuxostat is widely distributed to most tissues and organs.

Following administration of febuxostat to mice, rats and dogs, metabolic profiles in plasma and urine appeared to be qualitatively similar between the species. Febuxostat was the major component found in the plasma of all species studied. Several metabolites were present at relatively lower concentrations in all species.

Following either i.v. or p.o. administration of [14C] febuxostat to mice, rats or dogs, faecal excretion was generally the main route of elimination (especially in dogs).

III.4 Toxicology

Febuxostat does not pose an acute toxicity hazard by the oral route based on studies performed in rats (lethal dose 300-600 mg/kg) and dogs (no deaths up to 2000 mg/kg).

In rats, and consequent to the histopathological changes at 48 mg/kg/day (31x human plasma exposure at 80 mg/day), various serum chemistry parameters (increased BUN, creatinine, phospholipids, triglycerides), haematology parameters (increased leukocytes, decreased erythrocytes) and urinalysis parameters (increased excretion of potassium and sodium) were altered. The no observed adverse effect level (NOAEL) for 26-week rat study was considered to be 12 mg/kg/day (8x plasma exposure at 80 mg/day).

In dogs, less significant changes in serum chemistry, haematology and urinalysis parameters were observed at 45 mg/kg/day (55x plasma exposure at 80 mg/day). The NOAEL for 52-week dog study was considered to be 5 mg/kg/day (0.5x plasma exposure at 80 mg/day).

A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.

In male mice, a tumorigenic effect was not observed up to doses of 18.75 mg/kg/day (4x human plasma exposure at 80 mg/day febuxostat). In female rats, a tumorigenic effect was not observed up to doses of 24 mg/kg/day (20x human plasma exposure based on AUC at 80 mg/day febuxostat).

In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use.

There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

III.5 Ecotoxicology/environmental risk assessment

Since febuxostat 80 and 120 mg film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamics, pharmacokinetics and toxicology of febuxostat are well-known. No new non-clinical studies were conducted, which is acceptable for generic applications.

There are no objections to the approval of these applications from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Febuxostat, a selective xanthine oxidase inhibitor, is mainly used for the treatment of chronic hyperuricemia in adult patients with gout, but also for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of tumour lysis syndrome (TLS).

The clinical pharmacodynamics, pharmacokinetics, efficacy and safety of the active ingredient in the proposed indications, doses and dosing regimens are well known.

Except for demonstrating bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Absorption: after oral intake approximately 85% of febuxostat is absorbed, with peak serum concentrations achieved after one hour (t_{max} of 1.0-1.5 h) in healthy subjects, however, the absolute bioavailability is unknown.

Administration with an antacid produces a delay in the time to peak concentration but no change in the extent absorbed. Administration with food has resulted in a delay in the time to peak and a slight reduction in the extent absorbed; however, no reduction in pharmacodynamic effect was observed. Thus, febuxostat can be administered without regard to antacid or food intake.

Distribution: febuxostat in the blood is highly bound to plasma proteins, mainly albumin (99%). The elimination half-life is approximately 4-6 hours.

Biotransformation: febuxostat is mainly metabolized by conjugation (via liver uridine diphosphate-glucuronosyltransferase (UGT) enzyme system) into acylglucuronide metabolites (22%–44%), and to a lesser extent (2% – 8%) to its active oxidative metabolites 67M-1, 67M-2, and 67M-4 (via cytochrome P-450 system). Three oxidative metabolites have been identified in plasma and urine.

Elimination: febuxostat is eliminated by both hepatic and renal pathways. In faeces, unchanged febuxostat was one of the major peaks, although it accounted for only a small part of the dose. The unchanged febuxostat in faeces might be unabsorbed drug, but it is likely also absorbed drug excreted unchanged or re-formed from excreted glucuronide. In urine, unchanged drug accounted for less than 4% of the dose. The major compound in urine is febuxostat glucuronide. The oxidative metabolites are excreted in urine and faeces, unchanged or as glucuronides.

IV.2.2 Bioequivalence studies

In support of the application, the applicant has submitted the following bioequivalence study reports.

One pilot and one pivotal bioequivalence studies have been reported in the submitted dossier in order to support essential similarity between Denofix 120 mg film-coated tablets (Test) and Adenuric® 120 mg film coated tablets (manufactured by Menarini – Von Heiden GmbH, Germany, for Menarini International Operations Luxembourg S.A., Luxembourg, (Reference) in healthy adult male subjects under fasting conditions according to the bioequivalence guideline in force (CPMP/EWP/QWP/1401/98/ Rev 1/Corr** 2010).

The pilot study was an open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of febuxostat 120 mg Test and Reference products in normal, healthy, adult, male subjects under fasting conditions.

There was an adequate washout period between the two periods.

On the basis of the results of the pilot bioequivalence study the single dose of the Test product and a single dose of Reference product seem to be bioequivalent in healthy adult subjects under fasting conditions.

No new safety concern was identified.

The pivotal study was a single-dose, randomized, open-label, crossover, two-period, two-treatment, two-sequence bioequivalence study of febuxostat 120 mg film-coated tablets with an adequate washout period between the two periods, in healthy male volunteers under fasting condition.

The results are summarised below.

Parameter	Ratio Test/Reference	Confidence interval	Intrasubject CV %
C_{max}	98.20	84.96 – 113.50	38.1
AUC_{0-T}	99.69	95.71 – 102.83	10.4

The results support that a single dose of Test product is bioequivalent with a single dose of Reference product in healthy adult subjects under fasting condition.

Safety results

No death or serious adverse events occurred during the study.

No subject was withdrawn by the investigator for safety reason.

Most of the adverse events were mild in severity. There was no severe adverse event in this study.

Overall, the drugs investigated were well tolerated by subjects included in the study. No new safety concern was identified.

Conclusion on bioequivalence studies

Based on the results of the study reports, bioequivalence between the test and reference product has been demonstrated.

Biowaiver

The applicant claimed for biowaiver for the dose strength of 80 mg on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**).

As the lower strength has fulfilled all the criteria for the biowaiver laid in the EMA *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1 Corr**), the results and conclusions of the bioequivalence study can be extrapolated to the lower strength.

IV.3 Pharmacodynamics

The drug product contains the active substance febuxostat. It is a well-known substance. No new pharmacodynamic studies have been submitted.

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 these transformations are catalysed by xanthine oxidase.

Febuxostat is a selective inhibitor of xanthine oxidase. Febuxostat binds very tightly to the enzyme, and inhibits both the oxidized and reduced forms of it. Febuxostat is a more selective and potent inhibitor of xanthine oxidase than allopurinol and does not inhibit other enzymes involved in purine and pyrimidine metabolism, which are inhibited by allopurinol.

IV.4 Clinical efficacy

Febuxostat for the treatment of symptomatic hyperuricemia, showed superiority over allopurinol in the reduction of serum uric acid levels in several studies. Febuxostat in dose of 80 & 120 mg significantly reduces uric acid levels within 2 weeks after initiation of therapy and the effect is seen to be sustained as compared to allopurinol 300 mg in various studies. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion

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

IV.5 Clinical safety

Due to the long-term clinical experience, the adverse effects of febuxostat and its safety profile are well known.

Febuxostat is generally well tolerated in adults, also in older patients. The most commonly reported adverse reactions in clinical trials and post-marketing experience in gout patients are gout flares, liver function abnormalities, arthralgia, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity.

The incidence of cardiovascular (CV) side-effects (composite of myocardial infarction, stroke and CV death as defined by the Antiplatelet Trialists Collaboration events) was higher with Febuxostat than with allopurinol in both the Phase III and long-term extension studies.

The development of a hypersensitivity type cutaneous vasculitis (likely but not definitively FEB-related) early in treatment mandates caution, careful dose escalation, and close monitoring when FEB urate-lowering therapy of allopurinol-intolerant patients is considered.

The characteristics of Febuxostat are adequately reflected in the Summary of Product Characteristics and the indications and precautions for the use of this drug are justified by its pharmacological properties.

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

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	No experience in: - children and adolescents, - subjects in whom the rate of serum urate formation is greatly increased (e. g Lesch-Nyhan syndrome),

Summary of safety concerns	
	- organ transplantation, - severe hepatic impairment, - pregnancy and lactation, - off label use in patients with solid tumours (TLS specific), - interaction with standard therapy of haematological malignancies (TLS specific). Limited experience in: - severe renal impairment, - moderate hepatic impairment.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Denofix 80 mg and 120 mg film-coated tablets.

No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Denofix 80 mg and 120 mg film-coated tablets.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products 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.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2.2 are pivotal.

The application contains an adequate review of published clinical data and the bioequivalence between Denofix 120 mg film-coated tablets and Adenuric 120 mg film-coated tablets has been shown. As the lower strengths meet the biowaiver criteria specified in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1), the results and conclusions of the bioequivalence study can be extrapolated to the 80 mg strength.

Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Denofix 80 mg and 120 mg film-coated tablets. The future holder of authorisation is Zaklady Farmaceutyczne POLPHARMA SA.

The product is indicated for the treatment of chronic hyperuricemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). Moreover, febuxostat 120 mg film-coated tablets are also indicated for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of Tumour Lysis Syndrome.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator and reference products were Adenuric 80 mg and 120 mg film-coated tablets by Menarini International Operations Luxembourg S.A., authorised for marketing since April 2008 in the European Economic Area.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is therefore positive.

Based on the review of the quality, safety and efficacy data, the reference member state has granted marketing authorisation for Denofix 80 mg, 120 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached