European Medicines Agency
*Evaluation of Medicines for Human Use*

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**CHMP ASSESSMENT REPORT**
**FOR**
**Adenuric**

International Nonproprietary Name:
**febuxostat**

**Procedure No. EMEA/H/C/777**

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 Ipsen Manufacturing Ireland Ltd. submitted on 23 August 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Adenuric, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 15 December 2005.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication: treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

**Licensing status:**
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Heribert Pittner** Co-Rapporteur: **Bengt Ljungberg**

## 1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 23 August 2006.
- The procedure started on 27 September 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 December 2006. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 December 2006.
- During the meeting on 15-17 January 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 January 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 8 August 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 September 2007.
- During the CHMP meeting on 15-18 October 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing.

- Written explanations were provided by the Applicant on 17 January 2008.
- During the meeting on 18-21 February 2008, 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 Adenuric on 21 February 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 February 2008.

# 2. SCIENTIFIC DISCUSSION

## 2.1 Introduction

The Applicant seeks marketing authorization for Adenuric 80 mg and 120 mg tablets which contain febuxostat, a non-purine inhibitor of xanthine oxidase, for the treatment of hyperuricaemia in patients with chronic gout. At present the only commercial available xanthine oxidase inhibitor is allopurinol; its effects on hyperuricaemia and gout are known for more than 40 years.
Febuxostat has been developed by Teijin Pharma Limited (Teijin, Japan) and TAP Pharmaceutical Products Inc. (TAP, USA).

Gout is a disorder caused by deposition of urate crystals in joints and other tissues. There are four clinical stages: (i) asymptomatic hyperuricaemia; (ii) acute gouty arthritis; (iii) intercritical gout (intervals between acute attacks); and (iv) chronic tophaceous gout.

Hyperuricaemia is defined as a plasma or serum urate concentration >7 mg/dl (>420 μmol/l) and is present in approximately 5% of the population. The serum uric acid (sUA) is the single most important risk factor for developing gout. Sustained hyperuricaemia is a risk factor for acute gouty arthritis, tophaceous gout and uric acid nephrolithiasis, but most patients with hyperuricaemia will never have an attack of gout and no treatment is required. In the Normative Aging Study, the 5-year cumulative risk of gout development in subjects whose sUA level was >7 mg/dl or >10 mg/dl was 0.6% and 30.5%, respectively (Campion et al., 1987; Schlesinger, 2004). On the other hand it was reported that patients with sUA ≥10 mg/dl and a first gout attack had 100% recurrent attacks of gout, whilst those with sUA ≤6 mg/dl had a 20% annual incidence of recurrence (Shoji et al., 2004; Schumacher, 2005).

Treatment of chronic gout requires long-standing reduction in serum uric acid below the saturation level. The urate-lowering drugs used to treat chronic gout are the uricosuric drugs (such as probenecid, benzbromarone, sulfinpyrazone, micronized fenofibrate and losartan), the uricostatic drugs (xanthine oxidase inhibitors such as allopurinol) and the urolytic drugs (urate oxidase).

Allopurinol, a pyrazolopyrimidine and analogue of hypoxanthine, is widely regarded as the urate-lowering drug of choice (Rundles et al., 1966; Wortmann, 1998; Schlesinger, 2004) and is the only xanthine oxidase inhibitor on the market in European countries. As a xanthine oxidase inhibitor it lowers the oxidation of hypoxanthine to xanthine and xanthine to uric acid thereby reducing serum uric acid and uric acid excretion and increases the concentration of the hypoxanthine and xanthine in the blood and urine. Allopurinol is effective when the hyperuricaemia is due to overproduction or underexcretion of uric acid.

Because of the long half-life of the active metabolite oxipurinol (14-28 h), allopurinol can be given once daily. It can be given as a single dose of 300 mg/day and increased to 800 mg/day if needed (Schlesinger, 2004; Wortmann, 2005), but up-titration has been recommended . In some patients a dose of 100 mg/day to 200 mg/day is adequate (Emmerson, 1996). Because serious adverse reactions to allopurinol have been related to a decreased creatinine clearance rate and prolonged half-life of oxipurinol (14-28 h) it was proposed by Hande et al. (1984) to adjust the allopurinol dose according to the rate of creatinine clearance in order to reduce the risk of severe toxicity, which is now common practice. It has been said that some patients with gout and renal failure, treated with allopurinol may not sufficiently benefit from low allopurinol doses (Vazquez-Mellado et al., 2001; Bardin, 2004). Although allopurinol is rather well tolerated, about 5% of patients are unable to tolerate allopurinol because of side effects (Schlesinger, 2004). Rare life-threatening adverse events, such as the allopurinol hypersensitivity syndrome (AHS), have been observed.

The uricosuric drugs such as probenecid are the urate lowering drugs of choice in allopurinol-allergic patients, and underexcretors with normal renal function and no history of urolithiasis (Schlesinger, 2004). Uricosuric drugs are ineffective in overproduction of uric acid and contraindicated in patients with nephrolithiasis (Wortmann, 1998). The availability of probenecid is limited in some European countries.

Benzbromarone, a potent uricosuric drug, is hepatotoxic and several cases of hepatic failure with subsequent death of the patients in liver transplantation have been reported, leading to withdrawal from the market. Its availability in European countries appears very limited, it may be available in fixed combination with allopurinol.

Losartan, an angiotensin II receptor antagonist, used for treatment of hypertension, has uricosuric properties due to its binding to the URAT1 exchanger in the proximal tubule, thus inhibiting urate re-absorption in the kidney. Its use in patients with hypertension and gout has been recommended (Bardin, 2003), but losartan is currently not registered for the treatment of gout.

Fenofibrate, used for the treatment of lipid disorders, lowers serum urate by increasing urate clearance, in healthy volunteers and diabetic and non-diabetic patients with hyperlipidemia (Hepburn et al., 2003). Its use in patients with hyperlipidemia and gout has been recommended (Bardin, 2004), but fenofibrate is currently not registered for the treatment of gout.

Urate oxidase is an enzyme that converts uric acid to allantoin and is lacking in humans. Rasburicase (Fasturtec®), a recombinant form of urate oxidase, that catalyses enzymatic oxidation of uric acid to allantoin has been recently (2001) approved by a centralized procedure. It is indicated for "treatment and prophylaxis of acute hyperuricemiahyperuricaemia, in order to prevent acute renal failure in patients with haematological malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy". Long-term urate oxidase treatment for chronic gout has not been evaluated.

The proposed indication is 'Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history or presence of tophus, and/or gouty arthritis)'. The recommended oral dose is 80 mg once daily (QD). If serum uric acid is > 6 mg/dl (357 µmol/l) after 2-4 weeks, 120 mg (QD) may be considered.

## 2.2 Quality aspects

### Introduction

Adenuric is presented as immediate release film-coated tablets containing 80 mg and 120 mg of febuxostat as the active substance, for oral administration. The excipients used in this formulation are lactose monohydrate, hydroxypropylcellulose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and silica.

Adenuric is packed in clear PVC/Aclar/Aluminium blisters containing either 28 or 84 tablets.

### Active Substance

The active substance is a new chemical entity designated as 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid. The structure of febuxostat is shown in Figure 1.

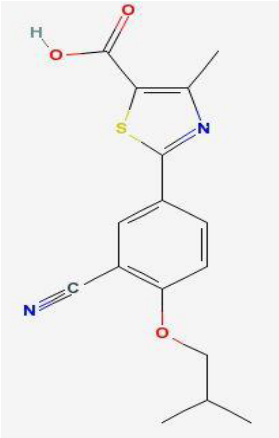


Figure 1: Chemical structure of febuxostat

The Active Substance Master File (ASMF) procedure was followed for the active substance.

Febuxostat is white crystalline powder practically insoluble in water, sparingly soluble in ethanol, soluble in dimethylsulfoxide, and freely soluble in dimethylformamide. The solubility of febuxostat in a wide range of pH buffer solutions shows that its solubility is low in acid and increases with the increase in pH from neutral to high pH. Febuxostat is a non-hygroscopic compound

- Manufacture

Febuxostat is synthesised in six steps from one starting material including crystallisation and milling. The structure of febuxostat was confirmed by elemental analysis, Mass spectroscopy, UV, Infrared and NMR spectroscopy.

- Specification

The active substance specifications include tests for description, identification (IR and HPLC), assay (HPLC), impurities (HPLC), polymorphism (X-ray diffraction), loss on drying, residue on ignition, heavy metals, residual solvents (methanol), particle size (laser light scattering) and microbial purity.

All analytical procedures have been adequately validated according to the ICH Q2A guidance. The assay and purity tests by HPLC have been validated for both linearity and precision.

Batch analysis data was provided on 16 batches manufactured at the proposed manufacturing site for the active substance. Additional batches used in the non clinical and clinical studies have been manufactured at an alternative manufacturing site manufactured according to the proposed routes of synthesis. The results from all batches confirm the consistency and uniformity of the active substance.

- Stability

Three pilot scale batches were stored at 25$^{o}$C/60% RH (long term storage conditions) and 40$^{o}$C/75% RH (accelerated conditions) for 48 months. Additional stability studies were performed on 3 batches, stored at 25$^{o}$C/60% RH and 40$^{o}$C/75% RH up to 24 month. Three commercial scale batches have been stored at 30$^{o}$C/65% RH and 40$^{o}$C/75% for six months. All batches have been manufactured using the proposed commercial method.

Stress testing at a temperature range between 50-70$^{o}$C in various container closure systems showed no changes in appearance assay, impurities content or degradation product and crystalline form.

The stability studies showed that the active substance is stable and confirm the proposed re-test period.

**Medicinal Product**

- Pharmaceutical Development

Based on the solubility, stability and permeability characteristics of febuxostat an immediate release oral dosage form was developed.

Well known excipients were used in the preparation of the formulation. The compatibility with the active substance was investigated by mixing the excipients with febuxostat and storing the samples in open vials at 40°C and 60°C, and exposing the samples to light. The results showed the active substance to be compatible with the excipients.

Hydroxypropylcellulose is used as a binder, lactose monohydrate and microcrystalline cellulose are used as fillers, croscarmellose sodium is used as disintegrant, magnesium stearate as a lubricant and silica as ant-adherent. All the excipients used in the formulation of febuxostat tablets comply with the Ph. Eur. A film-coating system was used consisting of polyvinyl alcohol, titanium dioxide, macrogol, talc and iron oxide yellow.

Changes were made to the formulation during the development and therefore bioequivalence studies were performed to confirm that the formulations used in the clinical trials are equivalent to the proposed formulation for commercialisation. In addition, discriminatory in vitro studies (dissolution studies) also showed that the release profile of the proposed formulation is comparable to that used in the pivotal clinical trials.

- Adventitious Agents

None of the excipients in the febuxostat blend are of animal origin, exception being the lactose monohydrate which is obtained from bovine milk sourced from healthy animals in the same conditions as milk collected for human consumption. TSE compliance statement from the supplier of the lactose monohydrate used in the manufacture of febuxostat tablets was provided. Magnesium stearate is of vegetable origin.

- Manufacture of the Product

The manufacturing process for febuxostat tablets uses standard pharmaceutical equipment and unit operations.

The manufacture of the finished product comprises (1) blending of the active substance with the excipients (2) wet granulation of the blend (3) drying of the granulation (4) sizing (5) addition of final excipients and blend (6) lubrication (7) tabletting (8) coating (9) packaging.

Process validation was carried out on three batches of each strength (80 mg and 120 mg) of febuxostat tablets. The results showed that the manufacturing process consistently produces tablets of the required quality.

- Product Specification

The product specifications include methods for appearance, identification (HPLC and IR), average mass, assay (HPLC), content uniformity (HPLC), degradation products (HPLC), dissolution (UV) and microbial purity. The HPLC methods have been validated for specificity, accuracy, reproducibility, linearity, robustness and stability of the solutions. The IR method was validated for specificity. The dissolution test method was fully validated for specificity, linearity, filter adsorption, accuracy, repeatability, intermediate precision and reproducibility. All other methods are described in the PhEur and therefore validation was deemed to be unnecessary.

- Stability of the Product

Three production scale batches of each strength of the proposed febuxostat formulation for commercialisation have been stored for up to 12 months at 25°C/60% RH and 30°C/65% RH (long term storage conditions) and for 6 months at 40°C/75% RH (accelerated conditions). The results showed that febuxostat tablets are stable as evidenced by the little or no change to the critical quality attributes of physical inspection, assay and dissolution during the stability studies. There were no degradation products observed above the ICH reporting threshold of 0.1%. There was no change in crystal form after storage under long-term or accelerated conditions. No trends or patterns of change were observed in any parameter, except loss on drying. Moisture levels increased over time but did not affect other quality attributes. No out of specification results occurred during the stability studies. The formulation was found not to be sensitive to light, as there was no change in any of the parameters tested for tablets exposed to ICH Q1B photostability conditions (including the exposed unprotected sample).

Based on the available stability data, the proposed shelf life and storage conditions, as stated in the SPC, are acceptable.

**Discussion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the drug substances and finished product has been presented in a satisfactory manner. The results of test carried out indicate satisfactory 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 the clinic.

## 2.3 Non-clinical aspects

**Introduction**

A comprehensive non-clinical development program was performed to evaluate the pharmacology, pharmacokinetics (including drug metabolism) and the toxicology in different animal species. The submitted non-clinical data are mainly from Teijin (Japan). The non-clinical toxicological studies were performed in accordance with GLP.

**Pharmacology**

- Primary pharmacodynamics

The primary pharmacodynamic effect of the new xanthine oxidase (XO) inhibitor febuxostat has been demonstrated by in vitro inhibition of bovine milk, mouse and rat liver xanthine oxidase as well as by in vivo inhibition of the enzyme in rats and male chimpanzees.
In vitro experiments:
Steady state kinetics measurements of inhibition bovine milk XO, rat and human liver XO by febuxostat showed mixed type inhibition with $IC_{50}$, Ki and Ki' values in the sub-nanomolar range. Inhibition of purified bovine milk XO by febuxostat (Ki 0.6 nM) and oxidative metabolites and 67M-1[R] (0.6 nM), 67M-1 [S] (0.8 nM), 67M-2 (1.6 nM), 67M-3 (2.0 nM) and 67M-4 (1.6 nM) showed a similar or only a slightly lower potency of the metabolites than the parent drug. The contribution of metabolites to the primary pharmacodynamic effect of febuxostat is therefore to be expected (see clinical aspects).

In vivo experiments (rat, mouse, chimpanzee):
In rodents (rat, mouse) uric acid is further metabolised to allantoin by uricase, whilst in chimpanzees similar as in men, purines are excreted mainly as uric acid. Single doses of febuxostat in normal rats reduced urinary excretion of uric acid/allantoin and increased the urinary excretion of xanthine in a dose-dependent manner.

Rat: Inhibition of xanthine oxidase by febuxostat in the hyperuricaemic rat model resulted in a dose-dependent reduction of serum uric acid (ED50 for febuxostat was 1.6 mg/kg vs. 9.1 mg/kg for allopurinol at uricase inhibition by oxonate over 6 days [Horiuchi at al., 1999] indicating that febuxostat is 5-6 times more potent than allopurinol. In another study in the hyperuricaemic rat model the ED50 for the sUA lowering effect was 1.5 mg/kg for febuxostat and 5.0 mg/kg for allopurinol at uricase inhibition by oxonate for 1 h prior drug application and the ED50 for the combined effect of decrease in serum urinary uric acid and allantoin was 2.1 mg/kg for febuxostat and 6.9 mg/kg for allopurinol [Osada et al., 1993], indicating febuxostat is about 3 times more potent than allopurinol.

Chimpanzees: In chimpanzees' inhibition of xanthine oxidase by febuxostat resulted in an apparent dose-dependent reduction of serum uric acid at 2, 5 and 12.5 mg/kg febuxostat p.o. The ED50 for the reduction of serum uric acid for febuxostat and allopurinol on Day 3 (approximate steady state) were 2 mg/kg and 6 mg/kg, respectively, indicating that febuxostat is about 3-times more potent than allopurinol in chimpanzees.
Comparison of the effect of febuxostat and allopurinol (done at a single dose level of 5 mg/kg p.o.) showed a reduction of serum uric acid as well as a decrease in urinary uric acid excretion, an increase of serum xanthine and urine xanthine excretion for both drugs.

In vivo studies with febuxostat metabolites were not performed in animals.

Generally, the studies demonstrate the primary pharmacodynamic effects of febuxostat.

- Secondary pharmacodynamics

The anti-inflammatory effect of febuxostat and allopurinol was studied in vitro (effect on leukotriene B4 production in rat basophilic leukaemia cells) and in vivo (effect on serum cytokine levels induced by lipopolysacharide in rats). The postulated anti-inflammatory effect of febuxostat has not been sufficiently characterized.

A study was performed in dogs with established pacing-induced congestive heart failure (CHF) to examine whether acute administration of febuxostat could enhance left ventricular (LV) function and improve myocardial high energy phosphate content and coronary endothelial function. Febuxostat treatment in this CHF dog model revealed no significant effect on coronary blood flow induced by acetylcholine or sodium nitroprusside.

The study on the heart failure model after coronary ligation in rabbits described a smaller reduction of the shortening fraction and ejection fraction than allopurinol, and a lesser degree/progression of heart failure after treatment with febuxostat compared to vehicle or allopurinol application. The mechanism of this febuxostat effect is unclear and the relevance for humans is not established.

At concentrations up to 100 µM, febuxostat had no significant effects on the activities of the following enzymes of purine metabolism (guanine deaminase (GD), hypoxanthine-guanine phosphoribosyl-transferase (HGPRT), purine nucleoside phosphorylase (PNP) and pyrimidine metabolism (orotate phosphoribosyltransferase (OPRT) and orotidine-5V-monophosphate decarboxylase (OMPDC), [Takano et al., 2005], which is in line with the Applicant's claim that febuxostat is a selective XO inhibitor.

- Safety pharmacology programme

The *in vitro* safety pharmacology program consisted in evaluations of the febuxostat effects on hERG (K+) channel, cardiac Ca2+ channel, cardiac Na+ channel and Purkinje fibre action potential.

In a human cardiac Na+ channel expressed in mammalian cells febuxostat showed inhibition of the inward Na+ current with a calculated IC50 value of 75 µM (about 470 times the free Cmax (maximum plasma concentration) in man following a 120 mg dose.

The effects of febuxostat on Ca2+ channel currents were studied in guinea pig cardiac myocytes.. Febuxostat blocked gpCaCh currents in a concentration-dependent manner, with an average block of 4, 12, 14 and 37% at 5, 50, 100 and 500 µM, respectively. The estimated IC50 value was 733 µM (about 4600 times the free Cmax in man following a 120 mg oral dose). This concentration range which inhibited ICa is therefore unlikely to be reached in humans. The positive control nifedipine significantly blocked gpCaCh current at 0.1 µM.

In a cloned hERG channel expressed in human embryonic kidney (HEK293) cells or Chinese hamster ovary (CHO) cells febuxostat had an agonist effect which was voltage dependent. Two types of response were observed, an initial maximal effect (0-3 min.) followed by a lower sustained effect. The EC50 values were 0.003 and 0.07 µM, respectively. Thus, the agonistic effect on the hERG activation occurred at concentrations reached at therapeutic doses in humans. The effect was highly use-dependent, implying a more pronounced effect at high heart rates. The clinical relevance of this finding is unclear. Febuxostat as a hERG agonist did not shorten normal APD or the sotalol-induced prolonged action potential in isolated Purkinje fibres at 1 µM, however, it selectively shortened the prolonged APD induced by an agonist for the late sodium current.
The free febuxostat concentration at a 120 mg dose in man, used in the submitted files for the estimation of safety margins was about 0.16 µM assuming about 1% free (unbound) febuxostat.

Febuxostat had no effect on platelet (human) aggregation by ADP, activated partial thromboplastin time and prothrombin time at doses of 3, 10, 30 or 100 µM (100 µM is about 600 times the free drug Cmax at 120 mg human dose).

The *in vivo* pharmacological safety program included a battery of conventional tests which covered CNS, cardiovascular, respiratory, renal, gastrointestinal system, platelet function, blood coagulation and the potential for causing hypersensitivity. In most in vivo studies, febuxostat was administered by oral dosing up to 100 mg/kg, which is about 40-fold greater than the intended maximum human dose (120 mg p.o., about 2 mg/kg at 60 kg BW). Pharmacokinetic data were only collected in one safety study in conscious dogs.

CNS effects:
Febuxostat caused a slight decrease in locomotor activity at 100 mg/kg p.o. in the Irwin behavioural test and at 30 mg/kg p.o. in another test in conscious mice.

Renal effects:
Febuxostat doses of 10 mg/kg p.o. or 30 mg/kg p.o. did not alter urine volume or electrolyte excretion in Wistar rats, but doses of 100 mg/kg increased urinary volume, urinary K+ and Cl- and decreased Na+/K+ ratio. All tested doses caused a dose-dependent increase in xanthine excretion. These effects have been related to the formation of xanthine crystals/calculi in kidney tubules. Renal xanthine calculus formation in Wistar rats after treatment with febuxostat for 28 days was absent at doses of 1 and 3 mg/kg and observed in only 1/30 animals at 10 mg/kg, however present in all animals (30/30) at 30 mg/kg and 100 mg/kg (29/29 animals). Renal xanthine calculus formation after treatment with allopurinol was absent at doses of 3 and 10 mg/kg and observed in only 2/30 animals at 30 mg/kg and 28/29 animals at 100 mg/kg. The relative ratio febuxostat/allopurinol for urinary xanthine excretion was 4.34, for the incidence of crystal/calculus formation 3.3 and the relative ratio of lowering plasma uric acid was from 3 to 6. Thus, the potency for crystal/calculus formation was closely related to the xanthine excretion in both drugs.
Xanthine calculus formation was also observed at lower febuxostat doses in mice and rats in long-term studies and judged as exaggerated pharmacodynamic effect, which may lead to kidney damage and to the formation of bladder tumours.

Cardiovascular effects:
In anaesthetized dogs (10, 100 mg/kg intraduodenal) febuxostat had no effect on respiration rate, blood pressure, heart rate, left ventricular pressure, left ventricular contractility**,** femoral blood flow or ECG.

In conscious, radiotelemetry instrumented Beagle dogs, febuxostat was applied at 5 mg/kg/d or 50 mg/kg/d p.o. over 14 days, four single incidents of acute decreases in blood pressure out of a total of 168 dosing events were observed in 2/6 dogs at 50 mg/kg (both on Day 1 of dosing) and 2/6 dogs at 5 mg/kg (on Day 6 or 7) and lasted approximately 1.3 to 2 hours. Because of the sporadic nature of the events and lack of a clear dose-response relationship the Applicant assumed that these effects were not drug related. There was no significant effect on heart rate, respiration rate or ECG. Pharmacokinetics, performed on days 2 and 14, showed average Cmax values on Day 14 of 1.73 and 38.12 µg/ml for the 5 and 50 mg/kg doses, respectively. The Cmax for the low dose can be approximated by a 50 mg p.o. dose in humans. The Cmax for the high dose was about 8 times the Cmax (4.98 µg/ml) in man following application of 120 mg p.o.
Febuxostat treatment in a CHF dog model (pacing-induced heart failure) revealed no significant effect on coronary blood flow induced by acetylcholine or sodium nitroprusside.

- Pharmacodynamic drug interactions

Two pharmacodynamic drug-drug interaction studies, one with nifedipine and one with glibenclamide, were performed.

Overall, in vitro safety studies showed an agonist (stimulatory) effect on the IKr channel in cultured hERG expressing mammalian cells at concentrations achievable in clinical use. Stratification of QT intervals of the sub-study of clinical Phase III study (APEX) according to heart rate showed that febuxostat does not significantly reduce the QT interval at the recommended doses of 80 and 120 mg/d.
No significant cardiovascular or CNS effects were reported.

**Pharmacokinetics**

ADME-studies for febuxostat have been investigated in mice, rats and dogs. The studies were carried out primarily with oral administration, which is the proposed clinical route of administration.
Toxicokinetic studies were carried out for all repeat-dose toxicity studies, the carcinogenicity studies, one reproductive study and one in vivo genotoxic study in mice, rats, rabbits and dogs.

- Absorption

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 (area under the concentration time curve) 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.

Based on comparisons between mean AUC values after p.o. and i.v. administration, approximately 57%, 85% and 45% of the total radioactive dose administered orally to mice, rats and dogs, respectively, was absorbed. The absolute bioavailability of febuxostat was determined to be approximately 78% in rats and 48% in dogs. Absorption in mice showed a gender difference, with approximately 2-4-fold higher AUC values in female mice than in males and in female dogs (up to 2.4-fold) compared to males following single and multiple doses.

In the single dose studies in rats at 1, 3 and 10 mg/mg p.o. the AUCt and AUC∞ values for febuxostat increased only roughly in a dose proportional manner; the absorption at 1 mg/kg was less than dose proportional. In the same study there was no apparent time dependence of total radioactivity or febuxostat judged from the AUC values at Day 1 and Day 14 at the 1 mg/kg dose.

In the toxicokinetic studies in rats (using higher doses of febuxostat) a clear dose- and time-dependence was apparent. In the repeated dose study in dogs at 5 and 50 mg/kg p.o. there was a clear dose-dependence. The toxicokinetic studies in dogs showed a clear dose- and time-dependence..

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

- Distribution

In vitro and ex vivo plasma protein binding studies with [$^{14}$C]febuxostat showed that the drug is highly bound in rat plasma (≥98.8%).
The distribution of total radioactivity in male Sprague-Dawley rats given a single dose of 1 mg/kg [$^{14}$C]febuxostat p.o. was studied by autoradiography and quantitative tissue distribution (sampling time: 1, 8, 24, 48, 96 168 h). In a second study a single dose and daily oral doses of 1 mg/kg [$^{14}$C]febuxostat for 14 days; sampling time: 1, 8, 24, 48, 96, 168 h) was studied by quantitative tissue distribution. The studies showed that febuxostat is widely distributed to most tissues and organs.
At 24 h after the 14th dosing the radioactivity concentrations in the liver, large intestine, adrenal gland, skin, small intestine and spleen were 16.7-7.2 times that in the plasma (15.56 ng eq./ml). The radioactivity concentrations in the lung, kidney, stomach, thyroid gland, and bone marrow were 5.9-4.2 times that in the plasma. The radioactivity concentrations in the mandibular lymph node, mandibular gland, brown fat, urinary bladder, mesenteric lymph node, pancreas, heart, thymus, epididymis, fat, testis and trachea were 3.8-1.3 times that in the plasma.
The half-lives of radioactivity in the plasma, thyroid gland and blood were 19-28 h. The half-lives of radioactivity in the large intestine, stomach, thymus, adrenal gland, pancreas, bone marrow, heart, mandibular gland, mesenteric lymph node, testis, smal1 intestine, mandibular lymph node, lung, spleen, brown fat, skeleta1 muscle, epididymis and urinary bladder were 47-75 h. The half-lives of radioactivity in the kidney, trachea, fat, eyeball, skin, and liver were 90-110 h.
The single or multiple dose applications showed that the radioactivity at 24 h was considerably higher than in plasma not only in the gastrointestinal tract and metabolizing and excreting organs of liver and kidney, but also in several other tissues.

The distribution ratio (whole blood/plasma concentration) of radioactivity into red blood cells ranged from 0.58-0.68 at timepoints ranging from 1 to 24 hours post-dose in rats, and from 0.28-0.46 in dogs within the first hour after dose administration.

Placental and lacteal transfer was investigated in pregnant and lactating Sprague-Dawley rats. One mg/kg [$^{14}$C] febuxostat p.o. was given on the 19$^{th}$ day of pregnancy or 2 weeks post-partum. Febuxostat crosses the placenta. The transfer of radioactivity to the foetus was estimated to be 0.0085% of the dose administered to the dams. The transfer of radioactivity to milk was high at 1-4 h (milk to plasma ratio of 7.6), thereafter the concentrations in milk and plasma decreased in a parallel manner.

- Metabolism

Several *in vitro* and *in vivo* studies were conducted to elucidate the metabolism of febuxostat in laboratory animals. Results from these studies demonstrated that febuxostat is metabolized by both oxidative and glucuronidation pathways.
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. In urine, the identified metabolites common between mice, rats and dogs included the hydroxylated febuxostat metabolites 67M-1 and 67M-2, metabolite 67M-3 (desbutylated febuxostat), and metabolite 67M-4 (dicarboxylic acid of febuxostat). Additional metabolites identified in mouse and/or rat urine samples include the sulphate conjugates of metabolites 67M-1 and 67M-3, and glucuronide conjugates of 67M-3 and parent drug. The major metabolite in bile of mice and rats was febuxostat glucuronide. It is of note, that 67M-3, the desbutylated metabolite isolated *in vivo* in rats and dogs, was not found in plasma of humans.

- Excretion

Following either i.v. or p.o. administration of [$^{14}$C]febuxostat to mice, rats or dogs, faecal excretion was generally the main route of elimination (especially in dogs), accounting for approximately 53-57%, 47-78% and 85-90%, of the radioactive dose, respectively. The faecal radioactivity largely derived from bile and contained both unchanged febuxostat and glucuronides and other metabolites depending on the species.
An average of approximately 18-48% of the total [$^{14}$C]febuxostat dose i.v. or p.o. administered to bile duct cannulated male and female mice was recovered in the bile within 24 hours post-dose. Similarly, 52-57% of the total radioactivity administered to male rats was recovered in the bile within 48 hours after administration of an intravenous or oral dose of [$^{14}$C]febuxostat. Urinary recovery of total radioactivity ranged from 9-48% in the rodent species and less than 10% in dogs. Following an i.v. dose of [$^{14}$C]febuxostat to chimpanzees, recovery of radioactivity in the urine was 49% and that in faeces 24%.
Excretion and disposition in man were broadly similar to those in animals (see clinical aspects).

***Drug Interactions***
No pharmacokinetic drug-drug interaction studies were performed in animals.

## Toxicology

In the Applicant's toxicology program febuxostat was given orally to mice, rats and dogs.

- Single dose toxicity

Single-dose toxicity studies with orally administered febuxostat were performed in rats and dogs.
In rats the approximate lethal dose for febuxostat was within 300 and 600 mg/kg p.o. The highest non-lethal dose for febuxostat in rats was 300 mg/kg p.o. (M + F). Death occurred between 6 h after drug application and 4 days. In the 600 mg/kg group, 4/5 males and 3/5 females died during the first 24 hours after administration. 1/5 male died on day 4 after administration. Clinical signs observed in diseased animals were a decreased locomotor activity after 5-25 minutes, cyanosis, lying on its side or belly, decreased body temperature. Autopsy: Ulcer-like black mottles with dosing material like substances were found in stomach and discoloration (haemorrhage) in the duodenum and ileum.

In Beagle-dogs no death was observed at doses up to 2000 mg/kg p.o., e.g. the highest non-lethal dose for febuxostat p.o. was 2000 mg/kg. Clinical signs were severe vomiting at all dose levels, prone position, lateral position, depression, decrease in locomotor activity, ptosis, decreased body surface temperature, salivation, loose stools. Beginning complete recovery of clinical signs was observed at post administration day 1.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies with orally administered febuxostat were performed in mice, rats, dogs and chimpanzees. Two repeat-dose toxicity studies with febuxostat p.o. were performed in mice (4 weeks: 0, 62.5, 125, 250, 500, 1000 mg/kg/d; 13 weeks: 0, 3, 12, 24, 48 mg/kg/d), four in rats (5 weeks: 0, 3, 15, 75, 150 mg/kg/d; 13 weeks: 0, 3, 12, 24, 36 or 0, 48, 75, 150 mg/kg/d; 6 month: 0, 3, 12, 48 mg/kg/d); two in Beagle-dogs (13 weeks: 0, 5, 20, 80 mg/kg/d; 52 weeks: 0, 5, 15, 45 mg/kg/d). one in chimpanzees (only for 3 days).
The major target organs identified in the repeat-dose toxicity studies were the kidney, urinary bladder, thyroid gland, liver and haematopoietic system.

Urinary tract (kidney, bladder):
The toxicology studies revealed dose- and duration dependent effects on the kidney and bladder in mice, rats and dogs. Biochemical and histopathological changes showed kidney damage, stones and/or bladder calculi and mucosal epithelial hyperplasia in all three species.
Main changes in the kidney were: Mouse: Cloudy white urine (M: ≥12 mg/kg/d; F: ≥3 mg/kg/d [13 wk]); dilated kidney tubules and interstitial fibrosis (M: 48 mg/kg/d [13 wk]). Rat: Round granules in urine; basophilic deposits in collecting tubules and papillary ducts, variable degrees of interstitial

inflammation and/or fibrosis and basement membrane changes (≥15 mg/kg/d [5 wk], ≥12 mg/kg/d [13 wk, 26 wk). Renal tubular epithelial necrosis (M, F: ≥48 mg/kg [13 wk]. Increased BUN (blood urea nitrogen), creatinine (≥75 mg/kg/d [5 wk, 13 wk]; (M: 48 mg/kg [26 wk]. Dog: Round granules (urine analysis), kidney calculi, renal pelvic calculi and hyperplasia of pelvic mucosa (≥20mg/kg/d [13 wk]; ≥15mg/kg/d [52 wk]); increased BUN and creatinine (45 mg/kg/d [52 wk]).
Main changes in the bladder were: Mouse: Stones in the bladder (M: ≥24mg/kg/d; F: ≥12mg/kg/d [13 wk]); transitional cell hyperplasia (M, F: ≥24 mg/kg/d [13 wk]). Rat: Calculi and epithelial hyperplasia (≥15 mg/kg/d [5 wk], ≥12 mg/kg/d [13 wk, 26 wk]), epithelial hyperplasia (≥75 mg/kg/d [5 wk], 48 mg/kg/d [26 wk]). Dog: Bladder calculi and mucosal epithelial hyperplasia (≥20mg/kg/d [13 wk], 45mg/kg/d [52 wk]).

The pathological effects in the kidneys and bladder were considered to be consequences of xanthine crystal deposition and subsequent damage to the kidneys and bladder and the lining urothelium, which is acceptable. The xanthine crystals in rodents have been identified using two different analytical techniques (thin-layer chromatography and Fourier transform infrared spectroscopy), however calculi in the urinary tract of dogs have not been identified as xanthine crystals. As outlined by the Applicant, the morphology of the granular deposits in dogs and site of occurrence plus understanding of the action of febuxostat on purine metabolism made it reasonable to assume that they consist of xanthine, and that they represent the same pattern of effect as in rodents. Although these arguments appear reasonable, an experimental verification should have been performed.

The NOAEL values determined in the toxicity studies, which were based on kidney toxicity, were 3 mg/kg/d in mice and rats and 5 mg/kg/d in dogs. In the 26-week rat study the exposure at NOAEL was 12.8 µg.h/ml (male) and 16.3 µg.h/ml (female) giving an AUCanimal/AUChuman ratio of 0.8 and 1.2, and in the 52-week dog study the exposure at NOAEL was 4.0 µg.h/ml (male) and 5.0 µg.h/ml (female) giving an AUCanimal/AUChuman ratio of 0.25 and 0.31 (using the human mean AUC value of 16.0 µg.h/ml reported from single or multiple 120 mg QD (once daily) in Phase I studies, n=64). Thus, using the usual calculation of safety margins (multiples of exposure in animals at the NOAEL level vs. exposure at therapeutic doses in humans) it is evident that no reliable safety margins are apparent from the animal toxicology studies.
The Applicant concluded that XO inhibition in humans at therapeutic doses does not lead to the same consequence because there is a much higher relative production of xanthine in the laboratory species and a higher relative urine output in man. Urinary xanthine in the rat at NOAEL (3 mg/kg) was 56.3 mg/dl and urinary xanthine in human urine was at 11.8 mg/dl at 120 mg febuxostat and 18.5 mg/dl at 240 mg febuxostat.
The solubility of xanthine in human urine was reported to be 13 mg/dl at 37°C, pH 7.0 (Klinenberg et al., 1965, Seegmüller, 1968). The solubility of xanthine in human serum was reported to be 10 mg/dl at 37°C, pH 7.4 and 5 mg/dl at 37°C, pH 5.0 (Seegmüller, 1968).

Thyroid:
Thyroid hyperplasia was observed in rats, but not in mice and dogs. With febuxostat a decrease in T3, T4 and hyperplasia of follicular epithelium was observed in the 5-week rat study only at high doses (75 and 150 mg/kg/d in male and females, respectively). In the 6-month rat study it occurred in males only during the recovery period at 48 mg/kg (at an about 14-fold higher exposure than the total exposure at 120 mg/day in humans). The exposure at the NOAEL for thyroid changes (males, 12 mg/kg/d, 52 µg.h/ml) is about 3-times higher than total exposure in humans at 120 mg/kg/d. The mechanism of the anti-thyroid effect is unknown. It has been discussed that thyroid hormones in rats are easier metabolized because they are only weakly bound to albumin and that rat thyroid follicular cells are specifically sensitive to drugs with anti-thyroid action and prone to hyperplasia. A special study in rats demonstrated that thyroid alterations caused by high doses of febuxostat (150 mg/kg/d) are prevented by concomitant application of T4.
Clinical findings on thyroid function are described below (see clinical aspects).

Liver:
In rats an increase in ALP and γ-GTP (GGT) was observed in a 13-week rat study (M: ≥15 mg/kg), and an increase γ-GTP in the 26-week rat study (M: 48 mg/kg/d). Bilirubin in the 26-month rat study

was increased, but within the upper normal range. Liver weights, transaminases and histopathology were unchanged up to 24 mg/kg/d in the 2-year carcinogenicity rat study.
Increased ALP and ALT levels in dogs were only observed in the 52-week dog toxicity study in moribund sacrificed animals (M, F: 48 mg/kg). In both species no histological liver changes were observed. Increased ALT and AST levels were observed in a 3-day study in monkeys, which received in addition ketamine for sedation. It was argued that a possibly ketamine induced effect cannot be clearly distinguished from test article induced effects.
A mechanism for the increase in liver enzymes in rats at high febuxostat doses has not been established. The Applicant calculated that the exposure level in male rats (at 48 mg/kg/d, AUC 238.5 µg.h/ml) was approximately 14-fold higher than the total exposure in humans at a single 120 mg oral dose, but the exposure at NOAEL for liver changes in male rats was only about 3-times higher than the human exposure at 120 mg/day.
Clinical findings on liver function test are described below (see clinical aspects).

Haematology:
Haematology findings in rats were: Decreased erythrocyte count, haemoglobin level and haematocrit; increased WBC counts and segmented neutrophil percentage; decreased lymphocyte percentage (≥75 mg/kg/d [5 wk], ≥12 mg/kg/d [13 wk], 48 mg/kg/d [26 wk].
Haematology findings in dogs were: Moribund sacrificed animals: Increased erythrocyte count, haemoglobin level and haematocrit, % neutrophils, % monocytes; decreased % lymphocytes; prolonged aPPT (45 mg/kg/d [52 wk]). Animals sacrificed at schedule: Decreased erythrocyte count, haemoglobin level and haematocrit; increased reticulocytes, increased platelet count (45 mg/kg/d [52 wk]).
The Applicant discussed that increases in WBC count could be due to an inflammatory response to the ongoing kidney injury in these animals and that a decrease in erythropoietin release (expected due to extensive injury to the kidney caused by xanthine crystals and/or calculi) could have contributed to the alterations in red blood cell parameters. Both in rats and in dogs the haematological changes were observed at dose levels that also caused kidney injury.
The exposure at the target organ effects was 14-18-fold (rat) and 33-fold (dog) higher than that in humans, however, the exposure at the apparent NOAEL for the RBC decrease in rats was only about 3-5-fold higher than that in humans at 120 mg/d febuxostat and the exposure at the apparent NOAEL for the RBC decrease and platelets increase in dogs was only about 2-fold higher than that in humans at 120 mg/d febuxostat.
Clinical findings on haematology are described below (see clinical aspects).

Comment on safety margins
According to the Applicant, NOAEL values were based on kidney toxicity. Exposure in the toxicology studies is generally considerably higher than in humans at therapeutic doses. However, from the calculated multiples of exposure in mice, rats and dogs at the NOAEL levels vs. exposure at therapeutic doses in humans (AUCanimal/AUChuman) it is evident that no reliable safety margins are apparent from the animal toxicology studies (based on kidney toxicity). The exposure in dogs at the NOAEL level is markedly lower than in humans at the recommended 120 mg QD dose. The exposure in mice and rats at the NOAEL level is lower (male mice) or in the range (female mice, male and female rat) of the human exposure at 120 mg febuxostat. There was a slight gender difference.

The exposure at NOAEL for thyroid changes in male rats (AUC 52 µg.h/ml), liver changes in male rats (AUC 52 µg.h/ml), haematological changes in the rat (M: AUC 52.9 µg.h/ml; F: 86.2 µg.h/ml) or dogs (AUC 38.7 µg.h/ml) are only about 3-4 fold greater than the exposure in humans at 120 mg febuxostat QD (17.2 µg.h/ml).

Reversibility of febuxostat effects
The reversibility of kidney and bladder alterations caused by xanthine calculi/crystal deposition observed at the end of the recovery periods in rats (4 weeks in the 5-week rat study) and end of the recovery period in dogs (6 or 13 weeks in the 13-week and 52-week studies, respectively) was very low or absent.
At the end of the 4-week recovery period in the 5-week rat study changes including increased water consumption, decreased erythrocyte count, haemoglobin level and haematocrit, increased Na excretion

in the urinalysis, increased serum phosphate levels, and renal tubular regenerative changes, cellular infiltration, and interstitial fibrosis remained approximately the same as at the end of administration period.
At the end of the 13-week recovery period in the 52-week dog study calculi or granules were observed in the kidneys. Dilatation of the pelvis, hyperplasia of the pelvic mucosa, cellular infiltration in the pelvic submucosa, cellular infiltration in the interstitium, fibrosis of the interstitium, atrophy of the renal tubules, dilatation of the renal tubules, a basophilic change in the tubular epithelium and dilatation of Bowman's space were also observed at the completion of the recovery period.

- Genotoxicity

A standard series of conventional *in vitro* and *in vivo* tests was performed to test for a possible genotoxicity of febuxostat including 5 in vitro mutagenicity tests (Ames test and E. coli assay, gene mutation assay in mouse lymphoma cells, chromosomal aberration test in Chinese hamster lung fibroblasts and human peripheral blood lymphocytes) and 3 in vivo mutagenicity tests (Micronucleus test in bone marrow of BDF1 mice and Wistar rats, unscheduled DNA synthesis in F344 rat hepatocytes). In one *in vitro* chromosomal aberration test in cultured Chinese hamster cells a chromosomal aberration was observed in the absence or presence of S9 mix at high doses (1.336 and 2 mM). It is agreed that these changes are related to the cytotoxicity, since they were only found at high doses in the presence of moderate to severe cytotoxicity. All other *in vitro* and *in vivo* tests gave negative results. The *in vivo* chromosomal aberration study in Wistar rats was performed at a very high exposure, more than 100-fold of the human exposure at 120 mg febuxostat QD. Febuxostat appears to have no genotoxic potential.

- Carcinogenicity

Two carcinogenicity studies were performed; one in mice and one in rats to estimate the potential carcinogenicity of febuxostat.

A 104-week carcinogenicity study in $B6C3F_1$ mice (50/sex/group; 0, 3, 7.5, 18.75 mg/kg/day febuxostat) the mortality was 8%, 8%, 14% and 20% in males and 18%, 16%, 24% and 24% at 0, 3, 7.5 and 18.75 mg/kg/day febuxostat, respectively, higher in females than in males. Urinary bladder tumours in female mice (transitional cell papilloma in 3/50 females, transitional cell carcinoma in 1/50 females) were found at the high dose group of 18.75 mg/kg/day, but none in controls or at lower febuxostat dose levels. No urinary bladder tumours were found in male mice (up to 18.75 mg/kg).
Prominent pathological/histopathological findings were: Increase in kidney weights (F: HD); increased incidence of fibrosis (M: MD, HD; F: HD) and calculi (F: HD) in the kidney.
Bladder: transitional cell hyperplasia, oedema, lymphocytic infiltration, fibrosis and hyaline droplet deposition in the transitional epithelium (M, F). Bladder calculi were observed in 44/50 females and 48/50 males at 18.75 mg/kg/day. It is therefore somewhat surprising that no bladder tumours were observed in male mice. The febuxostat exposure in mice at 13 weeks at the highest dose of febuxostat in males (18.75 mg/kg/d; average AUC24: 27 µg.h/ml) and females (18.75 mg/kg/d; average AUC24: 96.6 µg.h/ml) were approximately 6-fold higher (females) than in humans after 120 mg febuxostat oral dose (2 mg/kg QD with a mean AUC value of 17.6 µg.h/ml,).

In the 104-week carcinogenicity study in F344 rats (50/sex/group; 0, 3, 6, 12 and 24 mg/kg/day febuxostat) the mortality was 24%, 20%, 18%, 20% and 36% in males and 22%, 30%, 30%, 40% and 34% at 0, 3, 6, 12 and 24 mg/kg/day febuxostat, respectively. A statistically significant increase in urinary bladder tumours in male rats (transitional cell papilloma in 10/50 males; transitional cell carcinoma in 7/50 males) was found in the high dose group (24 mg/kg/day). In female rats transitional cell papilloma was found in controls, at 12 and 24 mg/kg (only 1 in each group).
Prominent histopathological findings were calculi, transitional cell hyperplasia in the bladder, kidney and urethra. Calculi in the urinary bladder at 24 mg/kg/d were higher in males (12/50 animals) than in females (2/50 animals) as well as in the urethra (15/50 males; 2/50 females). Calculi found in the kidney at the high dose were similar in males and females (47/50 males; 44/50 females).
The febuxostat exposure in rats (in term of AUC) at the highest dose of febuxostat in males (24 mg/kg/d; average AUC 194 µg.h/ml at 13 weeks) and females (18.75 mg/kg/d; average AUC 201.8

µg.h/ml) were approximately 1.5-fold and 1.2-fold higher than in humans after 120 mg febuxostat oral dose (2.0 mg/kg QD with a mean AUC value of 17.6 µg.h/ml.

The incidence of urinary bladder tumours in female mice and male rats was considered secondary to the long-term irritation of the urinary bladder epithelium by xanthine calculi. The Applicants judgment is acceptable. The postulated non-genotoxic mechanism of bladder cancer in mice and rats receiving febuxostat is supported by the negative results of the mutagenicity studies and the close association between observed calculi and tumours at least in the rat. Furthermore, a direct damage to the uroepithelium, cytotoxicity and consequent regenerative hyperplasia by urinary calculi has been observed in mice (Saccata et al, 1988, Carcinogenesis 9, 1271-1276) and rats (Shirai et al., 1986, Cancer Research 46, 2062-2067) by uracil feeding. As pointed out by these investigators a prolonged, continuous stimulus to increase cell number and cell proliferation is adequate to result in carcinomas being generated in a significant proportion of rats or mice over their life-time and no DNA altering effects has to postulated for this agent to result in tumours.

In mice an increase in urine pH and/or urine volume reduced/inhibited the formation of xanthine calculi in the urinary bladder and prevented the occurrence of urinary bladder transitional cell hyperplasia in febuxostat treated animals. An increase in urine volume also reduced the uracil-induced bladder effects in mice. The study supports the postulated non-genotoxic mechanism of bladder tumour development as observed in the mouse and rat carcinogenicity studies.
The less than a 6-fold greater exposure in mice and less than 2-fold greater exposure in rats than in humans is low, however in the case of the assumed non-genotoxic carcinogenic effect the safety in humans might depend on the risk of treatment-induced xanthine calculi formation.

- Reproduction Toxicity

Reproduction and development studies were performed in rats and rabbits at doses of 3 mg/kg, (LD) 12 mg/kg (MD) and 48 mg/kg (HD).
Febuxostat had no effect on male or female fertility in rats at doses up to 48 mg/kg/d. Toxic effects in male and female rats included deposition and/or calculus of xanthine crystals in the kidney (M, F) or bladder (M) at the high dose (48 mg/kg/d). Similar effects on dams were observed in the Embryo-foetal development study in rats (but not in rabbits) as well as in the Pre- and Postnatal development rat study at 48 mg/kg. Embryotoxicity was not observed in rats and rabbits (NOAEL 48 mg/kg/d). There was no evidence for a teratogenic potential in both animal species.
In the Pre- and Postnatal development rat study toxic effects were seen in the $F_1$ generation of dams receiving the high dose of 48 mg/kg. $F_1$ pups showed a decreased body weight at birth (M, HD) and decrease in body weight gain (M, F: HD), and had urinary tract changes such as calculus in the kidney, bladder and urethra and increased thyroid weights (HD) suggesting febuxostat exposure via the dams milk. A slowed development and a decreased weaning index (HD) was observed, which was considered to be secondary to renal damage in the $F_0$ dams caused by xanthine crystal deposition in the kidney.
The exposure in pregnant rabbits was quite high (AUC at NOAEL was about 400 µg.h/ml), which represents an about 23 to 24-fold higher exposure than in females at 120 mg/d (mean AUC was 17.5 µg.h/ml, 16 µg.h/ml at single or multiple doses in Phase I studies, n=30).
Exposure in pregnant rats has not been measured, but AUC values in non-pregnant Fisher 344 rats reached 338-375 µg.h/ml at 48 mg/kg in the 13-week toxicokinetic study, suggesting a high exposure at the highest dose level in the rat reproduction studies.
The safety margin in the rat development study at NOAEL level (3mg/kg, and assuming a similar exposure value as in the 13- week toxicokinetic study: AUC: 16.4 µg.h.ml) might be low and around 1. However, the risk of developmental toxicity in humans would apparently depend on the risk of treatment-induced calculi formation.

Adenuric should not be used during breast-feeding.

- Local tolerance

Local tolerance testing is not relevant to the administration route of this medicinal product.

- Other toxicity studies

*Antigenicity*
A passive cutaneous anaphylaxis test in mice and guinea pigs and an active systemic anaphylaxis (ASA) test in guinea pigs gave negative results indicating no antigenic febuxostat effect.

**Ecotoxicity/environmental risk assessment**

An environmental risk assessment including Phase I was carried out.
The Applicant calculated a Phase I $PEC_{SURFACEWATER}$ of 0.006 µg $L^{-1}$ using the default values specified in the CHMP/SWP/4447/00 draft guideline. However, the Fpen used by the Applicant was 0.01 % rather than the default of 1 %. The use of an Fpen of 0.01 % was not supported by appropriate references. The correct $PEC_{SURFACEWATER}$ is 0.6 µg $L^{-1}$ which is well above 0.01 µg $L^{-1}$ and a Phase II assessment was requested by CHMP.

A Phase II investigation according to the Guideline on the environmental Risk Assessment of Medicinal Products for human use (EMEA/CHMP/SWP/4447/00) was performed, as requested in the CHMP LoOI), which included the following tests: Activated sludge respiration inhibition test (OECD 209), Assessment of ready biodegradability by measurement of Carbon Dioxide Evolution (OECD 301B), Activated sludge adsorption isotherm (OPPTS 835.1110), Inhibition of growth to the alga Pseudokirchneriella subcapitata (OECD 210), Fish toxicity testing to Pimephales promelas (OECD 203 and 210) and acute and chronic effects to Daphnia magna (OECD 211).
As requested by CHMP the applicant commits to perform a study on aerobic transformation in aquatic sediment systems (OECD 308) for febuxostat to complete the Phase II environmental fate and effect analysis and to prove that febuxostat is unlikely to be a concern for the environment.

## 2.4 Clinical aspects

**Introduction**

A comprehensive clinical program was performed to evaluate the pharmacology, pharmacokinetics, efficacy and safety. The submitted clinical pharmacology data included 25 *in vitro* studies and 36 *in vivo* studies.
The clinical efficacy data included 5 studies (1 dose response study, 2 pivotal Phase III studies, and interim analyses of 2 ongoing open-label long-term extension studies)
At the time of EU MAA application, the US clinical studies include a total of 2531 subjects who had received at least one dose of febuxostat across the Phase 1, 2 and 3 trials. Approximately 900 subjects were ongoing in the long-term extension studies. Sixty-one of these subjects had been treated for more than 4 years.
The safety data are mainly based on the 2 pivotal Phase III studies and interim analyses of the ongoing 2 open-label long-term extension studies.
The Japan clinical program for febuxostat included 6 Phase I trials, 7 Phase II trials, and 2 Phase III trials. However, since at the time of EU application, the Japan program evaluated a different indication (hyperuricaemia/gout) and lower doses of febuxostat (doses up to 40 mg QD) than those being developed in the United States (80 mg QD and 120 mg QD, the efficacy of febuxostat in the current application is mainly based on the US clinical studies. Japanese studies were considered regarding safety.
No paediatric studies have been conducted.
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.

**Pharmacokinetics**
The Phase 1 clinical pharmacology program included 25 *in vitro* studies and 36 *in vivo* studies. (In addition, two population PK analyses were performed.

- Absorption

*In vitro* studies:
The apparent permeability coefficient (Papp) of febuxostat was determined in a Caco-2 absorption assay. When tested at pH 7.4, the absorption of febuxostat was similar to that of salicylic acid, which is known to have a medium permeability. Verapamil did not appear to have an effect on the transport rate of febuxostat, indicating that P-glycoprotein is not involved in the transport of febuxostat. However, some other efflux system(s) was probably involved in febuxostat transport since transport rates from basolateral to apical were higher than those from apical to basolateral at the 10 μM concentration. At pH 5.5, the absorption rate of febuxostat at both the 10 and 100 μM concentrations increased, ranking it among drugs of high permeability (such as testosterone). In addition, transport rates from apical to basolateral were higher than those from basolateral to apical, indicating that a transport carrier with a pH-dependent mechanism was facilitating absorption.
According to the Biopharmaceutics Classification System febuxostat is classified as a Class 2 compound (low solubility, high permeability).

*In vivo* studies:
A single oral dose of 80 mg [$^{14}$C] febuxostat was given to 6 male volunteers. The absorption of radioactivity was rapid (tmax 0.58 h). The major peak in plasma was febuxostat, which accounted for an average of 94% of the total radioactivity at Cmax (Cmax total [$^{14}$C]: 4.19±1.67 μg/ml; Cmax febuxostat: 3.95±1.58 μg/ml). AUC febuxostat represented 83% of total radioactivity AUC (AUC total [$^{14}$C]: 10.25±2.69 μg.h/ml; AUC febuxostat: 8.48±2.18 μg.h/ml). Values for the maximum unbound febuxostat (Cmax,u) and exposure to unbound febuxostat (AUC24,u) were not given. Metabolites observed in plasma at 4 h were relative low compared to febuxostat (84.7%). 67M-1 (4.36%), 67M-2 (5.45%), 67M-4 (1.25%), regio-isomers of acyl-glucuronide (3.8%) of febuxostat, and the sulfate conjugate of 67M-1 (0.5%).

A placebo-controlled, dose-escalation study of febuxostat in 154 healthy adult volunteers investigated PK and PD data at daily oral doses of 10-240 mg QD and 30 mg bid (twice daily) over 14 days. The pharmacokinetics of total febuxostat (bound + unbound) was neither time nor dose dependent at oral doses of 10 - 120 mg/day. For doses greater than 120 mg a greater than dose-proportional increase in AUC was observed, whilst Cmax appeared to increase proportional to the dose between 10 mg and 240 mg QD.

A study investigated PK and PD parameter (Part A) in healthy male and female subjects receiving 300 mg febuxostat QD over 7 days (design: Phase 1, double-blind, placebo-controlled, randomized, single-centre study). This dose of 300 mg febuxostat QD resulted in the highest exposure of all clinical studies on febuxostat. The study demonstrated again the non-linearity of AUC for febuxostat at higher doses. AUCτ of febuxostat at the 300 mg QD dose at day 7 was about 4 times that at the 120 mg QD dose (11.9 μg.h/ml) at day 14 in the dose-escalation study. Cmax of febuxostat at the 300 mg QD dose at day 7 was about 2.6 times that at the 120 mg QD dose (5.31 μg/ml) at day 14 in the dose-escalation study, which would indicate approximate dose proportionality up to 300 mg QD for Cmax. The total febuxostat AUCτ and unbound febuxostat AUCτ,u on day 7 was 48.3 and 0.339 μg.h/ml, respectively, approximately 6 times the observed mean total plasma exposures with 80 mg of febuxostat in controls of special population studies in healthy subjects (7.50, 7.61 and 8.15 μg.h/ml AUCτ and 0.065, 0.051 and 0.055 μg.h/ml AUCτ,u in studies TMX-xx- 008 , TMX-xx-012 and TMX-01-016, respectively.

The absolute bioavailability was not determined in humans because of unavailability of an intravenous febuxostat formulation. An absorption of febuxostat of about 84% or even greater has been postulated as judged from the finding in Cxx-040 that only 6-16% of radioactivity was recovered as unchanged febuxostat in faeces.

Concomitant food intake reduced the absorption of febuxostat. The three food studies gave similar results, namely a decrease of Cmax for total febuxostat of 46%, 49%, 38% and a decrease of $AUC_{\infty}$ for total febuxostat of 19%, 18% and 16% in the three studies, following a high-fat meal vs. fasting conditions. The Applicant stated on grounds of a not substantial difference in the decline of serum urate under fasting or non-fasting conditions (58% non-fasting vs. 51% fasting) that febuxostat can be taken with or without food (which is recommended also in the SPC). The Applicants argument, based on pharmacodynamic findings, appears to be acceptable, but neglects the pharmacokinetic finding of a reduction of total exposure up to 19%. It is noted that the treatment description in the pivotal studies (APEX, FACT) does not specify whether febuxostat had to be taken under fasting or non-fasting conditions.

Bioequivalence of the 20 mg US and Japanese tablet formulations were demonstrated. In addition, bioequivalence was demonstrated for the combinations of tablet strengths (20, 40, 80 and 120 mg) that were utilized in clinical trials, as well as for tablets manufactured at the pilot scale and those manufactured at the proposed commercial scale. In the biopharmaceutical studies intrasubject variability of febuxostat was low for Cmax (CVs of 23-34%) and AUC∞ (CVs of 9-12%). The intersubject variability was slightly higher (CVs of 27-48% for Cmax and CVs of 23-39% for AUC). For tmax, the intrasubject and intersubject variability was high (CVs of 41-73% and 54-90%, respectively).

For the foreseen febuxostat (Adenuric) EU tablets no bioequivalence study has been performed which compares tablets manufactured for the EU market with the tablets used in Phase III studies. Dissolution profiles were shown as bioequivalence surrogate.

Two population pharmacokinetic studies were performed using data from study TMX-xx-005 or data from the APEX study . The structural model was a 2-compartment model with first order absorption rate and a lag time. The population pharmacokinetic-pharmacodynamic model estimated population means for Cl, Vc, Vp, Q, Ka, $t_{lag}$, Kin, $IC_{50,}$ and $K_{out}$.

The population PK analysis included only 125 subjects out of 665 on febuxostat (80, 120 and 240 mg QD) in the Phase III APEX study and 87 of 116 subjects in the open label LTE study TMX-01-005. In both studies pharmacokinetic and pharmacodynamic samples were taken at steady state (during week 16-28 in the APEX study and during week 28-52 in study TMX-01-005).

Population PK from TMX-xx-005 data identified baseline creatinine clearance and smoking status for Cl and baseline serum urate for $K_{out}$ as statistically significant covariates. Smoking as a significant covariate could not be confirmed in the APEX study. Population PK from the APEX data identified BUA for $K_{in}$ and CrCl, weight (WT) and fibrate status for Cl as statistically significant covariates. Covariates for $K_{out}$ were not estimated. Fibrate decreased the febuxostat clearance and increased exposure. The estimated population mean $IC_{50}$ was 0.209 µg/ml (inter-individual variability: 48.4%) in study TMX-xx-005 and 0.239 µg/ml (inter-individual variability: 66.7%) in the APEX study .
The population PK reports were not very detailed and lacked several elements necessary to allow for a full secondary assessment of the analyses. Additional evaluation of the population PK analyses would be needed if any claims were to be based on these analyses or if the models were to be used in future simulations.

- Distribution

Protein binding:
Febuxostat is highly bound to human plasma proteins (determined by ultrafiltration): 97.9-98.9%, 98.1-99% and 98.3-99% at nominal 0.4, 2.0 or 10 µg/ml [$^{14}$C]febuxostat concentrations in two *in vitro* studies, predominantly to serum albumin (98.1% to 99.1%), mainly at the diazepam bindings site. Binding to α1-acid glycoprotein was low (average 15.6 %). Binding of metabolites 67M-1, 67M-2 and 67M-4 to plasma proteins (determined by ultrafiltration) was less than observed with the parent drug and approximately 90%, 81.7% and 91.7%, respectively, measured at 200 ng/ml.

Febuxostat appears to have a low to medium volume of distribution of approximately 0.7 L/kg. The mean apparent volume of distribution (Vc+Vp) for febuxostat was estimated as 54.4 L in the population PK analysis. Febuxostat has an apparent elimination half-life of approximately 4-6 hours.

- Elimination

***Metabolism***
Febuxostat is mainly metabolized to its acyl-glucuronide and by oxidation of the isobutyl moiety leading to the formation of 4-hydroxy metabolites 67M-1, 67M-2, and 67M-3 and 67M-4; as detailed in non-clinical metabolism section 67M-3 is not observed in humans.
Glucuronidation of febuxostat is the major metabolic pathway. Three oxidative metabolites have been identified in plasma and urine in several studies from healthy volunteers or from healthy volunteers and patients with renal impairment (or hepatic impairment and in subjects of different gender or age. Similarly to febuxostat, 4-hydroxy metabolites also undergo conjugation, but to a lower extent as compared to febuxostat, indicating that conjugation plays a less major role in elimination of febuxostat oxidative metabolites. However, reduced renal elimination of conjugated febuxostat as observed in patients with severe renal impairment can influence the pharmacokinetics.

Several different UGT isoforms catalysed formation of febuxostat glucuronide. At least CYP1A1, 1A2, 2C8 and 2C9 are involved in the formation of 67M-1 and 67M-2. The relative importance of different isoforms has not been determined. The enzyme responsible for formation of 67M-4 from 67M-1 has not been identified, but it does not appear to be a CYP isoenzyme.

Of the urine and faecal samples evaluated an average of 86.8% (46.2% urine and 40.6% faeces) of the dose was evaluated, with the known metabolites and febuxostat accounting for 82.3% of the dose, and the remaining 4.4% were from 8 unidentified peaks (P0, P1, P2, P4, P6, P7, P15, P16), which could not be evaluated because the concentrations were too low to be identified (each less than 2% of the total radioactive dose).

***Excretion***
The mean (SD) cumulative recovery of [$^{14}$C] radioactivity in excreta was 94.1 ± 0.7% (49 ± 9.8% urine and 44.9 ± 10.1% faeces) at 216 hours post-dose. Febuxostat represented a combined total of 10%-18% (1%-3% urine and 8%-16% faeces) of the dose. Other studies confirmed these results.
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 was febuxostat glucuronide. The oxidative metabolites are excreted in urine and faeces, unchanged or as glucuronides.

- Dose proportionality and time dependencies

Dose proportionality has been investigated in one Phase I study in healthy volunteers at doses ranging from 10-240 mg/day febuxostat (TMX-99-001), and in one Phase II study in patients with gout at doses of 40, 80 and 120 mg/day febuxostat (TMX-00-004: Becker et al., 2005).

In the dose-escalation study TMX-99-001**,** pharmacokinetics of febuxostat was neither time nor dose-dependent at doses of 10 - 120 mg/day. Daily doses in the range of 10 - 120 mg produced dose-proportional increases in maximum febuxostat plasma concentrations (Cmax) and area under the plasma concentration versus time curves (AUC). For doses greater than 120 mg a greater than dose-proportional increase in AUC was observed, whilst Cmax appeared to increase proportional to the dose between 10 mg and 240 mg QD.

In study TMX-xx-004 the median trough febuxostat concentrations at steady state were linearly related to the febuxostat dose.

- Special populations

Renal impairment:
A multicentre, parallel group Phase I study (n=32) investigated the pharmacokinetics, pharmacodynamics and safety of febuxostat in male and female subjects with normal renal function or patients with renal impairment. Febuxostat (80 mg/day; administered as 4x20 mg tablets was orally administered for 7 days to subjects with normal renal function (n = 11, CLcr >80 ml/min/1.73 $m^2$) or to subjects with mild (n = 6, CLcr 50-80 ml/min/1.73 $m^2$), moderate (n = 7, CLcr 30-49 ml/min/1.73 $m^2$), or severe renal impairment (n = 7, CLcr 10-29 ml/min/1.73 $m^2$). The higher dose of 120 mg/day, intended for treatment of gout, was not investigated.
PK: Mean tmax for febuxostat was fast (about 1.00 hour) for all treatment groups. Mean Cmax and mean AUC24 for total febuxostat were 2.87 ± 1.25 µg/ml and 7.50 ± 2.68 µg.h/ml and mean Cmax,u and mean AUC24,u for unbound febuxostat were 25.01 ± 12.8 ng/ml and 65.5 ± 28.1 ng.h/ml in controls. Total mean AUC24 was approximately 48%, 48% and 76% higher for subjects with mild, moderate and severe renal impairment, respectively. Unbound mean AUC24,u was approximately 52%, 40% and 127% higher for subjects with mild and moderate and severe renal impairment, respectively, than in controls. The variability was higher and protein binding slightly lower in the severe renal impairment group than in the other groups, and there were no patients with CLcrea<15 ml/min in the study. The AUC of active metabolites increased proportionally more than the parent compound in all groups and the urinary excretion of total metabolites (67M-1, 67M-2 and 67M- 4, unchanged plus conjugated) was generally lower in subjects with renal impairment than with normal renal function. As active metabolites have higher free concentrations than febuxostat, this could be expected to lead to a greater change in activity than the change in total concentrations.
$AUC_{0-24}$ for febuxostat all three metabolites showed a linear relationship with $Cl_{cr.}$ The Clr of the unchanged metabolites in severe renal impairment group was more than 10-fold lower than in subjects with normal renal function.

PD: The mean serum 24-h UA concentrations decreased from baseline (which was higher in subjects with renal impairment) to a similar extent in subjects with normal renal function (58.2%) and in patients with mild, moderate or severe renal impairment (63.6%, 56.7%* and 55.1%, respectively; *p<0.05). The mean serum xanthine concentration in subjects on 80 mg febuxostat increased from 0.15 mg/dl in subjects with normal renal function to 0.21, 0.38 and 0.63 mg/dl in and in patients with mild, moderate or severe renal impairment.

Overall, due to the large variability in severe renal impairment, the shift in febuxostat/metabolite ratio and the pharmacodynamic results, it is not considered possible to extrapolate safety data from healthy volunteers who have received high doses for a short period of time (2 weeks) to patients with severe renal impairment. From a purely pharmacokinetic point of view, the increase in febuxostat exposure at mild or moderate impairment does not warrant dose adjustments.

Hepatic impairment
An open-label, parallel group Phase I study (n=27), investigated the pharmacokinetics, pharmacodynamics (and safety) of febuxostat in male and female subjects with normal hepatic function (n=11) and subjects with mild (n=8) and moderate (n=8) hepatic impairment (Child-Pugh classification). Patients with severe hepatic impairment were excluded. 80 mg febuxostat was given once daily for 7 days.
PK: Mean Cmax and mean AUC24 for total febuxostat were 2.84 ± 0.94 µg/ml and 7.61 ± 2.65 µg.h/ml and mean Cmax,u and mean AUC24,u for unbound febuxostat were 19.1 ± 7.2 ng/ml and 51.2 ± 19.2 ng.h/ml in controls. Total Cmax was approximately 23% and 53% higher and total AUC24 was approximately 29% and 54% higher for subjects with mild and moderate hepatic impairment, respectively. The higher dose of 120 mg/d recommended for gout treatment, was not investigated. Unbound Cmax,u was approximately 24% higher and unbound AUC24,u approximately 28% and 24% higher for subjects with mild and moderate hepatic impairment, respectively. The steady state clearance for unbound febuxostat was only reduced in the mild hepatic impairment group (about 28% reduction). Elimination half-lives were similar for each hepatic function group (4.9 to 5.5 h). None of the differences between subjects with mild or moderate hepatic impairment and subjects with normal hepatic function was statistically significant ($P > 0.05$).

PD: Serum uric acid Cmean,24 values decreased (mean of 62.5% (normal), 48.9% (mild) and 47.8% (moderate)) and urinary uric acid Cmean,24 concentrations decreased (64.0% (normal), 62.7% (mild) and 42.5% (moderate) at mild or moderate hepatic impairment compared with normal hepatic function. Serum xanthine Cmean,24 values increased statistically significant and the total urinary xanthine Cmean,24 and the total daily xanthine excretion decreased significantly in patients with mild or moderate decrease in hepatic function compared to patients without hepatic impairment. Urinary hypoxanthine Cmean,24 concentrations increased substantially for each hepatic function group.

Overall, mild to moderate hepatic impairment did not significantly affect exposure to febuxostat or its active metabolites. However, metabolic impairment in the subjects included in the study might not have been significant.

Age and Gender
A study investigated the pharmacokinetics and pharmacodynamics of 80 mg oral febuxostat/day in 24 healthy male and 24 healthy female subjects given over 7 days (design: Phase 1, parallel-group, open-label, multiple-dose study in male and female subjects between the ages of 18 and 40, inclusive and 65 years of age and older). Subjects were categorized into different study groups based on age and gender. Each subject received febuxostat once daily for 7 consecutive days after an overnight fast of at least 8 hours.
The Applicant's statement that the pharmacokinetics and pharmacodynamics of febuxostat appeared not to be substantially affected by age or gender and that no dose adjustment is required based on differences in age is substantiated by data and acceptable. Unbound febuxostat Cmax and AUC values were statistically significantly ($p<0.05$) higher in females than in males probably due to slightly lower total body clearance and/or volume of distribution of febuxostat in females as compared to males. The differences could be largely accounted for by weight differences between male and female subjects and were therefore not due to gender differences alone.

Ethnic differences in efficacy of febuxostat between Caucasian and non-Caucasian subjects were reported in the pivotal Phase III studies (combined data). PK differences were not reported. 78% of patients treated with febuxostat in the pivotal Phase III studies (APEX, FACT studies) were Caucasians. In the Black and Hispanic subgroups, response rates in the febuxostat groups were smaller than in the Caucasian subgroup. These differences were statistically significant in the febuxostat 80 mg and 120 mg groups, but not in the 240 mg group. The response rate in the Asian and 'other' subgroups was generally similar to that seen in the Caucasian subgroup. It is difficult to draw a correct conclusion on real differences regarding febuxostat efficacy in gout patients in different ethnic groups due to the small number of patients in the non-Caucasian subgroups.

- Pharmacokinetic interaction studies

An *in vitro* study in human microsomes investigated the potential of febuxostat to inhibit the metabolic activities of cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Febuxostat was found to be a competitive inhibitor of the CYP2D6 catalyzed O-demethylation of dextrometorphan ($K_i$ = 40 µM, 12.6 µg/ml). This $K_i$ value is about 2-fold greater than the Cmax for total febuxostat (5.3 µg/ml) and more than 100-fold greater than the free (unbound) concentration of febuxostat at the clinically recommended maximal dose of 120 mg/d (study TMX-99-001). For all other isoenzymes the $K_i$ values were >100 µM. Considering the low free drug concentration of febuxostat at the recommended maximal daily dose of 120 mg it is agreed that the interaction with concomitantly administered drugs via a metabolic inhibition mechanism is low/unlikely.

Eight *in vivo* drug-drug interaction studies were performed. These studies investigated the possible influence of colchicine, naproxen, indomethacin, desipramine, antacid, hydrochlorothiazide or warfarin on the pharmacokinetics of febuxostat and the possible effect of febuxostat on the pharmacokinetics of colchicine, naproxen, indomethacin or warfarin. The concomitant application of the above drugs in the treatment of gout with febuxostat does not require any dose adjustments for either febuxostat or the investigated drugs.

A significant drug-drug interaction was observed with the combination febuxostat (80 mg QD, 7 days) and naproxen (500 mg BID, 7 days). Co-administration of naproxen increased the febuxostat $C_{max}$ , $AUC_t$, $AUC_{24}$, and $t_{1/2}$ by approximately 28%, 41%, 41%, and 26%, respectively, in comparison with febuxostat alone and the mean oral clearance (Cl/F) decreased by 28%. This was suggested to be due to inhibition of glucuronidation. This increase in plasma exposure to febuxostat is not expected to raise any safety concerns, and no dose adjustment for febuxostat is required.
Co-administration of an antacid with febuxostat decreased Cmax, but not AUC. The decrease in Cmax is not likely to be clinically important because the effect on total exposure to febuxostat was not affected, since a correlation between total febuxostat AUC and sUA has been shown.

The investigation with desipramine suggested that febuxostat is a slight inhibitor of CYP2D6.

Interaction between febuxostat and fibrate has been described in the population PK.

The *in vitro* study on febuxostat effects on cytochrome P450 did not include isoenzyme CYP2C8, which may be involved in febuxostat metabolism, nor CYP2B6. There is also no *in vitro* study to evaluate whether febuxostat is a Pgp inhibitor.

The Applicant has committed to perform a post-marketing study for the evaluation of the in vitro inhibitory potential for CYP2C8 and for CYP2B, as requested by the CHMP.

- Pharmacokinetics using human biomaterials

Human biomaterials were used in *in vitro* studies (including plasma, liver microsomes, expressed cytochrome P450 [CYP] enzymes, and CaCo-2 cells) to characterize the metabolism, permeability, and potential enzyme inhibition profile of febuxostat.

**Pharmacodynamics**

- Mechanism of action

Febuxostat is a potent inhibitor of xanthine oxidase (XO). Febuxostat binds very tightly to both the active and the inactive desulfo-form of the enzyme. The crystal structure of the active sulfo-form of milk XO complexed with febuxostat and determined at 2.8-A resolution revealed the inhibitor molecule bound in a long, narrow channel leading to the molybdenum-pterin active site of the enzyme. It filled up most of the channel and the immediate environment of the cofactor. Inhibition of the activity of the enzyme occurs through the prevention of substrate binding. Although the inhibitor did not directly coordinate to the molybdenum ion, numerous hydrogen bonds as well as hydrophobic interactions with the protein matrix were observed (Okamoto et al., 2003). This is in contrast to allopurinol (oxipurinol), which binds to the molybdenum-pterin active site of the enzyme. Furthermore, febuxostat is not oxidized by the XO, whilst allopurinol is oxidized to oxipurinol, which coordinates tightly to the pterin-bound molybdenium ion and prevents catalysis (Massey et al., 1993; Okamoto et bal, 2003). Thus the mechanism of XO inhibition by febuxostat and allopurinol is different.

- Primary and Secondary pharmacology

The primary pharmacodynamic effect of febuxostat in healthy volunteers has been investigated in several Phase I studies: Cxx-023, TMX-xx-001 (Becker et al., 2004), TMX-xx- 008 (Mayer et al., 2005), TMX-xx-012 (, Khosravan et al., 2006) and TMX-xx-016 (Khosravan et al., 2005).
TMX-xx-001 is a placebo-controlled dose-escalation Phase I study (dose range: 10-240 mg QD over 14 days), all other studies are open-label studies. Study Cxx-023 investigated 300 mg QD over 7 days, TMX-01-008, TMX-01-012, TMX-xx-016 investigated 80 mg QD over 7 days. The results clearly demonstrate the primary pharmacodynamic effects of febuxostat in healthy volunteers. The primary pharmacodynamic effect of orally administered febuxostat was also shown in a Phase II placebo-

controlled dose-finding study in patients with hyperuricaemia/gout (TMX-00-004; Becker et al., 2005).
In the well planned and well performed Phase I dose escalation study TMX-xx-001 the oral application of febuxostat (10 mg to 240 mg QD over 14 days) to healthy volunteers resulted in a dose-dependent decreased uric acid and increased xanthine concentrations in both serum and urine and a decrease in the total daily urinary excretion and urinary uric acid concentration and a substantial increase in total daily urinary excretion, urinary concentration, and renal clearance of xanthine. Serum concentrations of hypoxanthine remained unchanged, but the urinary concentration and total daily urinary excretion and renal clearance of hypoxanthine were increased.
The percent change in the 24-hour mean serum urate versus plasma febuxostat AUC24 data appeared to follow a baseline $E_{max}$ model. The estimated average maximum percent decrease in serum urate following multiple dosing with febuxostat up to 240 mg QD at Day 14 was predicted 81.4 ± 2.4%. It was estimated that a febuxostat AUC24 of 3.306 ± 0.389 µg.h/ml (achieved over the dose range of 30-40 mg QD) would result in a percent decrease of serum urate of approximately 40% (about half of the maximum predicted % decrease in serum urate Cmean,24). The maximum measured decrease of sUA was 76% at 240 mg QD at day 14.
The plot of xanthine Cmean24 versus the total plasma exposure to febuxostat (AUC24) at steady state on Day 14 fitted a baseline Emax model with a correlation coefficient of 0.81. The plot of serum urate Cmean24 versus the total plasma exposure to febuxostat (AUC24) at steady state on Day 14 fitted a baseline Emax model with a correlation coefficient of 0.88. [Emax model: E = E0 + ((Emax – E0).AUC24/EAUC50 + AUC24)].

At 120 mg febuxostat QD (the recommended maximum daily therapeutic dose) and Day 14 the 24-h mean concentration of serum uric acid decreased from baseline 4.66 to 1.66 mg/dl (66%), urine uric acid decreased from baseline 29.8 to 8.1 mg/dl (73%), and the uric acid excretion $A_{e24}$ (amount excreted in urine over 24 h) was reduced by 73 %. Cmean,24 of xanthine increased markedly in serum from baseline 0.026 to 0.191 mg/dl (7.3-fold) and urine from 0.446 to 11.5 mg/dl (25-fold), serum hypoxanthine was more or less unchanged (0.135 vs. 0.141 mg/dl), but urine hypoxanthine increased from baseline 0.36 to 2.64 mg/dl and $A_{e24}$ was increased from 6.9 to 45 mg. 80 mg febuxostat was not investigated in the dose escalation study. 40 mg febuxostat QD, which was the maximal daily dose used in Japanese clinical studies, is obviously a sub-optimal dose, as clearly demonstrated in the dose-escalation study.

In study Cxx-023 following oral administration of febuxostat 300 mg QD for 7 days, the 24-hour mean serum uric acid concentrations decreased by approximately 87% (from 4.068 mg/ml to 0.577 mg/ml on Day 7), which was slightly higher than the predicted value (76%), based on the baseline Emax model which was used to fit the data from the dose-escalation study. Mean xanthine serum concentrations increased from 0.039 to 0.229 mg/dl. Serum hypoxanthine was marginally affected (increase of 4%). Urinary uric acid Cmean,24 declined by approximately 93% (from 18.131 mg/dl to 1.353 mg/dl on Day 7) and uric acid mean $A_{e24}$ decreased by approximately 93%. Urinary xanthine Cmean,24, Ae24, and Clr on Day 7 increased to 32 (10.5 mg/dl), 25, and 5 times its baseline values, respectively.

Administration of 80 mg febuxostat QD (the recommended usual daily therapeutic dose) orally over 7 days in three Phase I studies in healthy volunteers (control groups in special population studies) gave similar qualitative results as obtained in the dose-escalation study. Cmean24 serum uric acid concentration was reduced from baseline by 55% to 62%, Cmean24 urinary uric acid was reduced from baseline by 28 to 64% (28% was obtained in young subjects only, but was about 63% in subjects >65 years), serum Cmean24 of xanthine increased 3.3 to 6.1-fold and urine Cmean24 of xanthine increased 26 to 33-fold. Serum hypoxanthine was little affected, but urine hypoxanthine Cmean24 and Ae24 were increased.

In the Phase II dose-response efficacy (safety) study TMX-xx-004 febuxostat caused a dose-dependent decrease in the mean serum uric acid and a reduction in urinary urate excretion.

The 4 oxidative metabolites have been shown to be active as inhibitors of purified bovine milk xanthine oxidase in vitro, and their potency (Ki values of 0.6-2.0 nM) was similar to that of febuxostat

(Ki value of 0.6 nM). The estimated contribution of oxidative metabolites 67M-1, 67M-2 and 67M-4 to the pharmacological efficacy of febuxostat, estimated from healthy male volunteers, were about 29% (calculated from AUC values) or about 32% (calculated from Cmax values).

Secondary pharmacodynamic effects of orally applied febuxostat in healthy subjects were not investigated.

The pharmacodynamic effect of allopurinol in healthy male and female volunteers over 14 days were investigated in 30 subjects at allopurinol doses of 100 mg once daily (QD), 300 mg QD, or 300 mg twice daily (10 subjects each) over 14 days. The relative potencies of febuxostat: allopurinol, estimated from the pharmacodynamic effect (lowering serum uric acid) of febuxostat in healthy volunteers and allopurinol over 14 days, was about 5.6, which is almost two times greater than the relative potency of 3.0 estimated in chimpanzees.

**Clinical efficacy**

- Dose response study

A single dose-response study (TMX-00-004) was performed in patients with hyperuricaemia and gout (design: Phase II, multicenter, placebo-controlled, double-blind, randomized, dose-response study). Subjects received febuxostat 40 mg (n=38), 80 mg (n=37) or 120 mg (n=40) or placebo (n=38) once daily for 28 days and colchicine (0.6 mg twice daily) prophylaxis for 14 days prior to (wash out phase) and 14 days after randomization. The primary endpoint (PE) was the proportion of subjects with sUA levels <6.0 mg/dl on day 28.

The study population consisted primarily of white men (84-89% in the 4 groups) with a mean age of 52-56 years in the four groups. The baseline data in the investigated groups were comparable regarding sUA levels (the baseline mean sUA levels were 9.24-9.58 mg/dl in the three febuxostat groups and 9.87 mg/dl in the placebo group), but not regarding present tophi (16%-29% of patients in the febuxostat groups; 24% in the placebo group). The study demonstrates an apparently dose-related efficacy of febuxostat in lowering sUA concentrations in patients with hyperuricaemia and gout and significant differences vs. placebo (primary and secondary endpoints). Significant differences in the success rate between the three febuxostat treatment groups (40, 80 and 120 mg/d) have not been clearly established. Regarding the PE there was no statistical significant difference between the 40 mg and 80 mg dose groups (using the enzymatic or HPLC method), which has been partially attributed to different baseline sUA. Furthermore, the success rates (PE) between the 120 mg and 40 mg groups (judged from the HPLC method data) were not statistically significant. Regarding the secondary endpoint (percentage decrease from baseline) the group differences were statistically significant.

The primary endpoint was met by 56%, 76%, and 94% of patients at 40 mg, 80 mg and 120 mg QD febuxostat (enzymatic sUA determination); placebo had no effect. Secondary endpoints: The percent reduction in serum urate level from baseline at day 28 was -36.6%, -44.3% and -59.1% during at 40, 80 and 120 mg QD febuxostat vs. -2.1% in the placebo group (enzymatic sUA determination). The mean percent reduction from baseline to Day 28 in urine uric acid levels ranged from 43.6 to 46.5% among the febuxostat treatment groups compared to a mean percent increase from baseline of 5.9% in the placebo group. The effect of the short-term treatment on tophi was negligible and not evaluable from the small number of patients.
During colchicine prophylaxis gout flares occurred at a frequency of 9-15%. In the absence of colchicine prophylaxis the incidence of gout flares in the ITT population was similar between the placebo (37%) and febuxostat 40 mg QD (35%) treatment groups, but higher flare rates were observed at higher doses (41% at 80 mg QD, and 56% at 120 mg QD). A comparison of febuxostat treatment with or without concomitant colchicine treatment is acceptable for the Phase II study in order to demonstrate the effectiveness of a colchicine prophylaxis and/or the necessity of prophylaxis against symptoms of gout flares during treatment of gout.

PK data in study TMX-xx-004 were missing in the original application files and were requested by CHMP. As outlined by the Applicant in the response to the D120 LoQ, only trough samples were collected for plasma and urine febuxostat in study TMX-00-004, therefore it was not possible to provide Cmax and AUC for total and unbound febuxostat concentrations. Instead mean and median trough serum febuxostat values have been provided. The median trough febuxostat concentrations at steady state are linearly related to the febuxostat dose.

- Main studies

Main studies were two Phase III studies with double blind treatment for 28 weeks (APEX) or 52 weeks (FACT) in patients with hyperuricaemia/gout. Both studies were performed in North America, mainly in the United States. Patients in the APEX study were recruited at 167 sites in the United States. Patients in the FACT study were recruited at 106 study sites in the United States and 6 study sites in Canada.
Inclusion criteria were male or female subjects (but only 6% or 4% of patients were females who received 80 mg/d or 120 mg/d febuxostat, respectively) between 18 and 85 years of age, inclusive, with hyperuricaemia defined as a serum urate level of ≥8.0 mg/dl on the Day -2 Visit and a history or presence of gout. In the APEX study at least 30% of the subjects were to have a Day -2 serum urate value of ≥10.0 mg/dl (not required in the FACT study ).
The primary efficacy endpoint in both studies was a serum urate concentration of < 6 mg/dl at each of the last three monthly measurements.
Secondary endpoints in both studies were: Proportion of subjects whose serum urate levels were <6.0 mg/dl; percent reduction in serum urate levels; percent reduction in primary tophus size as determined by physical measurement in the subset of subjects with a primary palpable tophus at the Screening Visit; reduction in the total number of tophi in the subset of subjects with palpable tophi at the Screening Visit; proportion of subjects requiring treatment for a gout flare between weeks 8 and weeks 28 (APEX) or weeks 52 (FACT).

The Apex Study was a 28-week, multicenter, double blind, randomized, placebo- and active-controlled, parallel group, 5-arm Phase III study in patients with hyperuricaemia and gout.

Patient population:
1599 patients were screened and 1072 patients were randomized. The ITT/safety population included 134 patients on placebo, 267 patients on febuxostat 80 mg/day, 269 patients on 120 mg/day febuxostat, 134 patients on 240 mg/day febuxostat, and 268 patients on 300/100 mg/day allopurinol. The study population consisted primarily of white man (78%) with a mean age of 51.8 years; the number of included women was small (about 6%). The baseline data in the investigated groups were comparable.

Baseline disease characteristics:
The subjects had gout for an average of 10.9 years and 28% of subjects had tophi or a history of tophi. Urolithiasis was not reported (patients with renal calculi were excluded from the study). About 27% of patients had serum urate levels < 9 mg/dl, about 34% of patients had sUA levels between 9 and 10 mg/dl and about 40% had serum urate levels >10 mg/dl (the study protocol for the APEX study required that at least 30% of the patients had to have serum urate levels >10 mg/dl).

Outcome - primary endpoint:
The proportion of subjects whose last 3 serum urate levels were <6.0 mg/dl (357 µmol/l) (primary endpoint) was 0%, 48%, 65%, 69%, and 22% in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD groups, respectively. Both, febuxostat 80 mg
QD and febuxostat 120 mg QD were statistically superior compared to the fixed dose of allopurinol 300 mg QD [Table 1]. Subgroup analysis revealed that the proportion of patients with the last 3 serum urate levels <6 mg/dl treated with febuxostat or allopurinol was dependent on the baseline sUA concentrations: The PE was met by 66-51% at 80 mg febuxostat, 76-74% of patients at 120 mg febuxostat and 67-73% at 240 mg febuxostat at baseline sUA levels of <9 mg/dl or 9-10 mg/dl. In the allopurinol group the effect was greatest at baseline sUA levels of <9 mg/dl (37%) and considerably

lower at sUA levels of 9-10 mg/ dl (23%). The decline in efficacy was more pronounced at sUA levels of >10 mg/dl (allopurinol 10%).

**Table 1 APEX Study - Proportion of Subjects Whose Last 3 Serum Urate Levels were <6.0 mg/dL - ITT Subjects**

| Last 3 Serum Urate Levels <6 mg/dl | Placebo n/N % | Febuxostat 80 mg QD n/N % | Febuxostat 120 mg QD n/N % | Febuxostat 240 mg QD n/N % | Allopurinol 300/100 mg QD n/N % |
|---|---|---|---|---|---|
| Yes | 0/134 (0%) | 126/262 (48%) p.m.h | 175/269 (65%) p | 92/134 (69%) p.h | 60/268 (22%) p. |
| No | 134/134 (100%) | 136/262 (52%) | 94/269 (35%) | 42/134 (31%) | 208/268 (78%) |

| | Difference in Proportions | 97.5% CI (c) | P-value (d) |
|---|---|---|---|
| Febuxostat 80 mg vs. Allopurinol 300/100 mg | 26% | (16.7%, 34.7%) | <0.001 a |
| Febuxostat 120 mg vs. Allopurinol 300/100 mg | 43% | (34.0%, 51.3%) | <0.001 a |

(c) 97.5% CI = 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution

(d) P-values from CHM test stratified by baseline by renal function (serum creatinine ≤1.5 mg/dl vs. >1.5 mg/dl); p Statistically significant difference versus placebo ($p<0.05$) using Hochberg's procedure for multiple comparison for the febuxostat groups vs. placebo; a Statistically significant difference versus allopurinol 300/100 mg QD ($p<0.05$) using Hochberg's procedure for multiple comparison; m Statistically significant difference versus febuxostat 120 mg QD ($p<0.05$); h Statistically significant difference versus febuxostat 240 mg QD ($p<0.05$).

Outcome - secondary endpoints [Table 2]

The proportion of subjects whose serum urate levels were <6 mg/dl at wk 28 (febuxostat: 76% (80 mg QD), 87% (120 mg QD), 94% (240 mg QD) vs. allopurinol 41%) and at final visit (febuxostat 72% (80 mg QD), 79% (120 mg QD), 92% (240 mg QD) vs. allopurinol 39%) were statistically significantly greater in each of the febuxostat groups than in the allopurinol 300 mg QD group – and greater than in the primary endpoint. As shown for the primary endpoint, a dose-dependence was apparent with the three tested febuxostat dose levels.

Each of the febuxostat groups had statistically significantly greater percent decrease from baseline in serum urate concentrations than in the allopurinol 300 mg QD group.

Gout flares at screening were similar between treatment groups at baseline (7-10%). Gout flares during the obligatory 1-8 wk prophylaxis period were greater in the 80 mg, 120 mg and 240 mg febuxostat groups (28%, 36%, 46%, respectively) than in the 300/100 mg allopurinol group (23%) and placebo group (20%). As shown Table 2 below, this was not statistically different in febuxostat 80 mg group vs allopurinol group. In all five treatment groups there was an increase in gout flares at weeks 8-12, when the obligatory prophylaxis had been stopped and gout flare treatment was left to the discretion of the investigators (except in the 240 mg febuxostat group), but the incidence of gout flares declined in all groups at weeks 12-16 (Table 2, Fig. 2).

There were no statistically significant differences between treatment groups for the percent change from baseline in primary tophus size at the week 28 or final visits or between treatment groups for the mean change from baseline in the total number of tophi per subject (except for placebo vs. 120 mg febuxostat).

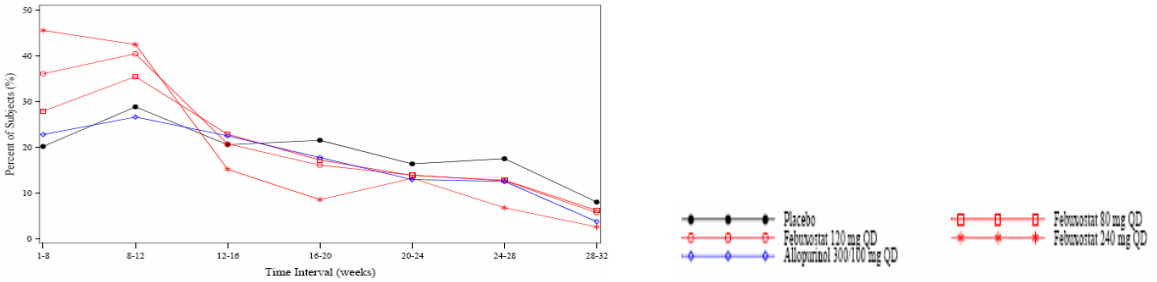
**Table 2 APEX Study – Summary of results on secondary endpoints**

| Secondary endpoints | Placebo n/N (%) | Febuxostat (80 mg/d) n/N (%) | Febuxostat (120 mg/d) n/N (%) | Febuxostat (240 mg/d) n/N (%) | Allopurinol (300/100 mg/d) n/N (%) |
|---|---|---|---|---|---|
| Proportion of pat. with sUA | | p.a.h | p.a | p.a | |

| | | | | | | |
|---|---|---|---|---|---|---|
| at wk 28 (x) | <6mg/dl | 1/99 **(1%)** | 122/161[m] **(76%)** | 163/188 **(87%)** | 78/83 **(94%)** | 85/208 **(41%)** [p.] |
| | <5mg/dl | 0/99 **(0%)** | 82/161[m] **(51%)** | 135/188 [h] **(72%)** | 72/83 **(87%)** | 28/208 **(13%)** [p.] |
| | <4mg/dl | 0/00 **(0%)** | 34/161[m] **(21%)** | 77/188 [h] **(41%)** | 65/83 **(78%)** | 5/208 **( 2%)** |
| Proportion of pat. with sUA at final visit (x) | <6mg/dl | 1/127 **(1%)** | [p.a.h] 183/253 **(72%)** | [p.a] 209/265 [h] **(79%)** | [p.a] 116/126 **(92%)** | 102/263 **(39%)** [p.] |
| | <5mg/dl | 0/127 **(1%)** | 116/253[m] **(46%)** | 171/265 [h] **(65%)** | 106/126 **(84%)** | 34/263 **(13%)** [p.] |
| | <4mg/dl | 0/127 **(1%)** | 46/253[m] **(18%)** | 100/265 [h] **(38%)** | 95/126 **(75%)** | 6/263 **( 2%)** |
| Serum urate concentration: Baseline mean±SD (mg/dl) | | 9.8 ± 1.36 | 9.96 ± 1.33 | 9.88 ± 1.22 | 9.81 ± 1.19 | 9.78 ± 1.21 |
| % change in from baseline at final visit (y) | | -2.99 ± 13.3 | -45.2 ± 18.2 [p.a.m.h.] | -51.9 ± 18.0 [p.a.h.] | -66.2 ± 20.6 [p.a.] | -33.7 ± 14.7 [p.] |
| Proportion of pat. with sUA <6 mg/dl at last visit according to baseline conc. | | | | | | |
| Baseline < 9 mg/dl | | 1/32-**(3%)** | 56/61 [p.a.] (92%) | 66/74 [p.a.] (89%) | 30/31 [p.a.] (97%) | 44/79 [p..] (56%) |
| Baseline 9 to 10 mg/dl | | 0/50 **(0%)** | 65/89 [p.a.h.] (73%) | 66/78 [p.a.] (85%) | 43/46 [p.a.] (93%) | 39/95 [p.] (41%) |
| Baseline >10 mg/dl | | 0/45**(0%)** | 62/103 [p.a.h.] (60%) | 77/113 [p.a.h] (68%) | 43/49 [p.a.] (88%) | 19/89 [p.] (21%) |
| Subjects requiring treatment for gout flares: Screening | | 12/134 **(9%)** | 21/262 **(8%)** | 28/269 **(10%)** | 13/134 **(10%)** | 20/268 **(7%)** |
| Day 1 to wk 8 (prophylaxis) | | 27/134 **(20%)** | 73/262**(28%)**[m.h] | 97/269**(36%)**[p.a.] | 61/134 **(46%)** [p.a.] | 61/268 **(23%)** |
| Wk 8-12 | | 34/118 **(29%)** | 79/223 **(35%)** | 97/240 **(40%)** | 45/106 **(42%)** | 63/237 **(27%)** |
| WK 12-16 | | 23/112 **(21%)** | 47/206 **(23%)** | 47/227 **(21%)** | 15/989 **(15%)** | 51/227 **(22%)** |
| Wk 24-28 | | 21/103 **(20%)** | 26/172 **(15%)** | 101/268 **(15%)** | 7/89 **(8%)** [p] | 31/216 **(14%)** |
| Wk 8-28 | | 62/119 (52%) | 122/223 (55%) | 129/240 (54%) | 60/106 (57%) [p.a] | 110/237 (46%) |
| Tophus size changes from baseline (median) at wk 28 | | 21 (-40.3%) | 26 (-45.6%) | 35 (-54.2.6%) | 14 (-53.2%) | 46 (-31.5%) |
| at final visit | | 26 (-52.0%) | 42 (-33.8%) | 50 (-42.4%) | 24 (-47.0%) | 61 (-22.6%) |
| No.of patients (change in no. of tophi/patient, median %) | | 22 (0) wk 28 | 28 (0) wk 28 | 38 (0) wk 28 | 16 (0) wk 28 | 47 (0) wk 28 |
| mean % | | -0.3 | -0.3 | -1.2 | -0.4 | -0.4 |

p Statistically significant difference versus placebo ($p<0.05$); a Statistically significant difference versus allopurinol 300/100 mg QD ($p<0.05$); m Statistically significant difference versus febuxostat 120 mg QD ($p<0.05$); h Statistically significant difference versus febuxostat 240 mg QD ($p<0.05$); & Based on each subject's actual prophylaxis period; denominator is the number of subjects with at least 1 prophylactic dose; (x) Comparisons between treatment groups made with a CMH test stratified by baseline renal function (serum creatinine <1.5 mg/dl vs. >1.5 mg/dl). (y) Comparisons between treatment groups were made with a two-way ANOVA with treatment and baseline renal function (serum creatinine <1.5 mg/dl vs. >1.5 mg/dl) as factors. Note: Baseline was defined as the average of serum urate measurements within the baseline window (Days -10 to 1). If a subject had more than 3 measurements within the baseline window, the last 3 measurements were used.

**Fig. 2 APEX Study - Subjects Requiring Treatment for Gout Flares**




**The FACT Study** was a 1-year, multicenter, double blind, randomized, active-controlled, parallel group, 3-arm Phase III study in patients with hyperuricaemia and gout.

Patient population/treatment:

1283 patients were screened and 762 patients (96 % male, 4% women) were randomized. The ITT/safety population included 760 patients: 256 patients on febuxostat 80 mg QD, 251 patients on 120 mg QD febuxostat and 253 patients on 300 mg QD allopurinol.
Prophylaxis against gout flares was provided during weeks 1 through week 8 with naproxen (250 mg twice daily, BID) or colchicine (0.6 mg QD) or at the beginning of the screening phase in patients, who were receiving allopurinol or uricosuric agents prior to the study.

Baseline disease characteristics:
Baseline characteristics were comparable between groups. The average number of years with gout was 11.9 years, 23-26% of patients had a history or presence of tophi and 42-45% of patients had a previous urate-lowering therapy. Baseline serum urate concentrations were similar between groups (9.80±1.24, 9.84±1.26 and 9.90±1.23 mg/dl in the 80 mg febuxostat, 120 mg febuxostat and 300 mg allopurinol group, respectively). About 27% of patients had serum urate levels <9 mg/dl, 34% of patients had a baseline urate concentration between 9-10 mg/dl and 41% of patients had a baseline urate concentration of >10 mg/dl. The number of patients with sUA levels <9 mg/dl was somewhat lower in the allopurinol group (25%) than in the febuxostat groups (27-29%).

Outcome - Primary endpoint:
The proportions of subjects whose last 3 serum urate levels were <6.0 mg/dl (primary endpoint) were **53% (**febuxostat 80 mg QD)**, 62% (**febuxostat 120 mg QD)**,** and **21% (**allopurinol 300 mg QD). The proportion was significantly higher in the febuxostat groups than in the allopurinol group (P<0.001). Both, febuxostat 80 mg QD and febuxostat 120 mg QD were statistically superior compared to the fixed 300 mg QD dose of allopurinol [Table 3].
Subgroup analysis revealed that the proportion of patients with the last 3 serum urate levels <6 mg/dl treated with febuxostat or allopurinol was dependent on the baseline sUA concentrations

**Table 3 FACT Study – Proportion of Subjects Whose Last 3 Serum Urate Levels were <6.0 mg/dL - ITT Subjects**

| **Last 3 Serum Urate Levels <6 mg/dl** | **Febuxostat 80 mg QD** | | **Febuxostat 120 mg QD** | | **Allopurinol 300 mg QD** | |
|---|---|---|---|---|---|---|
| | **n/N** | **%** | **n/N** | **%** | **n/N** | **%** |
| Yes | 136/255 | (53%) | 154/250 | (62%) | 53/251 | (21%) |
| No | 119/255 | (47%) | 96/250 | (38%) | 198/251 | (79%) |
| | Difference in Proportions | | 97.5% CI [a] | | P-value [a] | |
| Febuxostat 80 mg vs. Allopurinol | 32% | | (23.1%, 41.3%) | | <0.001 [b] | |
| Febuxostat 120 mg vs. Allopurinol | 41% | | (31.5%, 49.5%) | | <0.001 [b] | |

a 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution;
b P-values from the Fisher's exact test; & Statistical significance versus allopurinol 300 mg QD at the 0.05 level based on Hochberg's procedure for multiple comparisons

Outcome - Secondary endpoints [Table 4]
The proportion of subjects whose serum urate levels were <6 mg/dl at wk 52 (81% and 82% at febuxostat 80 mg or 120 mg QD, respectively, vs. 39% with allopurinol) and at final visit (74%, 81% vs. 36%) were statistically significantly greater in each of the febuxostat groups than in the allopurinol 300 mg QD group – and greater than in the primary endpoint. Similarly as in the PE, no dose-dependence was apparent with the two tested febuxostat dose levels.
Gout flares at baseline and during the obligatory 1-8 wk prophylaxis period were greater in the 120 mg febuxostat group than in the 80 mg febuxostat group and in the 300/100 mg allopurinol group. However, in the three treatment groups there was a marked increase in gout flares at weeks 9-12 [Fig. 3], when the obligatory prophylaxis had been stopped and prophylaxis was left to the discretion of the investigators.

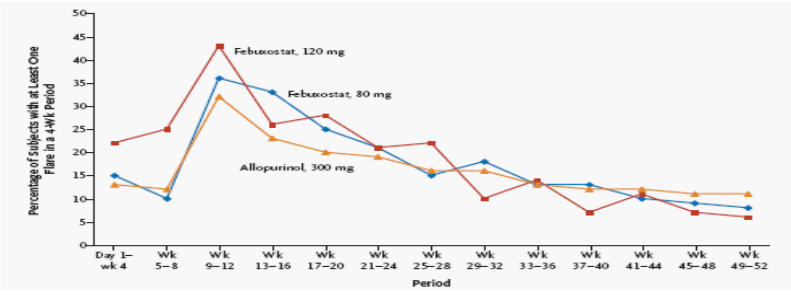
The median percentage reduction in tophus area was 83% for subjects receiving 80 mg of febuxostat, 66% for those receiving 120 mg of febuxostat, and 50% for those receiving allopurinol, but there was little/no change in the number of tophi over time in any of the treatment groups at 52 weeks.

**Table 4 FACT Study – Summary of results on secondary endpoints**

| **Secondary endpoints** | **Febuxostat (80 mg/d)** n/N (%) | **Febuxostat (120 mg/d)** n/N (%) | **Allopurinol (300 mg/d)** n/N (%) |
|---|---|---|---|
| Proportion of Patients with sUA at wk 52 | | | |
| <6mg/dl | 129/159 [a] **(81%)** | 119/145 [a] **(82%)** | 70/178 **(39%)** |
| <5mg/dl | 87/159 [a†] **(55%)** | 103/145 [a] **(71%)** | 26/178 [a] **(15%)** |
| <4mg/dl | 36/159 [a†] **(23%)** | 100/145 [a] **(45%)** | 3/178 [a] **(2%)** |
| Proportion of Patients with sUA at final visit | | | |
| <6mg/dl | 185/249 [a] **(74%)** | 193/242 [a] **(80%)** | 88/242 **(36%)** |
| <5mg/dl | 118/249 [a†] **(47%)** | 160/242 [a] **(66%)** | 31/242 [a] **(13%)** |
| <4mg/dl | 50/249 [a†] **(20%)** | 100/242 [a] **(41%)** | 4/242 [a] **(4%)** |
| Percent change in sUA concentration from baseline at final visit (Mean ± SD) Wk 28 | -46.3 ± 15.7 [a†] | -53.0 ± 18.2 [a] | -34.7 ± 12.9 |
| Wk 52 | -47.7 ± 17.5 [a†] | -53.0 ± 19.3 [a] | -34.7 ± 13.5 |
| Final visit | -44.7 ± 19.1 [a†] | -51.5 ± 19.9 [a] | -32.9 ± 15.3 |
| Proportion of pat. with sUA <6 mg/dl at last visit according to baseline conc. | | | |
| Baseline < 9 mg/dl | 58/71 (82%) [b] | 58/67 (87%) [b] | 35/61 (57%) |
| Baseline 9 to 10 mg/dl | 57/74 (77%) [b††] | 73/79 (92%) [b] | 31/78 (40%) |
| Baseline >10 mg/dl | 70/104 (67%) [b] | 62/96 (65%) [b] | 22/103 (21%) |
| Subjects requiring treatment for gout flares | | | |
| Screening | 20/255 **( 8%)** | 28/250 **(11%)** | 20/251 **(8%)** |
| Day 1-wk 8 (prophylaxis) | 55/255 **(22%)** | 90/250 **(36%)** [a] | 52/251 **(21%)** |
| WK 8-16 | 110/228 **(48%)** | 115/215 **(53%)** | 101/234 **(43%)** |
| WK 16-24 | 75/210 **(36%)** | 69/191 **(36%)** | 67/216 **(31%)** |
| Wk 49-52 | 13/167 **(8%)** | 9/153 **(6%)** | 20/185 **(11%)** |
| Wk 8-52 | 147/228 (64%) | 150/215 (70%) | 150/234 (64%) |
| Tophus changes from baseline at wk 52 | | | |
| No. of patients (median % change in area) | 32 (-83) | 26 (-66) | 30 (-50) |
| No. of patients (median % change in no. of tophi/patient) | 33 (0) | 28 (-1) | 35 (0) |

a Statistically significant difference versus allopurinol 300 mg QD ($p \leq 0.05$) using ANOVA
† Statistically significant difference versus febuxostat 120 mg QD ($p \leq 0.05$) using ANOVA
b Statistically significant difference versus allopurinol 300 mg QD ($p \leq 0.05$) using Fisher's exact test
†† Statistically significant difference versus febuxostat 120 mg QD ($p \leq 0.05$) using Fisher's exact test

**Fig. 3 Study FACT - Subjects Requiring Treatment for Gout Flares**




- Analysis performed across trials (pooled analyses and meta-analysis)

In both pivotal Phase III studies the number of patients, who discontinued prematurely, was high. The main reason was loss to follow-up.
In the APEX,study 65%, 74% and 64% of patients treated with 80, 120 or 240 mg febuxostat completed the 28-week study compared to 79% on allopurinol. Discontinuation due to gout flares in the febuxostat groups (80 mg/d: 13/267= 4.8%; 120 mg/d: 6/269=2.2%, 240 mg/d: 8/134=5.9%) was clearly greater than in the allopurinol group (1/268=0.37%). Discontinuation due to AEs was higher in the allopurinol group.
In the FACT study only 66% and 61% patients treated with 80 or 120 mg febuxostat completed the 52-week study compared to 74% on allopurinol. Discontinuation due to the incidence of gout flares was markedly higher in the 120 mg febuxostat group (11%) than in the 80 mg febuxostat group (3.8%) and the allopurinol group (3.5%). Discontinuation due to AEs/gout flare in the febuxostat groups (80 mg/d: 26/257 = 10.1%; 120 mg/d: 51/251 = 20.3%) was greater than in the allopurinol group (17/254 = 6.7%).

The proportion of subjects (ITT population) whose serum urate levels were <6 mg/dl at wk 2 and wk 52 was similar, demonstrating that a near maximum effect is reached already after 2 weeks of treatment with either febuxostat or allopurinol.

Generally, it is agreed that both pivotal studies demonstrate superiority of either daily 80 mg or 120 mg febuxostat vs. a fixed dose of 300 mg allopurinol daily regarding the primary endpoint, which is to be expected if the potency of febuxostat is greater than that of allopurinol. However, allopurinol was not up-titrated (if the primary target was not met), which would allow a better judgement on the difference in potency of febuxostat and allopurinol. The maximal recommended daily dose according to the literature is 800 mg/day [Goodman & Gilmen, 2001; Schlesinger, 2004; Wortman, 2005]. Thus, superiority of febuxostat versus allopurinol could only mean that 80 mg or 120 mg febuxostat once daily are superior versus the conventionally used daily dose of 300 mg allopurinol.

An allopurinol response rate of at least 60% was expected (Amendment 1, APEX study ) based on published studies, but not observed. The maximum response in allopurinol treated patients (primary endpoint) was 37-40%, which was achieved only in patients with baseline sUA of <9 mg/dl.

In both studies prophylaxis against acute gout with naproxen or colchicine was performed for only 8 weeks (as outlined in the study protocols), and thereafter flares of gout were treated according to the investigators judgement. However, withdrawal of prophylaxis was initially accompanied by a markedly increased incidence of gout flares in all groups (greatest in the 120 mg febuxostat group), which declined over time, indicating that the selected time period of 'intended' 8-week prophylaxis was apparently to short (see later section on prophylaxis).

Efficacy in the combined pivotal Phase III studies (sUA levels <6 mg/ml) was significantly greater in Caucasians compared to non-Caucasians (not further specified) in the 120 mg treatment groups (68% vs. 46%).

In the Phase III pivotal study CXX-010 Quality of Life (QOL) assessments resulted in statistically significantly greater improvements from baseline for the allopurinol 300 mg QD treatment group as compared to the febuxostat 80 and 120 mg QD group (most notably vs. 120 mg) at the final visit.

Clinical studies in special populations

Please refer to the pharmacokinetic evaluation in patients with hepatic or renal impairment.

- Supportive studies

**Long-term studies**
Two open-label long-term studies were conducted, which both had not been finalised at the time of CHMP opinion. Efficacy results were described in two interim analyses in each study.

**Study TMX-xx-005** was Phase 2, open-label, multicenter study designed for subjects who had completed 4 weeks of double blind dosing in study TMX-xx-004 and had not experienced any serious study-drug related adverse event. 120 subjects were planned, 116 subjects were enrolled (23 centers in the USA) and randomized to 40 mg febuxostat (n=10), 80 mg febuxostat (n=83) and 120 mg febuxostat (n=23).
The study is ongoing up to 5 years, and the results are described in two Interim analyses (at 2 and 4 years of treatment). The primary efficacy variable was the proportion of subjects whose serum urate levels decreased to or was maintained at <6.0 mg/dl. The secondary efficacy variable was the percent reduction in serum urate levels from baseline using the enzymatic determinations.

The efficacy data up to 2 years (1st Interim analysis) showed that the mean proportion of all subjects with enzymatic sUA levels <6.0 mg/dl (primary endpoint) was 78% (63/81 patients) at week 52 and 77% (54/70 patients) at week 104. The effect was greater at 80 mg (week 28-104) and at 120 mg (week 104) than at 40 mg febuxostat QD. The mean percent reduction (SD) of sUA from baseline (secondary endpoint) was -47.8% at week 52 and -47.3% at week 104 for all patients. Mean percent reduction of sUA from baseline at Week 104 was greater at 80 mg (-46.73%) and 120 mg febuxostat (-54.68%) than at 40 mg febuxostat (-38,9%). The efficacy data up to 4 years (2nd Interim analysis) showed that 84% (54/64 patients) and 90% (52/58 patients) of all subjects (combined febuxostat dose groups) had enzymatic sUA levels <6mg/dl after 3 years and 4 years on treatment, respectively. Data on the secondary endpoint were not given for years 3 and 4.
The incidence of gout flares during the first month of prophylaxis was low (9%, all patients), but increased to 45% (49/109 patients) during month >1 –3 and declined to about 14% at week 104. The incidence of gout flares in the second interim analysis was shown in 2-month intervals up to 48 month, which did not properly show the low incidence of gout flares during the first month with prophylaxis. The incidence of gout flares from month 26 to 48 ranged from 1-6% in the reported 2-month intervals.

Overall, this is the only submitted long-term study in which patients have been treated up to 3 years (64 patients) and 4 years (58 patients). The small number of patients treated with febuxostat do not sufficiently support the Applicant's overall claim that the results from study TMX-xx-005 demonstrated the ability of febuxostat to lower and maintain serum urate levels for up to 4 years.

**Study Cxx-021** was a Phase III, open-label, multicenter, randomized, allopurinol-controlled, safety extension study for subjects who had completed the febuxostat Phase III studies. The study was initially intended for 2 years, but extended to continue for up to 3 years (study ongoing).
The objective of this study was to evaluate the long-term safety of febuxostat 80 mg and febuxostat 120 mg once daily doses required to reduce serum urate levels to <6.0 mg/dl in subjects with gout, as compared to allopurinol.
1086 subjects were enrolled (in 173 centers in the United States and Canada) out of 1280 subjects who completed the 28-week study (APEX) or the 52-week study (FACT) and randomized to 80 mg febuxostat (n=649), 120 mg febuxostat (n=292) or 300/100 mg allopurinol (n=145).
64% (403/633 patients) at initial treatment allocation to 80 mg febuxostat, 60% (171/286 patients) on initial treatment allocation to 120 mg febuxostat and 62% (83/138 patients) on initial treatment allocation to allopurinol had sUA <6 mg/dL.

The primary efficacy variable was the proportion of subjects whose serum urate levels decreased to or was maintained at <6.0 mg/dl.
At 1, 12, 20 and 22 month 81% (501/620), 89% (374/420), 88% (280/320) and 86% (198/230) of patients in the 80 mg febuxostat group responded to treatment (sUA <6 mg/dl), respectively. Only 57 patients are listed at month 24 (on going study).
At 1, 12, 20 and 22 month 87% (241/277), 89% (143/167), 84% (134/159) and 93% (25/27) of patients in the 120 mg febuxostat group responded to treatment (sUA<6 mg/dl), respectively. No patients are listed at month 24. At 1, 12, 20 and 22 month 46% (64/139), 82% (36/44), 81% (22/27) and 100% (8/8) of patients in the 300/100 mg allopurinol group responded to treatment (sUA <6 mg/dl), respectively. No patients are listed at month 24.
The study design, which allowed that a subject was discontinued from the study if the serum urate remained >6.0 mg/dl after a switch in therapy, removed apparent 'non-responder'. Thus, the outcome (maintenance of sUA >6mg/dl) does not reflect a true outcome for the total study population.

The percentages of subjects on initial treatment assignment (before any switch in medication) whose serum urate levels were <6mg/dL at the time of Final Visit were 71% (455/637 patients), 80% (227/283) and 32% (45/141) in the febuxostat 80mg, febuxostat 120mg, and allopurinol 300/100 mg treatment groups, respectively. The percentages of subjects on initial treatment assignment whose serum urate levels were <6 mg/dl at the time of Final Visit was similar as observed in the pivotal studies (see Tab. 2, Tab. 4). Regarding the febuxostat effect on gout flares and tophi see below.

- Discussion on clinical efficacy

Reduction of sUA:
Main Studies: The efficacy of febuxostat in the gout population studies (PE, secondary endpoint sUA ≤ 6 mg/dl, percent change of sUA from baseline, Tab. 1-4) is sufficiently demonstrated.
Long-term extension (LTE) studies: The efficacy of febuxostat, shown in patients on initial treatment assignment, is apparently maintained up to 20 months. However, assessment of the LTE studies relies on Interim Reports. The Applicant has committed to submit the finalized study reports of the two ongoing LTE studies (TMX-01-005,Cxx-021) to the CHMP.
In all clinical febuxostat studies, a fixed allopurinol dose of 300 mg QD was used (except in the case of renal impairment, where the dose was reduced to 100mg QD) without any attempt to up-titrate allopurinol in `non-responders`.

*Gout flares:*
The medicinal product`s potency in lowering sUA levels resulted in a high frequency of gout flares during the first months of treatment leading to a high dropout rate from the pivotal studies and worsened QOL (assessed using a non-validated QOL tool).

*Prophylaxis*:
Further to CHMP comments in the D120 LoQ, the applicant considers in the response to the D120 LoQ that the prophylaxis of 8 weeks may be too short and agrees with the CHMP suggestion to recommend the duration of prophylaxis for 6 months. Recommendation of prophylaxis for 6 months has been included in the SPC.

*Dose titration*:
The Applicant proposed in the response to the D120 LoQ that febuxostat treatment is started with 80 mg/d and increased to 120 mg after 2-4 weeks if the primary goal (serum urate below 6 mg/dl) is not met. The question whether the frequency of gout flares could be reduced by starting treatment with a lower febuxostat dose (e.g. 40 mg/d) than used in the pivotal Phase III studies and the use of a slow up-titration is not sufficiently addressed. This question can probably only be answered if an appropriate dose-titration study is performed. As requested by CHMP the Applicant commits to perform a post-marketing dose-titration study to clarify whether patients would benefit from a dose-titration (starting with 40 mg febuxostat/d) and/or a slow up-titration. A reduction in the incidence of gout flares would indeed be a major benefit for patients. A preliminary study synopsis has been presented.

*Reduction of gout flares after long-term treatment:*
The reduction of gout flares is a primary treatment goal.
Main studies: In the 28-week APEX study about 15% of febuxostat treated patients required treatment for gout flares at weeks 24-28 (Tab. 2). In the 52-week FACT study 6-8% of febuxostat treated patients required treatment for gout flares at weeks 49-52 (Tab. 4).
In the Extension study Cxx-021the incidence of gout flares peaked in month 2-4 of febuxostat treatment (and was higher at 120 mg febuxostat QD than at 80 mg febuxostat QD) and declined thereafter. The incidence of gout flares in subjects on the originally assigned febuxostat doses (80 or 120 mg QD) at month >16-18, month >18-20, month >20-22 and month >22-24 was 3.0%, 2.7%, 3.0%, and 2.7%, respectively (combined data from 80 and 120 mg febuxostat).

*Tophi:*
Main Studies: The median % change in tophus area in the 28-week APEX study in the febuxostat group was not significantly different from the placebo group and somewhat greater in the febuxostat groups in the 52-week FACT study (see Table 2, Table 4). The clinical method of assessing tophi size is very unreliable, with enormous variations between assessments for the same assessor as well as between assessors. Tophi size evaluation is not considered to be a robust clinical endpoint in these phase III studies.
In the Extension study Cxx-021(approximately 20% had a tophus at entry to the pivotal study) 54% of subjects initially assigned to receive febuxostat 80 mg or 120 mg showed complete resolution of tophi at Month 24.

In summary**,** the efficacy issues raised in the D180 LoOI (gout flares and dose titration) are resolved.

**Clinical safety**

- Patient exposure

The safety analysis for febuxostat is mainly based on the US clinical febuxostat safety data base which included data from 24 Phase I studies and 5 Phase II/III studies including 2531 patients.
The mean duration of dosing was 379.7 days. Across the Phase I, II, III studies a total of 1678 subjects were exposed to febuxostat 80 mg and 1077 were exposed to febuxostat 120 mg. The duration of dosing (median [range]) in the febuxostat 80 mg was 187 [1-1724] days and in the febuxostat 120 mg groups 201 [1.1675] days.
In the pivotal Phase III studies 1170 patients treated with febuxostat vs. 519 patients treated with allopurinol were analysed for efficacy (ITT population). The mean cumulative exposure to febuxostat and the active comparator (allopurinol) was 208 days vs 233 days, respectively.
In the LTE studies 1143 subjects received febuxostat vs. 178 patients treated with allopurinol. The mean cumulative exposure to febuxostat and the active comparator was 618 days vs. 274 days, respectively.
As outlined by the Applicant, due to lower doses (up to 40 mg), and to the fact that not only gout patients but also hyperuricemic patients were included in Japanese clinical studies available at the time of MAA submission, Japanese studies were only considered supportive for safety, and only adverse events of rash, serious adverse events and premature terminations due to adverse events have been included in the current safety evaluation.

The majority of subjects included in the Phase II and III studies were male (90-95%), Caucasian (76-87%) and 45-65 years of age (56-59%). Over half of the subjects were obese, with a BMI $\geq$30 kg/m$^2$. Approximately half of the subjects had a medical history of hypertension, approximately one third had impaired renal function (defined as calculated Clcr (creatinine clearance) <80 ml/min), and one third had hyper-lipidaemia. The overall demographics and disposition of the subset of subjects included in the LTE studies remained similar to those reported in the pivotal Phase III studies.
It was stated in the Applicant's summary of safety, that at baseline more subjects in the LTE studies in the febuxostat group had a history of CHF (n=24, 2%) compared to none in the allopurinol group, and more subjects in the febuxostat group had impaired renal function (n=29, 3%) compared to the allopurinol group (n=1, <1%).

- Adverse events

Treatment-emergent AEs
In the pivotal Phase III studies the incidence of treatment-emergent adverse events in the febuxostat 80 mg (74%) and 120 mg (72%) treatment groups was statistically significantly lower (p = 0.028 and 0.002, respectively) compared with the allopurinol 300/100 mg treatment group (80%), which was not considered clinically relevant. In the long-term studies the incidence of treatment-emergent adverse events in the febuxostat 80 mg (74%) and 120 mg (69%), was higher than in the allopurinol group (57%).

Treatment-related AEs
In the pivotal Phase III studies the overall, unadjusted incidence of treatment-related adverse events in the pivotal Phase III studies was 23%, 21%, and 19% in the febuxostat 80 mg, 120 mg, and allopurinol 300/ 100 mg treatment groups, respectively, and 29% and 23% in the febuxostat 240 mg and placebo treatment groups, respectively. No statistically significant differences were observed between the febuxostat 80 mg, 120 mg, and allopurinol 300/100 mg groups for the overall incidence of treatment-related events or for specific events. Numerically higher incidences of treatment-related diarrhoea and nausea were noted in the febuxostat 240 mg group compared with the other treatment groups. The majority of treatment-related adverse events in each treatment group were mild or moderate in severity.
The 10 most commonly reported treatment-related adverse events in pivotal Phase III studies during febuxostat treatment (regardless of dose) included: diarrhoea, headache, nausea, liver function test

abnormal, dizziness, arthralgia, dyspepsia, hepatic enzyme increased, constipation and alanine aminotransferase (ALT) increased.

In the LTE studies the overall incidence of treatment-related adverse events was higher in the 80 and 120 mg febuxostat groups (14.7%, 12.6%) than in the allopurinol group (8.4%). In all febuxostat dose groups the incidence of treatment-related AEs was lower than that reported for the pivotal Phase III studies (except liver function and renal function analyses). The overall incidence of treatment-related adverse events per 100 PY was similar across treatment groups and lower in the LTE studies compared with the pivotal Phase III studies, primarily due to the lower frequency of visits in the LTE studies.
The 10 most common treatment-related adverse events in LTE studies by preferred term during febuxostat treatment (regardless of dose) were: hepatic enzyme increased, ALT increased, liver function test abnormal, AST increased, hyperlipidaemia, blood creatinine increased, nephrolithiasis, arthritis, blood urea increased, and gamma-glutamyltransferase (GGT) increased.

- Serious adverse events/deaths/other significant events

Death: Twelve deaths (11 male, 1 female) have been reported up to February 2006 (US safety data base) during treatment with febuxostat. None of the 12 deaths was considered related to study drug by the investigator. No death was observed in the Japanese studies. No deaths were reported in the febuxostat 40 mg and 240 mg groups, the allopurinol 300/100 mg group, or the placebo treatment group.
4 deaths occurred in the pivotal Phase III FACT study: 2 in the febuxostat 80 mg treatment group (retroperitoneal haemorrhage; respiratory failure) and 2 in the febuxostat 120 mg treatment group (respiratory failure/anoxic encephalopathy; colon cancer metastatic). 8 deaths occurred in the LTE studyCxx-021: 5 in the 80 mg groups (cardiorespiratory arrest/cardiac failure/congestive respiratory failure; sepsis; colon cancer metastatic; myocardial infarction; acute myocardial infarction) and 3 in the 120 mg groups (acute myocardial infarction; myocardial infarction; retroperitoneal haemorrhage). 9 of the 12 deaths were considered to be potentially cardiovascular in nature.
The overall all-cause mortality rate per 100 PY was 0.38 in the febuxostat total group and 0 in the allopurinol group. The exposure was different (febuxostat: 2605 PY vs. allopurinol 467 PY). The upper limits of the 95% CIs for death rate were similar in the febuxostat total (0.751) and allopurinol (0.770) groups.
There was one additional death due to myocardial infarction in study Cxx-021after the cut-off date February 2006 (on 80 mg febuxostat).

Other serious SAEs
The incidence of treatment-emergent SAE in the pivotal Phase III studies presented by MedDRA was 5% in the total febuxostat groups, 5% in the allopurinol group vs.1% in the placebo group. Cardiac disorders SAEs events occurred at an incidence of >1% (including cardiac failure, myocardial infarction atrial fibrillation, chest pain). Only one SAE (one case of renal impairment) was judged as treatment-related SAE in the pivotal Phase III studies. It was emphasized, that the majority of study subjects had underlying cardiovascular disease or risk factors.
The treatment-emergent incidence of SAE in the LTE studies was 10.5 % in the total febuxostat group vs. 7.5% in the allopurinol group. The incidence of SAE in the LTE studies presented by MedDRA HLT (high level terms) showed cardiac disorders as serious adverse events occurring at an incidence of >1%. The incidence of Coronary Artery Disorders NEC was 1% in the total febuxostat group vs. 0.6% in the allopurinol group. The incidence of Ischemic Coronary Artery Disorders was 1.5% in the total febuxostat group vs. 0.6% in the allopurinol group. A further analysis of cardiovascular AEs is presented below according to APTC (Antiplatelet Trialists Collaboration) criteria.
In both the pivotal Phase III and the LTE studies, the incidence of serious adverse events in subjects receiving treatment with febuxostat was 11.6 and 9.5 per 100 PY for the febuxostat total groups in the pivotal Phase III and LTE studies, respectively, and similar to the allopurinol group (8.1 and 11.3 per 100 PY in the pivotal Phase III and LTE studies, respectively.

***AEs by organ system and AEs of special interest***

Cardiovascular AEs:

The Applicant presented an analysis of cardiovascular AEs according to the APTC (Antiplatelet Trialists Collaboration) classification as primary APTC events (CV death, non-fatal myocardial infarction, non-fatal stroke, non-fatal cardiac arrest) and secondary APTC events (angina, revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic events, non-fatal congestive heart failure) for both the pivotal Phase III studies and the LTE studies. The data were presented as incidence rates plus 95% CI and per 100 patients years (PY) to account for the differences in exposure. For the open-label LTE studies safety assessment all cardiovascular safety events were reviewed and adjudicated in a blinded manner by an external Cardiologist.

In the pivotal Phase III studies the incidence of primary overall APTC events (combined incidence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, non-fatal cardiac arrest) were numerically higher in the febuxostat 80 and 120 mg groups (0.8% and 1.0%, respectively) than in the allopurinol group (0.2%), [Table 5]. Using analyses per 100 PY of exposure, the overall incidences were at least numerically higher for febuxostat 80 mg (1.3 per 100 PY) and 120 mg groups (1.6 per 100 PY) than in the allopurinol group (0.3 per 100 PY), [Table 6].

**Table 5 Incidence Rates and Confidence Intervals for Subjects with Investigator-Reported Treatment- Emergent Primary APTC Events in the Pivotal Phase III APEX and FACT Studies**

| | Treatment Group, n (%) | | | | | |
|---|---|---|---|---|---|---|
| | Placebo | Febuxostat | | | | Allopurinol |
| Primary APTC Events | (N=134) | Total (N=1177) | 80 mg QD (N=523) | 120 mg QD (N=520) | 240 mg QD (N=134) | 300/100 mg QD (N=521) |
| Overall | 0 | 9 (0.8) | 4 (0.8) | 5 (1.0) | 0 | 1 (0.2) |
| 95% CI[a] | (0.00-2.71) | (0.35-1.45) | (0.21-1.95) | (0.31-2.23) | (0.00-2.71) | (0.005-1.07) |
| CV death | 0 | 3 (0.3) | 2 (0.4) | 1 (0.2) | 0 | 0 |
| 95% CI[a] | (0.00-2.71) | (0.053-0.74) | (0.046-1.37) | (0.005-1.07) | (0.00-2.71) | (0.00-0.706) |
| Non-fatal myocardial infarction | 0 | 5 (0.4) | 2 (0.4) | 3 (0.6) | 0 | 1 (0.2) |
| 95% CI[a] | (0.00-2.71) | (0.14-0.99) | (0.046-1.37) | (0.119-1.68) | (0.00-2.71) | (0.005-1.065) |
| Non-fatal stroke | 0 | 1 (0.08) | 0 | 1 (0.2) | 0 | 0 |
| 95% CI[a] | (0.00-2.71) | (0.002-0.47) | (0.00-0.70) | (0.005-1.07) | (0.00-2.71) | (0.00-0.706) |
| Non-fatal cardiac arrest | 0 | 1 (0.08) | 0 | 1 (0.2) | 0 | 0 |
| 95% CI[a] | (0.00-2.71) | (0.002-0.47) | (0.00-0.70) | (0.005-1.07) | (0.00-2.71) | (0.00-0.706) |

Note: Subjects with one or more adverse events within a APTC criterion are counted only once in that criterion.

**Table 6 Subjects with Primary APTC Adverse events (investigator Reported) by APTC Criterion by 100 Patient-Years ofExposure in pivotal Phase III APEX and FACT Studies**

| Primary APTC Events | Placebo (n=134) PY - 59.9 | Febuxostat total (N=1177) PY – 671.1 | Febuxostat 80 mg (N=523) PY – 322.6 | Febuxostat 120 mg (N=520) PY – 304.5 | Febuxostat 240mg (N=134) PY – 54.0 | Allopurinol (300/100 mg) (N=521) PY – 333.7 |
|---|---|---|---|---|---|---|
| | | n (RPY) | n (RPY) | n (RPY) | n (RPY) | n (RPY) |
| Overall | 0 | 9 (1.30) | 4 (1.30) | 5 (1.6) | 0 | 1 (0.3) |
| Cardiovascular death | 0 | 3 (0.4) | 2 (0.6) | 1 (0.30) | 0 | 0 |
| Non-fatal myocardial infarction | 0 | 5 (0.7) | 2 (0.6) | 3 (1) | 0 | 1 (0.3) |
| Non-fatal stroke | 0 | 1 (0.1) | 0 | 1 (0.1) | 0 | 0 |
| Non-fatal cardiac arrest | 0 | 1 (0.1) | 0 | 1 (0.3) | 0 | 0 |

Abbreviations: The percentages are the rate per 100 patient-years of exposure; N, number of patients dosed; PY, total patient-year of exposure.

In the LTE studies the incidence of primary overall APTC (combined incidence of cardiovascular death, non-fatal myocardial infarction and stroke) events were numerically higher in the febuxostat 80 and 120 mg groups (2.2% and 1.7%, respectively) or 2.62% all febuxostat doses than in the allopurinol group (0.56%) [Table 7]. Using analyses per 100 PY of exposure, the overall incidences were numerically higher for febuxostat 80 mg (1.4 per 100 PY) and 120 mg (1.3 per 100 PY) group or 1.4 per 100 PY for all febuxostat groups than in the allopurinol group (0.7 per 100 PY), [Table 8].

**Table 7 Incidence Rates and Confidence Intervals for Subjects with Investigator-Reported Treatment-Emergent Primary APTC Events in the LTE Studies (to 8 February 2006)**

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | Febuxostat | | | | Allopurinol |
| Primary APTC Events | Total (N=1143) | 40 mg QD (N=12) | 80 mg QD (N=910) | 120 mg QD (N=522) | 300/100 mg QD (N=178) |
| Overall | 30 | 1 | 20 | 9 | 1 |
| Rate % | 2.62 | 8.3 | 2.2 | 1.72 | 0.56 |
| 95% CI[a] | (1.78-3.73) | (0.211-38.5) | (1.35-3.37) | (0.791-3.25) | (0.014-3.09) |
| CV death | 6 | 0 | 3 | 3 | 0 |
| Rate % | 0.52 | 0 | 0.33 | 0.57 | 0 |
| 95% CI[a] | (0.193-1.14) | (0-26.5) | (0.068-0.96) | (0.119-1.67) | (0-2.05) |
| Non-fatal myocardial infarction | 15 | 0 | 12 | 3 | 1 |
| Rate % | 1.31 | 0 | 1.32 | 0.57 | 0.56 |
| 95% CI[a] | (0.736-2.15) | (0-26.5) | (0.683-2.92) | (0.119-1.67) | (0.014-3.09) |
| Non-fatal stroke | 9 | 1 | 5 | 3 | 0 |
| Rate % | 0.79 | 8.3 | 0.55 | 0.57 | 0 |
| 95% CI[a] | (0.361-1.49) | (0.211-38.5) | (0.179-1.28) | (0.119-1.67) | (0-2.05) |

Studies included: C02-021 and TMX-01-005.
a 95% CI were calculated based on binomial distribution.

**Table 8 Incidence Rates and Confidence Intervals for Subjects with Investigator-Reported Treatment-Emergent Primary APTC Events per 100 Patient-Years in the LTE Studies (to 8 February 2006)**

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | Febuxostat | | | | Allopurinol |
| Primary APTC Events | Total N=1143 PY=2120.7 n (RPY) | 40 mg QD N=12 PY=34.6 n (RPY) | 80 mg QD N=910 PY=1384.5 n (RPY) | 120 mg QD N=522 PY=701.7 n (RPY) | 300/100 mg QD N=178 PY=145.4 n (RPY) |
| Overall | 30 (1.4) | 1 (2.9) | 20 (1.4) | 9 (1.3) | 1 (0.7) |
| 95% CI[a] | (0.95-2.02) | (0.07-16.11) | (0.88-2.23) | (0.59-2.44) | (0.02-3.83) |
| CV death | 6 (0.3) | 0 | 3 (0.2) | 3 (0.4) | 0 |
| 95% CI[a] | (0.104-0.62) | (0-10.67) | (0.05-0.63) | (0.09-1.25) | (0-2.54) |
| Non-fatal myocardial infarction | 15 (0.7) | 0 | 12 (0.9) | 3 (0.4) | 1 (0.7) |
| 95% CI[a] | (0.40-1.17) | (0-10.67) | (0.45-1.51) | (0.09-1.25) | (0.02-3.83) |
| Non-fatal stroke | 9 (0.4) | 1 (2.9) | 5 (0.4) | 3 (0.4) | 0 |
| 95% CI[a] | (0.19-0.81) | (0.07-16.11) | (0.12-0.84) | (0.09-1.25) | (0-2.54) |

N = number of subjects dosed; PY = patient year; RPY = rate per 100 patient-years of exposure; APTC = Antiplatelet Trialists' Collaboration.
Studies included: Cxx-021and TMX-01-005.

In the pivotal Phase III studies the incidence of primary and secondary overall APTC events were numerically higher in the febuxostat 80 and 120 mg groups (2.5% and 2.1%, respectively) than in the allopurinol group (1.3%). Using analyses per 100 PY of exposure, the overall incidences were numerically higher for febuxostat 80 mg and 120 mg groups (3.2 and 3.6 per 100 PY, respectively) than in the allopurinol group (2.1 per 100 PY).
In the LTE studies the incidence of primary and secondary overall APTC events were numerically higher in the febuxostat 80 and 120 mg groups (4.07% and 4.02%, respectively) than in the allopurinol group (2.25%) Using analyses per 100 PY of exposure, the overall incidences per 100 PY were similar for febuxostat 80 mg (2.9), 120 mg groups (3.3) and allopurinol (3.0).

In the response to the major objection of the CHMP D120 LoQ the Applicant concluded that the increased incidence of primary APTC events seen in the febuxostat groups compared to allopurinol in the Phase III studies (0.8% vs. 0.2%; 1.3 vs. 0.3 events per 100 PY) and LTE studies (2.62% vs. 0.56%; 1.4 vs. 0.7 events) is most likely due to chance. This statement was based on the following arguments: APTC events in the pivotal Phase III studies and LTE revealed no statistically significant difference between treatment groups. Kaplan-Meier plots showed no significant differences between the treatment groups. A meta-regression analysis of literature data on major cardiovascular events in 6 pooled studies was 1.26 per 100 PYs (99% CI, 1.15-1.37) vs. 1.26 per 100 PYs (95% CI, 0.51-2.02) for febuxostat. The adjusted total mortality rate of 10 pooled studies was 1.59 per 100 PYs (95% CI, 1.37-1.82), vs. 1.51 per 100 PYs for febuxostat (95% CI, 1.09-1.92). In the new updated analysis of the LTE studies (up to 02.2007) 2 additional events (1 myocardial infarction in the febuxostat group and 1 in the allopurinol group) were included in the analysis (primary APTC events 2.71% vs. 1.12%; 1.20 vs. 1.19 events per 100 PYs).

Although the incidence of primary APCT events in the 2 pivotal Phase III studies (APEX, FACT) in the febuxostat group was not significantly different from those observed with the comparator

allopurinol, the incidence of these serious AEs was numerically greater in the febuxostat group than in the allopurinol group. The incidence of primary APCT events in the LTE studies was numerically greater in the febuxostat group (2.7%) than in the allopurinol group (1.12%), but the incidence was about equal when calculated per 100 PY (e.g. including the different exposure to the drugs).

Risk factors for cardiovascular AEs were analysed, as requested. Risk factors with a significant association with APTC events were: medical history of atherosclerotic disease, medical history of myocardial infarction, baseline congestive heart failure, age >60 at baseline (Fishers exact test: p=0.001 for all 4 groups). A significant association was not found for hypertension, stroke, diabetes and hyperlipidaemia (Fishers exact test: p between 0.066 to 0.081*)*.

To account for this fact a warning has been included (section 4.4) as suggested by CHMP**,** and information has been added to section 4.8 (undesirable effects) in the SPC. A commitment to perform a postmarketing study for monitoring cardiovascular side effects is essential. The Applicant has provided a preliminary study synopsis in the response to the D180 LoOI. The study synopsis has been included in the Risk management plan.

Hypertension:
The incidence of hypertension-type treatment-emergent and treatment-related adverse events was low in both the pivotal Phase III and LTE studies and no clinically meaningful differences between treatment groups were observed.

Renal AEs
Pivotal studies: Mild renal insufficiency (defined as calculated Clcr <80 mL/min) was noted in 34-38% of subjects across treatment groups in the pivotal Phase III studies at baseline (45 placebo; 180 allopurinol and 418 febuxostat and 2-5% of subjects across treatment groups had moderate renal insufficiency (serum creatinine >1.5 mg/dl; exclusion criteria in the APEX study). There were a small number of reports of renal failure and individual cases with glomerulopathy and nephrosis during the clinical development program, which were not considered as treatment related.

Oedema NEC (4% in the febuxostat groups vs. <1% in the placebo group) was the most common treatment-emergent AE (and was explained by the Applicant as likely due to the use of NSAIDs/ calcium channel blockers). A shift to high in serum creatinine was reported in the febuxostat 80 mg, 120 mg, 240 mg, allopurinol 300/100 mg, and placebo groups (8%, 12%, 11%, 12% and 13%, respectively). The shift to high for BUN in the febuxostat 80 mg, 120 mg, 240 mg and allopurinol 300/100 mg groups was 19%, 19%, 24% and 17%, respectively compared with 13% for placebo. Furthermore, a higher incidence of 'potentially concerning' BUN values was observed at 120 mg and 240 mg febuxostat than in the placebo group or allopurinol group (BUN increases >31 mg/dl was 7%, 9%, 16% in the 80, 120 and 240 mg febuxostat groups, 7% in the allopurinol and 6% in the placebo group.
The claim that the increase in the incidences of high BUN in the pivotal phase III studies was partly due to NSAIDs/COX-2 inhibitors used for the treatment of gout flares could not be substantiated. The claim that oedema NEC was partly due to NSAIDs/COX-2 inhibitors used for the treatment of gout flares could not be substantiated.

LTE studies: No clinically relevant differences were observed between treatment groups. A statistically significantly higher proportion of subjects in the febuxostat 80 mg group than in the allopurinol 300/100 mg group shifted at some time during treatment to high in BUN.

Renal xanthine crystal/calculi formation
Xanthine crystal urinalysis by x-ray diffraction (XRD) and Fourier Transform Infrared Spectroscopy (FTIR) were performed in 2 Phase 1 studies and 2 Phase 2 studies. Four subjects (3 febuxostat 50 mg QD and 1 febuxostat 30 mg BID) had a total of 5 urine sediment samples with indeterminate results (very small possible traces of xanthine crystals) in one of the Phase 1 study. Each of the 3 subjects in the febuxostat 50 mg QD group had reports of very small possible traces of xanthine crystals through FTIR. With new a 40 mg dose panel and a repeat of the 50 mg panel with new subjects all urine samples were negative for xanthine crystals. Urinary xanthine concentration in these 4 subjects were shown, as requested in the D180 LoOI. In two subjects, who received a single dose of 50 mg QD, the urinary xanthine concentration measured 6-12 h after dosing was rather high (14.2 mg/dL and 12.9

mg/dL). No crystals were found in the Phase II studies. No crystals were found microscopically in the urine of subjects treated with febuxostat 300 mg.
High urine xanthine Cmean,24 values were observed at 120 mg febuxostat QD (11.5 mg/dl) in the dose escalation study TMX-01-99-001.
In subjects with renal impairment the maximum urine xanthine concentrations (control 26.7 mg/dL, mild renal impairment 13.1 mg/dL, moderate renal impairment 12.1 mg/dL, severe renal impairment 9.4 mg/dL) and Cmean,24 values (with the exception of the Cmean,24 value in patients with mild renal impairment; control 5.69 mg/dL; mild renal impairment: 6.89 mg/dL) following febuxostat treatment were lower in patients with renal impairment compared to normal renal function. It appears that patients with renal impairment are not at greater risk of developing xanthine stones as a result of increased urine xanthine levels.

Overall, it is agreed that patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) may be at increased risk of xanthine precipitation. The inclusion of the revised Warning in the SPC (section 4.4) is acceptable to CHMP.

Hepatic AEs
Pivotal Phase III studies: The overall incidence of treatment-emergent hepatic adverse events was comparable in the febuxostat 80 mg, 120 mg, allopurinol 300/100 mg and febuxostat 240 mg treatment groups (7%, 5%, 6% and 5%, respectively), and numerically lower in the placebo group (2%). The incidence of abnormal liver function analyses, which was 6%, 5%, 5% and 4% in the febuxostat 80 mg, 120 mg, allopurinol 300/100 mg and febuxostat 240 mg treatment groups, respectively, and numerically lower (2%) in the placebo group. Approximately one-half of the hepatic adverse events were considered treatment-related. The overall incidence of treatment-related hepatic adverse events was 3%, 4%, 4%, 3% and <1% in the febuxostat 80 mg, 120 mg, allopurinol 300/100 mg, febuxostat 240 mg and placebo groups, respectively.
Shifts in hepatic parameters in the Phase III studies were observed in all treatment groups. The incidence of ALT ≥2×ULN was 13%, 13% and 8% in the febuxostat 80 mg, 120 mg and 240 mg groups, 10% in the allopurinol 300/100 mg group and 6% in the placebo group. With respect to ALT ≥3×ULN, the incidence was 4%, 5% and 2% in the febuxostat 80 mg, 120 mg and 240 mg groups, respectively, 2% in the allopurinol 300/100 mg group, and <1% in the placebo group. The difference between the febuxostat 120 mg and allopurinol 300/100 mg groups was statistically significant. A total of 9 subjects (<1%) in the febuxostat 40-240 mg QD group and 6 subjects (1%) in the allopurinol 300/100 mg QD group experienced an ALT ≥5xULN. Finally, 3 subjects in the febuxostat 40-240 mg QD group and 1 subject in the allopurinol 300/100 mg QD group experienced an ALT >10 x ULN. The patterns for AST increases and concurrent ALT and AST increases were comparable. Few subjects had ALT ≥2×ULN concurrently with bilirubin ≥2 mg/dl (3 patients on febuxostat, 1 patient on allopurinol) and 2 patients had ALT ≥10×ULN with bilirubin ≥2 mg/dl (febuxostat group only). Discontinuation because of abnormal liver function test (including increases in ALT, AST, blood bilirubin, hepatic enzymes and abnormal liver function test) in the pivotal Phase III studies occurred in 2% of patients in the febuxostat groups and in <1% in the allopurinol group (treatment related in 1% and <1%, respectively).
There was no apparent dose-dependence of abnormal LFT.

Reversibility: ALT and AST values spontaneously returned to within the normal range or to below baseline values in 19/57, 10/17 and 2/2 in the febuxostat, allopurinol and placebo groups, respectively. ALT and AST values spontaneously returned to <1.5 x ULN or to <1.5 x the baseline value in 35/57, 12/17 and 2/2 in the febuxostat, allopurinol and placebo groups, respectively.
The Applicant's original claim that increases in abnormal LFT was in part due to the concomitant use of NSAIDs/COX-2 inhibitors or colchicine could not be substantiated.

LTE studies: The incidences of subjects with elevated LFT in the febuxostat 80 mg and 120 mg groups were similar to or slightly higher than in the allopurinol 300/100 mg group, and no statistically significant differences were observed. The treatment-related increase in ALT, AST and γ-GTP was reported in 0.8%, 0.5% and 0.2% of patients in the 40, 80 and 120 mg febuxostat groups (total 1.5%, 17/1143 patients) vs. zero % in the allopurinol group; the percentages of treatment related abnormal liver function tests was given as 0.9% (11/1143) in the febuxostat groups and 0.6% (1/178) in the

allopurinol group. Shifts in ALT or AST in the LTE occurred by about 10-15 % of patients in the febuxostat and allopurinol groups. A drug-induced severe liver injury was not observed in the clinical febuxostat studies.

Overall, changes in liver function tests observed under treatment with febuxostat and allopurinol in the pivotal Phase III and LTE studies were similar and greater than with placebo in the Phase III studies. Regarding hepatotoxicity there appears to be no difference between febuxostat and allopurinol. On grounds of the available data, liver function test should be carried out at the initiation of therapy with febuxostat and controlled during therapy**.** An appropriate warning has been included in the SPC, as suggested by the CHMP.

Gastro-intestinal AEs
Pivotal Phase III studies: The incidence of treatment-related diarrhoea was similar in the febuxostat 80 mg QD, febuxostat 120 mg QD, allopurinol 300/100 mg QD, and placebo treatment groups (3%, 2%, 2%, and 4%, respectively) but numerically higher in the febuxostat 240 mg QD treatment group (7%). Furthermore, the incidence of treatment-related nausea was similar in the febuxostat 80 mg QD, febuxostat 120 mg QD, allopurinol 300/100 mg QD, and placebo treatment groups (2%, 1%, <1%, and <1%, respectively) but numerically higher in the febuxostat 240 mg QD treatment group (4%).

LTE studies: The overall incidence of treatment-emergent and treatment-related gastrointestinal adverse events per 100 PY in the LTE studies was similar in the febuxostat and allopurinol groups, and numerically higher in the febuxostat 240 mg treatment group. The incidence of diarrhoea (per 100 PY) was increased at febuxostat 120 mg compared with the febuxostat 80 mg and allopurinol groups.
The gastro-intestinal AEs are adequately mentioned in the SPC. The Applicant claimed that the incidence of diarrhoea, nausea, and vomiting in the pivotal Phase III studies was lower at periods without co-medication of colchicine and that diarrhoea, nausea, and vomiting are partly due to the concomitant use of colchicine. The data presented in response to the D120 LoQ support the claim that the use colchicine increased gastrointestinal AEs.

Neurological AEs
Pivotal Phase III studies: One of serious AE (hemiparesis and EEG abnormal) was considered to be treatment related. Treatment-emergent headaches in the febuxostat groups were observed by 7% of patients and treatment-related headaches by 2% of patients in the febuxostat group. Treatment-emergent dizziness in the febuxostat groups was observed by 3% of patients and treatment-related dizziness by 1% of patients in the febuxostat. The incidence of treatment-emergent or treatment related somnolence was 1% or <1%, respectively. The incidence of treatment-emergent or treatment related paraesthesias or dysaesthesias was less the 1%.

LTE extension studies: The incidence of treatment-emergent neurological AEs (febuxostat groups vs. allopurinol) were: Headache (6.6% vs. 3.4%), dizziness (2.5% vs. 1.1%), paraesthesias (2.4% vs. 1.1%), somnolence (0.3% vs. 0%).
An appropriate warning on ability to drive and use machines has been included in the SPC (section 4.7).

Thyroid AEs
The Applicant concluded that there was no clinically meaningful differences in mean change from baseline and shift analyses between groups for TSH, total T4, total T3 or FT4 in the pivotal Phase III studies and similar results were obtained in the LTE studies. The only significant change in the LTE studies was a decrease in free T4 in the febuxostat vs. allopurinol group, which was explained to be due to greater number of visits during which laboratory evaluations were performed in the febuxostat group than in the allopurinol group. Furthermore, it was stated that the proportions of subjects with potentially concerning thyroid laboratory values were low and similar across the febuxostat 80-mg QD, febuxostat 120-mg QD, and allopurinol 300/100-mg QD treatment groups.

However, 6% of patients in the febuxostat groups in the LTE studies shifted to higher TSH (vs. 3% under allopurinol), about 3.3 % shifted to lower T4 (vs. 4% with allopurinol) or lower free T4 (vs. <1% with allopurinol).

Moreover, 5% of patients in the 80 mg group, 5% of patients in the 120 mg febuxostat group and 5.8% of patients in allopurinol group had TSH values of >5.5 µIU/ml indicating subclinical hypothyroidism. 1.2% and 1.8% of patients had TSH levels >10 µIU/ml, respectively.
1.7% (15/887) in the 80 mg group and 0.8% (4/503) of patients in the 120 mg febuxostat group had T4 values of <0.8xLLN. Low free T4 (<0.8xLLN) was observed in 0.67% at 80 mg and 0.19% of patients at 120 mg daily. There were apparently only 3 patients with a high TSH concomitantly with a shift to low free T4 and 2 patients with a high TSH concomitantly with a shift to low total T4.

Reversibility: In the subgroup of patients who had a potentially concerning TSH value recorded during the studies, TSH was within normal range at the final visit for 74% of patients (42/57) and 56% patients (15/27) treated with febuxostat 80 mg and 120 mg, respectively, and 29% of allopurinol-treated patients. In the subgroup of patients who had a potentially concerning TSH value recorded during the studies and elevated TSH at baseline, TSH was within normal range at the final visit for 64% of patients (9/37) and 40% patients (21/27) treated with febuxostat 80 mg and 120 mg, respectively, and 14% of allopurinol-treated patients.

Overall, the observed increase of blood TSH in a large portion of febuxostat treated patients in the LTE-studies, indicating sub-clinical hypothyroidism, remains unexplained. A mechanism has not been elucidated and should be further investigated. The potential risk of developing a decrease in thyroid function in humans after long-term febuxostat treatment cannot be excluded.

Thyroid disorder has been added as a potential risk in the current RMP. Thyroid disorders have been added to the safety specification. A warning regarding the possible increase in blood TSH during long-term treatment with febuxostat has been included in section 4.4 of the SPC, as suggested by the CHMP.

Bleeding AE and effects of anticoagulants
Pivotal Phase III studies: 25% of febuxostat total subjects, 21% of allopurinol subjects, and 30% of placebo subjects in the pivotal Phase III studies took one or more antithrombotic medications. Warfarin was used by 7 (5%) subjects in the placebo group, 15 (3%) subjects each in the febuxostat 80-mg and 120-mg QD groups, 2 (2%) subjects in the febuxostat 240-mg QD group, and 12 (2%) subjects in the allopurinol 300/100-mg QD group. Heparin was used by 6 subjects each in the febuxostat 80 mg and 120-mg QD group and by 2 subjects in the allopurinol group.
The proportion of subjects who experienced bleeding adverse events was similar in the febuxostat groups (4.7% in all febuxostat groups) and allopurinol group (4%), but somewhat lower in the placebo group (3%). The proportion of subjects who experienced bleeding adverse events while taking anticoagulants or antithrombotic agents was similar between groups (4.0% in all febuxostat groups, 12 patients; 9.3% in the allopurinol group, 1 patient; 5% in the placebo group, 2 patients).
The proportion of subjects who experienced bleeding adverse events taking warfarin was 6.7% (1 patient) in the 80 mg febuxostat group (none at 120 mg or 240 mg febuxostat) vs. 8.3% (1 patient) in the allopurinol group and zero in the placebo group. The only serious or severe bleeding adverse event while taking an anticoagulant or antithrombotic agent occurred in one subject who was taking warfarin (retroperitoneal hemorrhage).

LTE studies: The incidence of bleeding AEs was 6% in subjects of all febuxostat groups (69/1177 subjects, 3.6 events per 100 PY) and 1.7% the allopurinol group (3/178 subjects, 2.3 events per 100 PY). Warfarin was used by 27 (3.0%) subjects on febuxostat 80 mg, 19 (3.6%) subjects on febuxostat 120 mg, and 8 (4.5%) subjects on allopurinol 300/100 mg. Two subjects (4.2 events per 100 PY) in the febuxostat 80 mg group, 1 subject (3.6 events per 100 PY) in the febuxostat 120 mg group, and no subjects in the allopurinol 300/100 mg group had at least 1 bleeding adverse event while on warfarin. No subject had a serious or severe adverse event that occurred while taking warfarin and febuxostat concomitantly.
Heparin was used by 20 (2%) subjects in the febuxostat 80 mg group, by 11 (2%) subjects in the febuxostat 120 mg group and by 3 (2%) subjects in the allopurinol group. One subject (6.8 events per 100 PY) in the febuxostat 120 mg group had bleeding adverse events while taking heparin.
A possible risk of increased bleeding in febuxostat treated patients taking concomitantly warfarin cannot be completely excluded, judged from the reported bleeding AEs. The interaction study with

warfarin did not show significant interactions between febuxostat and warfarin. Recommendation for monitoring of anticoagulation activity in patients taking warfarin or similar agents following the initiation of febuxostat therapy, as already suggested previously by the Applicant, has now been included in the SPC.

Haematological effects
Pivotal Phase III studies: The overall incidence of any specific treatment-emergent haematological adverse events similar, 3%, 3%, 2% in the febuxostat 80 mg, 120 mg, and 240 mg groups, but lower in the placebo (1%) and allopurinol 300/100 mg group (<1%), however the overall incidences of specific treatment-related haematological adverse events were similar across treatment groups (<1%). Most of the adverse events were due to abnormal laboratory values.
LTE studies: There was 1 serious adverse event of idiopathic thrombocytopenic purpura (the patient had received allopurinol 300 mg until Day 71 and then switched to febuxostat 80 mg; the patient's serum in the presence or absence of final concentrations of febuxostat ranging from 0.01 to 10µg/ml did not cause significant platelet aggravation). The most common haematologic AE among febuxostat subjects was anaemia (anaemia NEC was 1% in the total febuxostat groups vs. 0% in the allopurinol group; Statistical Tab. 3.9.8.1; 0.6 per 100 PY). During the 18 to <24 month interval, statistically significant differences were observed in shifts to high platelet count between the febuxostat 80 mg (p=0.002) or febuxostat 120 mg (p=0.026) group and the allopurinol 300/100 mg group (<1% versus 8% for both comparisons).
A close pharmacovigilance activity on haematological effects is required.

Rash
Pivotal Phase III studies: The overall incidence of treatment-emergent rash adverse events was comparable in the febuxostat 80 mg, 120 mg, allopurinol 300/100 mg, febuxostat 240 mg and placebo treatment groups (8%, 7%, 8%, 4% and 5%, respectively). Dermatitis and eczema, erythemas, papulosquamous conditions, urticarias, and rashes, eruptions, and exanthems NEC were the only specific MedDRA HLTs reported by ≥1% and by at least 2 subjects in any treatment group. About 2% in the total febuxostat treated or allopurinol treated patient were judged as treatment related. 18 subjects (1 placebo, 9 febuxostat 80 mg QD, 5 febuxostat 120 mg QD, and 3 allopurinol 300/100 mg QD) had rash adverse events requiring oral or intravenous medication for treatment. 14 patients in the febuxostat groups, 2 patients in the allopurinol group and 1 patient in the placebo group discontinued prematurely because of rash/urticaria AEs.
LTE extension studies: The overall incidence of treatment-emergent rash adverse events per 100 PY was similar between groups (febuxostat total 6.1 subjects vs. allopurinol 5.3 subjects) and the treatment-related rash adverse per 100 PY was somewhat higher in the allopurinol group (febuxostat total 1.0 subjects vs. allopurinol 2.3 subjects). The most common rash MedDRA preferred terms per 100 PY were dermatitis contact (1.6 subjects) and rash (1.0 subject) among febuxostat total subjects and rash erythematous (1.5 subjects) among allopurinol subjects.
Stevens-Johnson syndrome or toxic epidermal necrolysis have not been observed in the febuxostat clinical studies. A hypersensitivity syndrome was neither observed with allopurinol nor with febuxostat in these clinical studies.

- Laboratory findings

Laboratory findings (renal, xanthine crystals, hepatic, thyroid and haematological) have been described in the section on adverse events

- Safety in special populations

A total account for safety data in special groups, given as total number of patients in the special populations and total time of exposure, in comparison to the general study population was requested in the D120 LoQ.

Renal impairment: As outlined in the response to the D120 LoQ, safety evaluation in patients with mild renal impairment was done in 350 patients (30%) in the pivotal Phase III studies and in 326 patients (29%) in the LTE studies. Safety evaluation in patients with moderate renal impairment done in 62 patients (5%) in the pivotal Phase III studies and in 69 patients (6%) in the LTE studies. Safety evaluation in patients with severe renal impairment was performed in only 12 patients (pivotal and LTE studies). 69% in the febuxostat total group of the renally impaired subjects were exposed to febuxostat (80-240 mg daily) for at least 6 months, with 25% exposed for at least 12 months. Similar proportions were recorded for subjects without renal impairment (71% and 24% exposed for ≥6 months and ≥12 months, respectively). 288 patients (72%) in the febuxostat total group of renally impaired subjects reached a cumulative exposure to febuxostat (40-120 mg daily) of at least 18 months
The overall incidence of treatment-emergent AEs was similar for patents with and without renal insufficiency within each of the treatment groups. Statistically significant differences were found for a few of the most common treatment-emergent AEs (≥5% in any treatment group overall): joint-related signs and symptoms, nausea and vomiting, and headaches NEC. The incidence of joint-related signs and symptoms, nausea and vomiting was higher in patients with renal insufficiency treated with 80 mg or 120 mg febuxostat compared to patients without renal insufficiency.
Febuxostat may be used in patients with mild and moderate renal impairment but a close monitoring is required. The use of febuxostat in severe renal impairment cannot be recommended as the safety and efficacy of febuxostat has not been fully evaluated in these patients.

Hepatic impairment:
Febuxostat cannot be recommended for patients with moderate or severe hepatic impairment since only patients with normal liver function were included in clinical studies. Active liver disease or hepatic dysfunction (defined as ALT and AST >1.5 × ULN) were excluded from pivotal Phase III studies and LTE studies.

Gender:
The male:female ratio in pivotal studies was 17.7:1, e.g. far greater than the sex ratio presented in epidemiological studies published in the literature. The overall incidence of adverse events and study drug-related adverse events during dosing in the Phase I study was higher in females than males. In the Phase III controlled studies, the overall incidences of treatment-emergent adverse events were higher for female subjects than for male subjects for each of the treatment groups. However, only about 6.4 % female patients were included which makes statistic evaluation uncertain.
Since so few female subjects were included in the pivotal studies, the Applicant has committed to further analyse postmarketing safety data with respect to gender in coming PSURs (see FUMs).

Age:
Only a small proportion of subjects enrolled in pivotal Phase III trials and the LTE studies were elderly (>65 years), representing between 8% and 18% of subjects in each of the febuxostat and allopurinol treatment groups. Close monitoring is required. The Applicant has committed to further analyse postmarketing safety data with respect to age in coming PSURs (see FUMs).

Ethnic differences:
Ethnic differences in efficacy of febuxostat between Caucasian and non-Caucasian subjects were reported in the pivotal Phase III studies (combined data). It has to be noted that 78% of patients treated with febuxostat in the pivotal Phase III studies (APEX, FACT) were Caucasians. In the Black and Hispanic subgroups, response rates in the febuxostat groups were smaller than in the Caucasian subgroup. These differences were statistically significant in the febuxostat 80 mg and 120 mg groups, but not in the 240 mg group. The response rate in the Asian and 'other' subgroups was generally similar to that seen in the Caucasian subgroup. However, it is difficult to draw a correct conclusion on

real differences regarding febuxostat efficacy in gout patients in different ethnic groups due to the small number of patients in the non-Caucasian subgroups.

Other:
Patients with excessive uric acid metabolism due to malignancies were not studied and there is a possibility that febuxostat may precipitate xanthine after aggressive concomitant treatment with chemotherapy in cancer patients, as has been the case after intensive treatment with allopurinol + chemotherapy in some cancer patients. Regarding the risk of high blood and urine levels of xanthine, with risk of precipitation of xanthine, during febuxostat treatment of patients with malignancies causing excessive nucleic acid metabolism a warning has been included in section 4.4 of the SPC.

Febuxostat did not differ from allopurinol in terms of hypersensitivity reactions in clinical studies. There *is very limited* data on exposing patients with a history of allopurinol hypersensitivity syndrome to febuxostat.

Overall, a limited number of female patients, elderly patients, patients with hepatic impairment, and patients with moderate and severe renal impairment were included in the pivotal studies. The Applicant has committed to further closely monitor and analyse postmarketing safety data in these population groups in coming PSURs.

- Safety related to drug-drug interactions and other interactions

Warfarin, digoxin, ibuprofen, captopril, bezafibrat, verapamil or nitrendipine did not affect the protein binding of febuxostat in human plasma in *in vitro studies*. Similarly, febuxostat did not significantly affect the protein binding of warfarin or ibuprofen in human plasma. The plasma protein binding of verapamil and nitrendipine appeared to decrease with the addition of 10 µg/ml febuxostat *in vitro*, but is not expected to lead to a clinically relevant interaction *in vivo*, as an increase in free fraction will also lead to increased clearance.

Febuxostat does not significantly inhibit the CYP isoforms typically involved in drug metabolism but was shown to be a weak inhibitor of CYP2D6. A clinical drug-drug interaction study with desipramine, a CYP2D6 substrate, showed that the inhibitory effect of febuxostat was very weak. Additional studies indicated that colchicine, indomethacin, naproxen and hydrochlortiazide do not have clinically significant effects on the pharmacokinetics of febuxostat. Multiple doses of febuxostat 120 mg co-administered with stable doses of warfarin for up to 14 days did not affect the pharmacokinetis or pharmacodynamics of warfarin.

Theoretically, theofyllin, mercaptopurine and azathioprine could be impacted by inhibition of XO. No interaction studies have been performed with any of these drugs and febuxostat.

- Discontinuation due to adverse events

Most adverse events leading to premature discontinuation of study drug were considered treatment-related and had similar incidence across treatment groups. The only treatment-related MedDRA HLTs reported by >or= 1% and by at least 2 subjects in any treatment group were adverse events classified under liver function analyses in the febuxostat 120 mg group (2%) as well as diarrhoea, and nausea and vomiting symptoms in the febuxostat 240 mg group (2% each).

- Post marketing experience

No post marketing data are available, since febuxostat has not been licensed in other regions.

## 2.5 Pharmacovigilance

**Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

**Risk Management Plan**

The MAA submitted a risk management plan. An updated RMP was submitted in the response to the D180 LoOI, which complies with Guidelines on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005). Epidemiological data from USA and Europe were included, as requested.

Risks: According to the Applicant's view no risk has been identified regarding cardiac, renal, CNS or haematological AEs.

Potential risks: Cardiovascular effects, hepatic effects, neurological effects, haematological effects, rash/hypersensitivity were considered as potential risk. Renal effects and thyroid effects are included in the updated RMP, as requested.
Routine Pharmacovigilance was suggested for these areas; an additional post-marketing safety study regarding cardiovascular AEs was suggested.

Missing information:
No experience in: Children and adolescents, Subjects in whom the rate of serum urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome). Organ transplantation, severe hepatic impairment, pregnancy and lactation are included in the updated RMP, as requested.
Limited experience in: Female patients, Elderly patients, severe renal impairment, moderate hepatic impairment are included in the updated RMP, as requested.

Regarding risk management minimization activities the Applicant stated that planned risk minimisation activities include clear and comprehensive instruction to the physician, patient, and caregiver in the SmPC and package leaflet. Routine risk minimisation measures are adequate at the moment.

The additional pharmacovigilance activity to investigate cardiovascular disorders has been included in the RMP.

Table Summary of the risk management plan

| **Safety issue** | **Proposed pharmacovigilance activities** | **Proposed risk minimisation activities** |
|---|---|---|
| **Potential risks** | | |
| Cardiovascular effects | Routine pharmacovigilance<br>Postmarketing study | Routine risk minimization (SPC, Patient Information Leaflet)<br>Section 4.4 of SPC:<br>*"Cardio-vascular disorders*<br>Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended (see section 4.8)."<br><br>Section 4.8 of SPC:<br>"A numerically greater incidence of investigator-reported cardiovascular events was observed in the febuxostat total group compared to the allopurinol group in the |

| | | |
|---|---|---|
| | | pivotal Phase III (1.3 vs 0.3 events per 100 PYs) and long-term extension studies (1.4 vs 0.7 events per 100 PYs), although no statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure." |
| • Hepatic effects<br>• Thyroid effects | Routine pharmacovigilance | Routine risk minimization (SPC, Patient Information Leaflet).<br>Section 4.4 of SPC :<br><br>*"Liver disorders*<br>During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement (see section 5.1).<br><br>*Thyroid disorders*<br>Increased TSH values (>5.5 µIU/ml) were observed in patients on long-term treatment with febuxostat (5.0%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function (see section 5.1)." |
| • Renal effects<br>• Neurological effects<br>• Haematological effects<br>• Severe rash/ hypersensitivity | Routine pharmacovigilance | Routine risk minimization (SPC, Patient Information Leaflet). |
| **Missing information** | | |
| No experience in :<br>• Children and adolescents<br>• Subjects in whom the rate of serum urate formation is greatly increased (e.g.malignant disease and its treatment, Lesch-Nyhan syndrome)<br>• Organ transplantation<br>• Severe hepatic impairment<br>• Pregnancy and lactation<br>• Limited experience in :<br>• Female patients<br>• Elderly patients<br>• Severe renal | Routine pharmacovigilance | Routine risk minimization (SPC, Patient Information Leaflet). |

| | | |
|---|---|---|
| impairment<br>• Moderate hepatic impairment. | | |

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

## 2.6 Overall conclusions, risk/benefit assessment and recommendation

**Quality**
Information on development, manufacture and control of the drug substances and finished product has been presented in a satisfactory manner. The results of test carried out indicate satisfactory 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 the clinic.

**Non-clinical pharmacology and toxicology**
Non-clinical issues (pharmacokinetics) are resolved with the commitment to investigate the in vitro inhibitory potential of febuxostat for CYP2C8 and CYP2B6, and to perform a study on aerobic transformation in aquatic sediment systems (OECD 308) for febuxostat to complete the Phase II environmental fate and effect analysis.

**Efficacy**
The clinical efficacy of febuxostat in the pivotal Phase III studies APEX (40, 80, 120 or 240 mg once daily over 28 week) and FACT (80 and 120 mg once daily over 52 week) in gout patients was assessed from the decrease and maintenance of sUA below 6 mg/dl (surrogate endpoint), but a clinical endpoint has not been defined. Febuxostat efficacy in the open-label LTE studies (TMX-01-005,Cxx-021) was only shown in interim analyses.

Patients did not receive any diet counselling per protocol, and no specific programme aiming at controlling weight was recommended.

Febuxostat is more potent then the active comparator allopurinol. The main reason for the lower efficacy of allopurinol is most probably the fact that allopurinol was only applied at the conventionally used dose of 300 mg once daily. Febuxostat is about 5.6 times more potent in lowering sUA (estimated in healthy volunteers).

Febuxostat in the proposed doses provides more rapid and more pronounced mean reductions of serum urate than allopurinol 300 mg. An increased incidence of gout flares was observed after initiation of febuxostat therapy (greater for febuxostat 120 mg than for febuxostat 80 mg and allopurinol and there was a higher drop-out rate due to adverse events among the febuxostat-treated patients. which is a concern. A clarification whether the prophylaxis (or duration of prophylaxis) for gout flares was adequate and/or the febuxostat doses were too high was requested. The Applicant considered that the prophylaxis of 8 weeks may be too short and agrees with the CHMP suggestion to recommend duration of prophylaxis for 6 months and to initiate treatment with febuxostat 80 mg in every patients. It is expected that the longer prophylaxis will reduce the frequency of gout flares, but AEs by the concomitant medication might increase.
However, the question whether the frequency of gout flares could be reduced by starting treatment with a lower febuxostat dose (e.g. 40 mg/d) than used in the pivotal Phase III studies and the use of a slow up-titration has not been properly addressed. This question can probably only be answered if an appropriate dose-titration study is performed. As requested by CHMP the Applicant commits to perform a post-marketing dose-titration study to clarify whether patients would benefit from a dose-titration (starting with 40 mg febuxostat/d) and/or a slow up-titration.

In the LTE studies efficacy has been shown up to about 20 month, judged from the reduction in sUA below 6 mg/dl (surrogate endpoint). Percent reduction of sUA in patients remaining at the original treatment assignment was similar in the LTE-study Cxx-021and the pivotal Phase III studies (Last Visit values). The Applicant commits to submit the finalized study reports of the two ongoing LTE studies (TMX-xx-005,Cxx-021) to the CHMP.

From a clinical perspective it is recognised that few effective pharmacological alternatives to allopurinol treatment exist. Allopurinol treatment can be difficult to handle and sometimes cannot be used, such as in renally impaired patients or in patients experiencing rash or true hypersensivity reactions. The experience from treatment with febuxostat is very limited in these subgroups as well as in patients with raised urate levels secondary to malignancy.

Overall, the efficacy of febuxostat judged from the reduction and maintenance of sUA has been shown. Efficacy issues raised in the D180 LoOI are solved.

**Safety**

A major safety objection was raised in the primary assessment concerning the possible increased risk of cardiovascular AEs. In the pivotal Phase III studies the incidence of primary APTC events (combined incidence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, non-fatal cardiac arrest) in the febuxostat treatment groups was about 4 to 5-times higher than in the allopurinol group either calculated as percent incidence (0.8% vs. 0.2%; 1.3 vs. 0.3 events per 100 PY). Similarly, in the LTE studies the incidence of primary APTC events was 3-4 times higher in the 80/120 mg febuxostat groups than in the allopurinol group (2.62% vs. 0.56%) and about 2-times higher per 100 PY (1.4 vs. 0.7 events). In the new updated analysis of the LTE studies (up to 02.2007) submitted in the response to LoQ, 2 additional events (1 myocardial infarction in the febuxostat group and 1 in the allopurinol group) were included in the analysis (primary APTC events were 2.71% vs. 1.12%; 1.20 vs. 1.19 events per 100 PYs), thus the incidence of primary APTC events was about the same expressed in events per 100 PYs. In a meta-regression analysis of literature data, submitted in the response to the LoQ, it was reported that incidence of APTC events was similar to major cardiovascular events or to the adjusted total mortality rate in a similar population group.

Although no statistically significant difference in APTC events in the primary assessment between febuxostat and the allopurinol treated patients was observed the overall incidence of these serious AEs in the combined febuxostat groups was 0.85% (n=10) in the pivotal Phase III studies and 2.7% (n=31) in the LTE studies. The increased incidence of serious cardiovascular adverse events with febuxostat compared to allopurinol remains a concern, and CHMP are not entirely convinced that the observed incidence of primary APTC events in the pivotal Phase III studies is due to chance. Cardiovascular AEs are included in the risk management plan as potential risk.

In addition, risk factors with a significant association with APTC events in febuxostat treated patients have been identified in subgroups of patients. Risk factors with a significant association with APTC events were: medical history of atherosclerotic disease, medical history of myocardial infarction, congestive heart failure.

As part of the risk minimisation of cardiovascular AEs the Applicant has accepted the following addition of statements in the SPC (section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects) and committed to perform a post marketing comparative cardiovascular safety study with allopurinol as comparator to clarify the cardiovascular risk profile of febuxostat vs. allopurinol. The preliminary study synopsis has been submitted.
The following wording has been agreed:

SPC 4.4:
"Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended (see section 4.8)."

SPC 4.8

*"A numerically greater incidence of investigator-reported cardiovascular events was observed in the febuxostat total group compared to the allopurinol group in the pivotal Phase III (1.3 vs 0.3 events per 100 PYs) and long-term extension studies (1.4 vs 0.7 events per 100 PYs), although no statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure."*

The high percentage of abnormal LFT/liver enzymes and the high percentage of TSH increase is a concern. Mechanisms have not been identified. Liver function testing should be carried out at the initiation of therapy with febuxostat and controlled during therapy. An appropriate warning has been included in the SPC. Furthermore, a warning regarding TSH increase has been included in the SPC.

Stratification of QT intervals of the APEX sub-study according to heart rate showed that febuxostat as a hERG channel agonist does not significantly reduce the QT interval at the recommended doses of 80 and 120 mg/d.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a user consultation testing on the package leaflet for Adenuric 80 mg and 120 mg film-coated tablets. The results showed that for each question more than 90% of subjects were able to find the information and 80% or more were able to understand it. 12 of the 16 questions achieved a 100% result for both finding and understanding thus exceeding the success criteria. In conclusion, the package leaflet appears to meet the requirements set for user testing.

**Risk-benefit assessment**

The benefit risk ratio could be considered as positive with the accepted warnings in the SPC (Section VI) and provided that the Applicant commits to perform the post-authorisation follow-up measures to be reported back to the CHMP within a specified time frame.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- no additional risk minimisation activities were required beyond those included in the product information.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Adenuric in the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis) was favourable and therefore recommended the granting of the marketing authorisation.