



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Febuxostat (FBX)

Proprietary Product Name: Adenuric

Sponsor: A Menarini Australia Pty Ltd

January 2015

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

List of the most commonly used abbreviations in this AusPAR	5
I. Introduction to product submission	7
Submission details	7
Product background	7
Regulatory status	8
Product Information	8
II. Quality findings	9
Drug substance (active ingredient)	9
Drug product	9
Biopharmaceutics	9
Advisory committee considerations	11
Quality summary and conclusions	12
III. Nonclinical findings	12
Introduction	12
Pharmacology	12
Pharmacokinetics	14
Toxicology	17
Nonclinical summary	25
Conclusions and recommendation	27
IV. Clinical findings	27
Introduction	27
Pharmacokinetics	29
Pharmacodynamics	31
Dosage selection for the pivotal studies	33
Efficacy	34
Safety	37
First round benefit-risk assessment	43
First round recommendation regarding authorisation	44
Clinical questions	44
Second round evaluation of clinical data submitted in response to questions	45
Second round benefit-risk assessment	45
Second round recommendation regarding authorisation	45
V. Pharmacovigilance findings	45
Risk management plan	45
VI. Overall conclusion and risk/benefit assessment	51

Quality	51
Nonclinical	51
Clinical	52
Risk management plan	58
Risk-benefit analysis	58
Outcome	68
Attachment 1. Product Information	69
Attachment 2. Extract from the Clinical Evaluation Report	69

List of the most commonly used abbreviations in this AusPAR

Abbreviation	Meaning
ACR	American College of Rheumatology
AE	Adverse Event
ANOVA	Analysis of Variance
APTC	Antiplatelet Trialists' Collaboration
ARA	American Rheumatology Association
AUC	Area Under Curve
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence interval
CL	Clearance
C _{max}	Peak (or maximum) concentration
CrCl	Creatinine clearance
CRP	C-Reactive Protein
CS	Corticosteroids
CV	Coefficient of Variation
ECG	Electrocardiogram
FBX	Febuxostat
GAQ	Gout Assessment Questionnaire
GCP	Good Clinical Practice
Gral	Granulation Batch Size
IC ₅₀	FBX Concentration resulting in 50% decrease in serum urate
INR	International Normalised Ratio
ITT	Intention-to-Treat
LLQ	Lower Limit of Quantification

Abbreviation	Meaning
LOCF	Last Observation Carried Forward
NSAID	Non-Steroidal Anti-Inflammatory Drug
OLE	Open-Label Extension
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per Protocol Set
PY	Patient-Years
QOL	Quality-of-Life
SAE	Serious adverse event
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
TSH	Thyroid Stimulating Hormone
T _{max}	Time to peak plasma concentration
t _{1/2}	Half-life of drug elimination
UGT	Uridine diphosphate Glucuronosyltransferase
ULN	Upper Limit of Normal
ULT	Urate Lowering Therapy
URTI	Upper Respiratory Tract Infection
VAS	Visual Analogue Scale
Vd	Volume of distribution
XO	Xanthine Oxidase

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	18 June 2014
Active ingredient:	Febuxostat (FBX)
Product name:	Adenuric
Sponsor's name and address:	A Menarini Australia Pty Ltd Level 8, 67 Albert Ave Chatswood NSW 2067
Dose form:	Film-coated tablets
Strength:	80 mg
Container:	Blister packs
Pack sizes:	4, 8 or 28 tablets
Approved therapeutic use:	<i>Treatment of chronic symptomatic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation) in adults with gout.</i>
Routes of administration:	Oral (PO)
Dosage:	The recommended oral dose of Adenuric is 40 mg or 80 mg once daily with or without food. The recommended starting dose of Adenuric is 40 mg once daily. If serum uric acid (sUA) is greater than 357µmol/L (6 mg/dL) after 2-4 weeks, ADENURIC 80 mg once daily is recommended.
ARTG number:	AUST R 205556

Product background

This AusPAR describes the application by the sponsor to register the new chemical entity Febuxostat (FBX) for the

Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). Adenuric is indicated in adults.

FBX is a first in class non-purine selective inhibitor of xanthine oxidase (XO) that inhibits the formation of uric acid from xanthine and therefore decreases serum uric acid.

Hyperuricaemia is defined as a level of serum or plasma urate concentration greater than 0.42 mmol/L (7 mg/dL) which exceeds the limit of solubility of urate in extracellular fluid (6.8 mg/dL). Symptomatic hyperuricaemia involves tissue deposition of urate crystals resulting in acute gouty arthritis and the development of tophi but may also affect renal

function. Current treatments for hyperuricaemia include allopurinol (a xanthine oxidase inhibitor) and uricosuric drugs (such as probenacid and sulfinpyrazone) however a significant number of patients fail to respond or are intolerant of treatment.

There are no specific European Union (EU) guidelines adopted by the TGA relevant to this submission, besides the general guidelines:

- [pp. 121 - 125 of Rules 1998 \(3C\) - 3CC5a](#): The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions. Effective: 12 February 2002
- [pp. 127 - 132 of Rules 1998 \(3C\) - 3CC6a](#): Clinical Investigation of Medicinal Products for Long-Term Use. Effective: 12 February 2002.

Regulatory status

This is a new chemical entity for Australian regulatory purposes.

FBX was first approved in EU in 2008 with the same indication and dosage (80 to 120 mg daily) as proposed for Australia. It was approved in USA in 2009 with a different indication and lower dose (40-80 mg daily) than that proposed for Australia. It was approved in Canada in 2010 (80 mg daily only) and New Zealand in 2012 (80-120 mg daily). The doses approved vary across the countries and the approved indications also vary as indicated below:

EU

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

Adenuric is indicated in adults.

USA

Uloric is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

Uloric is not recommended for the treatment of asymptomatic hyperuricemia.

Canada

Uloric® (FBX) is indicated to lower serum uric acid levels in patients with gout.

New Zealand

Treatment of chronic hyperuricaemia in patients with gout (including a history, or presence of, tophus and/or gouty arthritis).

Adenuric® is indicated in adults.

Product Information

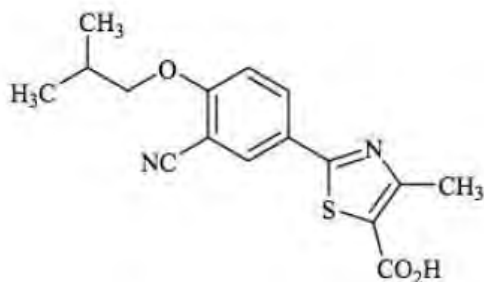
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Drug substance (active ingredient)

The drug substance, FBX, has the following structure:

Figure 1. Chemical structure of FBX.



No chiral centres are present. FBX is a 2-arylthiazole derivative.

It is a potent, non-purine, selective inhibitor of xanthine oxidase that prevents the normal oxidation of purines to uric acid.

FBX is manufactured by chemical synthesis. It is prepared as a crystalline powder and exhibits polymorphism. Only one crystalline form is reported (XRPD).

The drug substance is an acidic compound and is practically insoluble in water. Solubility is pH dependent FBX is stated to be Biopharmaceutics Classification System (BCS) class 2¹.

The drug substance specification includes tests and limits for no identified related substances. The limits for the single largest impurity are in line with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) identification threshold.

Drug product

The proposed products are immediate-release film-coated tablets. The manufacturing process involves conventional blending, wet high-shear granulation, further blending, lubrication, compression and film-coating.

With the exception of the proposed coating system, the tablet formulations are direct scales.

Excipients are conventional. Tablets are distinguished by size and debossing ('80' or '120').

Assay limits comply with TGO 78².

The stability data provided supports a shelf life of 36 months when stored below 30°C in the proposed packaging.

Biopharmaceutics

Nine biopharmaceutic studies were referenced.

Phase I study C##-054 (*Study Title: A Phase 1 Study to Assess the Effect of Food on the Pharmacokinetics of FBX Following a Single Dose with One 120 mg FBX Oral Tablet*)

¹ BCS Class II = High Permeability, Low Solubility

² Guidance on Therapeutic Goods Order No. 78 *Standard for Tablets and Capsules*

compared fed (administered with water 30 mins after a high fat meal) and fasted (administered with water) state active pharmaceutical ingredient (API) pharmacokinetics following a single 120 mg tablet dose. The study was performed using the development batch 02-077-4Q, made by Company A (not the proposed manufacturer) using 'B1 Formulation' (see formulation differences above between this and the proposed tablets). These tablets differed in relation to coating appearance and debossing text. The tablet was a green ovaloid tablet debossed with the "Company B" logo on one side and the tablet strength on the other side. The proposed market formulation in this submission is the same as the 'B1 Formulation' formulation, except for the colour of the Opadry used for the coating and a difference in tablet shape. All excipients are qualitatively and quantitatively the same.

For this study, standard acceptance limits of 80 to 125% were applied for area under the plasma concentration versus time curve (AUC) and peak plasma concentration (C_{max}) 90% confidence intervals (CIs).

The high-fat meal decreased the peak and exposures to FBX when compared with fasted conditions. For C_{max} , AUC from time 0 to T (AUC_t) and AUC from 0 to infinity (AUC_{∞}), the 90% confidence intervals for the relative bioavailability of FBX from Regimen B (one 120 mg tablet administered under non-fasting conditions) to Regimen A (one 120 mg tablet administer under fasting conditions) were not contained within the range of 80 to 125%. On average, there was a 38% decrease for C_{max} , 16% AUC_t and 16% for AUC_{∞} when administering 120 mg FBX tablet with food.

The extent of these FBX pharmacokinetic changes in exposure was consistent with those observed in two previous food effect studies (see below). In the first study, a single dose 40 mg fed versus fasted study (TMX-##-002), in which an average 46% decrease in C_{max} and a 19% decrease in AUC_{∞} were observed. In a second study, a daily dose of 80 mg for 6 days fed versus fasted study (C##-036) and an average 49% decrease for C_{max} and 18% for AUC_{24} (AUC over 24 h) were observed. In Study C##-036, it was also shown that, despite a decrease in the exposure to FBX, administering with food caused no clinically significant changes in FBX pharmacodynamics (serum uric acid).

Phase I study TMX-##-002 (*Study Title: Effects of Food on the Pharmacokinetics of TMX-67 in Healthy Subjects*) was also a single-dose food effect study for a 40 mg presentation (this tablet strength is not proposed for registration) and was summarised. This showed that the pharmacokinetics of FBX were affected by food. Administration of FBX 40 mg under non-fasting conditions decreased peak plasma concentration (C_{max}) by 46% and the AUC_{∞} by 19% compared to results obtained under fasting conditions. However, this decrease in exposure was not considered to be clinically significant. This study was conducted using the Company C tablet formulation (see above).

Phase I study C##-036 (*Study Title: A Phase 1, Multiple-Dose Study of 80 mg FBX (TMX-67) Comparing the Pharmacokinetics and Pharmacodynamics of FBX Under Fed Conditions to Those Under Fasting Conditions in Healthy Subjects*) was a steady-state food effect study for an 80 mg presentation also conducted using the B1 formulation and was summarized. This multiple dose study of 80 mg of FBX once daily for 6 days showed that administration with food lowered C_{max} by 49% and the AUC from 0 to 24 hours (AUC_{24}) by 18% but this decrease was not accompanied by a diminished pharmacodynamic effect. The difference in the percent change from baseline in serum urate 24 hour mean concentration ($C_{mean, 24}$) on Day 6 was not considered clinically significant.

Study C##-036 also investigated the effect of pharmacodynamics and it was concluded that no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose).

Phase I study TMX-##-009 (*Study Title: A Phase I Study to Evaluate the Bioavailability of TMX-67 20 mg Tablets Manufactured at Two Different Facilities, and to Assess the*

Bioavailability of TMX-67 from 80 mg Tablets Relative to 4 x 20 mg Tablets) was a comparison of the bioavailability of TMX-67 from 20 mg TMX-67 tablets manufactured at Company A relative to the 20 mg TMX-67 tablets manufactured at Company C; 2) to investigate dose proportionality of TMX-67 from 20 mg to 80 mg; and, 3) to determine the bioavailability of TMX-67 from 4 x 20 mg tablets relative to an 80 mg tablet manufactured at Company A, and was summarized.

Phase I study TMX-##-010 (*Study Title: A Phase I Study to Assess the Relative Bioavailability of Different Formulations of TMX-67 Tablets Manufactured by Company A*) was a comparison of the bioavailability of TMX-67 from 20 mg Formulation B TMX-67 tablets manufactured at Company A relative to the 20 mg TMX-67 Formulation A tablets manufactured at Abbott. Additionally, the study investigated dose proportionality of TMX-67 Formulation B from 20 mg to 80 mg and determined the bioavailability of 80 mg TMX-67 Formulation B tablets relative to 4 x 20 mg TMX-67 Formulation B tablets manufactured at Company A. This was summarised.

Phase I study TMX-##-018 (*Study Title: A Phase 1 Study to Assess the Relative Bioavailability of B1 Formulation TMX-67 Coated Tablets to Company C Tablets*) was a comparison of the bioavailability of B1 Formulation TMX-67 coated tablets to Company C TMX-67 tablets. Additionally, this study assessed the bioavailability of TMX-67 Formulation B1 4 x 20 mg coated tablets relative to 80 mg Formulation B1 coated tablets manufactured by Company A and dose proportionality from 20 mg to 80 mg. This study was summarised.

Phase I study C##-033 (*Study Title: A Phase 1 Study to Assess the Relative Bioavailability of TMX-67 from Two 40 mg Tablets to That From an 80 mg Tablet*) assessed the bioavailability of FBX (TMX-67) from two 40 mg Formulation B1 FBX tablets relative to one 80 mg Formulation B1 FBX tablet. This was summarised.

Phase I study C##-044 (*Study Title: A Phase 1 Study to Assess the Relative Bioavailability of 1 FBX 120 mg Tablet to 1 FBX 80 mg Tablet and 1 FBX 40 mg Tablet*) was a relative bioavailability study comparing one FBX Formulation B1 120 mg tablet to the combination of 1 FBX Formulation B1 80 mg tablet plus 1 FBX Formulation B1 40 mg tablet. This was summarised.

Phase I study C##-034 (*Study Title: A Phase I study to assess the relative bioavailability of TMX-67 from an 80 mg (300 L batch size) tablet to that from an 80 mg (75 L batch size) tablet*) was a comparison of bioavailability for 80 mg batches made at different scales. This was summarised. The means of FBX pharmacokinetic parameter estimates for one 80 mg (300 L batch size) FBX tablet (test) were within 94% to 119% of those parameters for one 80 mg (75 L batch size) FBX tablet (reference) and the differences between the two regimens for t_{max} , C_{max} , AUC_t , and AUC_{∞} were not statistically significant ($p > 0.05$). The 90% confidence intervals for the ratio of test and reference central values were well within the 0.80 to 1.25 range for FBX C_{max} , AUC_t and AUC_{∞} .

A formal justification for not submitting an absolute bioequivalence study and of the biostudy comparing the proposed formulation with an oral solution of the drug that is acceptable from a pharmaceutical chemistry perspective was provided.

Advisory committee considerations

This application was not submitted to the Pharmaceutical Sub Committee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

A number of issues were raised following the initial evaluation of this application but all issues have since been satisfactorily resolved. There are now no objections to registration of this product.

III. Nonclinical findings

Introduction

No substantial deficiencies were identified in the submitted data.

A number of in vitro and in vivo studies on efficacy were provided in which inhibition and selectivity against xanthine oxidoreductase was demonstrated against other enzymes involved in purine metabolism. The standard battery of studies concerning safety pharmacology on central nervous system (CNS), cardiovascular, gastrointestinal and renal systems were also provided; however, due to age (circa 1999), many of these were not Good Laboratory Practice (GLP) compliant. Pharmacokinetic studies were performed in mice, rats and dogs, as well as a single study in chimpanzees. The validation methods used to quantify plasma levels of FBX were not appended to the relevant study report to ascertain the sensitivity and appropriateness of the testing ranges. Although the validation studies were all submitted, these were not linked to the relevant study.

Pivotal toxicity studies in rats, dogs and rabbits generally adhered to the relevant guidelines, with appropriate study designs and test animal numbers used; however some studies did not provide relevant historical controls where necessary (for example, the carcinogenicity studies).

Pharmacology

Primary pharmacology

Several in vitro and in vivo studies provided confirmation that FBX inhibits xanthine oxidoreductase (XOR). For the in vitro studies XOR was sourced from bovine milk, rat or mouse liver homogenates or from human liver samples where an inhibitory action by FBX was confirmed by decreases in uric acid formation. FBX inhibited human XOR (inhibition constant (K_i): 10 nM), bovine milk XOR (K_i : 0.7 nM), mouse liver XOR (50% inhibitory concentration (IC_{50}): 1.8 nM), and rat liver XOR (IC_{50} : 2.2 nM) with only partial inhibition of aldehyde oxidase (Study NP-P1 and Osada *et al.*, 1993³), and had a slightly higher affinity for the oxidised form of XOR (XO, approximately 0.12 nM) compared to reduced form (XDH, approximately 0.9 nM)⁴ (Okamoto *et al.*, 2003). Metabolites of FBX had close to comparable inhibitory activity against XO and XDH (Study 18-P-##013) as the parent compound, with the optical stereoisomers of M1 (67M-1, hydroxylated FBX) being the most potent (K_i for bovine milk XOR: M1-R: 0.6 nM, M1-S: 0.8 nM compared to FBX 0.7 nM). Because FBX displays high plasma protein binding (>98%), inhibitory activity of FBX was partially attenuated in the presence of either bovine or human serum albumin (Study F4-##057).

Evidence of efficacy in vivo was demonstrated by a FBX-dependent reduction of plasma/serum levels of uric acid and allantoin in normal animals (mice, rats and chimpanzees), in animal models of hyperuricaemia (induced by feeding 2.5% oxonate in

³Osada *et al.*, (1993) *Eur. J. Pharmacol.* 241: 181-8

⁴Okamoto *et al.*, (2003). *J. Biol. Chem.* 278: 1848-55.

the diet) and in renal impairment (partial nephrectomised rats). FBX was 2.4 times more effective in reducing serum uric acid in rats with renal impairment than in those that were sham-operated, while allopurinol was 4 times more effective in reducing serum uric acid levels in renally impaired rats than in sham operated rats (Study 18-P-##001).

Comparative efficacy studies revealed that FBX was approximately 3 to 4 fold more potent than allopurinol in both rats and mice.³ Paralleling the decrease in plasma uric acid levels, a corresponding increase in plasma xanthine levels was reported in male SD rats, which induced renal calculi formation (Study 18-P-##008). Increases in urinary levels of xanthine were also noted in the chimpanzee; however xanthine was not detected in plasma (Study WSRC##0809) suggesting more efficient clearance of xanthine in this animal model than in rodents.

The selectivity of FBX was tested on enzymes related to purine and nucleoside metabolism because the purine analogue inhibitor allopurinol exhibits inhibitory activity against many of these enzymes. In vitro assays found no effect by FBX on the activities of guanine deaminase (GD), hypoxanthine guanine phosphoribosyl transferase (HGPRT), orotate phosphoribosyl transferase (OPRT), OMP decarboxylase (OMPDC), purine nucleoside phosphorylase (PNP), adenine deaminase, adenine phosphoribosyltransferase and guanase. Inhibition of Na-independent uridine and inosine transport by FBX was noted at a K_i of 4 μM .⁵

Secondary pharmacodynamics and safety pharmacology

FBX did not affect thrombin or time/concentration dependent platelet activation or impair the anticoagulant actions of heparin or warfarin; however it did weakly inhibit agonist induced platelet activation by adenosine diphosphate (ADP), epinephrine and arachidonic acid (Study ###05003665). Moderate anti-inflammatory effects of FBX (similar to dipyridamole) were observed in rats at 10-100 mg/kg orally (PO) as decreases in lipopolysaccharide (LPS) induced serum tumour necrosis factor (TNF)- α and increased levels of interleukin-10 (IL-10) (Study F3-##025). In a dog model of CHF, FBX restored lower levels of myocardial phosphocreatinine levels characteristic of the CHF state (Study ###04000449) while in a conscious rabbit model of CHF FBX improved ejection fractions but did not alter congestive heart failure (CHF) induced increases in end diastolic volume (EDV) (Study ##67).

Most of the submitted safety pharmacology studies were non-GLP and covered the CNS, cardiovascular, renal and gastrointestinal systems. The CNS studies did not reveal any anticonvulsant, analgesic or effects on body temperature by FBX (10 to 300 mg/kg). Decreases in locomotor activity were reported in one study, which was also a notable clinical sign in several of the repeat dose toxicity and in vivo genotoxicity studies.

In vitro FBX had no inhibitory effect on the potassium (K) hERG current, minimally inhibited whole cell cardiac sodium (I_{Na}) and calcium (I_{Ca}) currents (IC_{50} : 75 μM and approximately 733 μM , respectively), and partially shortened action potential duration (50 μM) by itself or after action potential prolongation by anemone toxin (ATX) II (late Na^+ current activation) but not sotalol (delayed rectifier activation).

In vivo studies in dog did not reveal treatment related effects on heart rate (HR), femoral blood flow, left ventricular pressure (LVP) or noted any changes in electrocardiogram (ECG) parameters. A transient reduction in blood pressure (BP) (1 to 2 h post dose) was noted in the conscious dog model (Study N0##049a), whereas no change was reported in the sodium pentobarbital anaesthetised dog model (Study 18-G-##021).

An in vivo renal systems study concerning FBX was conducted in rats where increased urinary volume, urinary K and chloride (Cl) and urinary xanthine levels at the highest

⁵Yamamoto et al., (2000). Pharmacology, 60: 34-40

tested FBX concentration were noted (100 mg/kg; Study 18-G-##030). A number of safety pharmacology studies also assessed renal function with allopurinol, presumably as a comparator to FBX. These were not evaluated because of a lack of immediate relevance but according to the nonclinical summary, FBX did not evoke noteworthy changes to renal parameters (blood urea nitrogen (BUN), creatinine and pyrimidine levels) under the tested conditions whereas allopurinol increased levels of these markers.

For gastrointestinal systems, intestinal transit time and motility were assessed either under an *in vivo* setting or from isolated intestinal tissues. FBX did not affect intestinal transport; however, there were slight reductions in amplitudes of spontaneous contractile activity.

Pharmacodynamic drug interaction studies showed that single co-administered doses of FBX (1 or 10 mg/kg) did not affect the hypotensive effects of nifedipine (Spontaneously Hypertensive rats (SHR)) or hypoglycaemic effects of glibenclamide (Sprague-Dawley (SD) rats).

Pharmacokinetics

FBX and its metabolites were quantified by validated high-performance liquid chromatography (HPLC) and Liquid Chromatography Tandem Mass Spectrometry (LC/MS-MS) methods. A table in the sponsor's Nonclinical Summary provided a rudimentary summary of the sensitivity of the detection methods used (lower limit of quantification (LLOQ) approximately 4 ng/mL for mouse, rat, dog and rabbit sera), which were deemed adequate. However, the sponsor's Nonclinical summary noted that validation methods for some studies (mouse, rat and dog plasma) were developed by Company B Pharmaceuticals in the US, whereas others were developed by Company C. (mouse, rat, rabbit and dog serum) and thus, different methods of analyses were used to interpret findings. Nevertheless, extraction procedures and chromatographic conditions were similar between the two facilities.

Absorption

Pharmacokinetic parameters were ascertained either from dedicated single or repeat-dose pharmacokinetic studies or from toxicokinetic assessments. Most studies used the clinical route (PO) but some studies included the IV route to determine bioavailability; data was collected from mice, rats and dogs. Not all studies provided the actual calculated pharmacokinetic parameters; some of the values collected in this evaluation report came from the sponsor's Nonclinical Tabulated Summaries. Time to C_{max} (T_{max}) in rodents was 0.4 to 1 h while in dogs it was later at higher doses (T_{max} : 1 to 4 h compared to clinical T_{max} : approximately 1 h; Study TMX##001). Plasma exposure (AUC) was dose proportional. There was no evidence of accumulation in any of the nonclinical repeat-dose studies. In mice, the AUC of females was about twice as high as males but this gender specific effect did not apply to rats or dogs. In contrast to Study 01-TAP.P##R3, which indicated low oral bioavailability to FBX in the rat (approximately 20%), apparent oral bioavailability (derived as $AUC_{oral}/AUC_{intravenous} \times \text{dose IV}/\text{dose PO}$) was high in rats (78%), moderate in dogs (48%) and low in mice (<20%) (Study CTB-##00-01). In humans apparent oral bioavailability was $\geq 84\%$ (Study C##-040).

Plasma levels of FBX were also influenced by food, as shown in a number of studies in the rat and dog where C_{max} and AUC values were lower in fed animals *cf.* to fasted animals. This effect was not influenced by the pH of the dose solution or composition of food (that is, fat or protein content). In the dosage and administration section of the proposed PI document it is recommended that an oral dose of Adenuric of 80 mg once daily can be given once daily with or without food on the basis that although there was a significant decrease in

C_{max} and AUC in subjects that consumed a high fat meal, this did not result in a clinically meaningful change to efficacy (that is, no significant change to % decreased serum uric acid levels).

Permeability of FBX was tested on parts of the rat gastrointestinal tract and in human epithelial cells (Caco-2 assay). In the rat study (Study 01-###.P01R3 – Part I) FBX permeability was found to be in the order: jejunum (Papp: 0.7)>ileum (Papp: 0.5)>colon (Papp: 0.06 at pH 7.4) = stomach (Papp: 0.06 at pH 7.4). A Caco-2 cell assay indicated that FBX transport across cells is unlikely to involve P-glycoprotein (Study 0##596).

Distribution

Plasma protein binding of FBX was assessed in rats and in an *in vitro* binding study using human plasma protein (albumin), in which high protein binding (>99%) was noted in both instances. Plasma protein binding was not ascertained in dogs, mice or rabbits. FBX metabolites also demonstrated high protein binding [82% (M2), 91% (M1, M4)], which was not affected by the addition of excess FBX suggesting that they bind to different regions than FBX. Mechanistic studies showed both specific ($K_d = 14 \mu\text{M}$) and non-specific binding by FBX to albumin (Study 18-K-##004). It was also determined that FBX does not bind to the same region as warfarin but instead to the diazepam site (Study 18-K-##012); however, this study did not ascertain the binding region(s) of FBX metabolites. Investigations on the extent of protein binding in special patient populations (renal and hepatic impairments; aged population; male versus female) revealed no differences from samples obtained from healthy subjects.

FBX appears to be widely distributed to most tissues and organs. Highest levels of radioactivity were seen in the gastrointestinal tract, which generally occurred by 1 h post-dose administration, followed by kidneys and urinary bladder, with lowest levels observed in the brain, eyes and muscle. The adrenals appeared to be an unusual area of radioactivity localisation (Study CTB##0001). Accumulation of FBX was not apparent since most of the radioactivity was low or almost below the level of quantification/detection by the last examined time point (168 h post-dose). There was no evidence to suggest an affinity for melanin-containing tissues (that is, eyes, skin) (Study PK-##3). Limited amounts of radiolabelled FBX were found to pass from the maternal circulation to fetal tissue (Study HTB##24), suggesting low permeability of FBX across the placenta. Radioactivity was distributed mainly in the maternal gastrointestinal tract, liver, kidney, spleen and mammary glands (of which may reflect the passage of FBX into the milk), while negligible levels were detected in fetal tissue at 8 h postdose. FBX (1 mg/kg PO, on postnatal day (PND) 14) was shown to be readily excreted through milk, peaking at 4 h postmaternal dose (at 1.56 $\mu\text{g/mL}$, which corresponds to a milk: plasma ratio of 7.9).

Metabolism

Unchanged FBX accounted for the highest proportion of reaction product in many of the *in vitro* studies. FBX metabolites *in vitro* were mostly oxidation and glucuronide conjugation products of various cytochrome P450 (CYP) and uridine 5'-diphospho-glucuronosyltransferase (UGT) isoforms: hydroxylation (M1 and M2 or 67M-1 and 67M-2, respectively), desbutylation (M3 or 67M-3), carboxylic acid reactions (M4 or 67M-4), as well as two glucuronide conjugates (G1 – glucuronide conjugate of M3 and G2 – glucuronide conjugate of unchanged FBX). The hydroxylated metabolites 67M-1, 67M-2 and 67M-3 were the major metabolites generated by male mouse, rat, dog and human liver microsomes, with trace amounts of metabolite 67M-4. However, glucuronide conjugation of FBX appears to be the major route of FBX metabolism in mice, rats, dogs and humans *in vivo*. Investigation of CYP dependent metabolism using CYP isozymes (Study 18-K-##002) indicated a minor role in FBX metabolism.

Neither FBX nor allopurinol increased activities of a host of typical liver enzymes, while phenobarbital as the positive control increased activities. Although FBX was not found to induce liver enzymes, a small and statistically significant reduction in liver weight and microsomal protein levels by an unknown effect was noted. FBX did not exhibit significant CYP inhibitory activity against the common CYP isoforms 1A2, 2C9, 2C19 and 3A4 ($K_i > 100 \mu\text{M}$), although there was weak inhibition of the O-demethylation of dextromethorphan by 2D6 (K_i approximately $40 \mu\text{M}$; Study 18-K-##005).

Excretion

Excretion of FBX was predominantly via faeces for all tested species. Excretion through faeces was highest in the dog (beagle) irrespective of whether FBX was administered by the oral or intravenous route. Similarly in rodents both mice and rats had the highest recovery of radioactivity in faeces. In the dog (Study 18K##007) unchanged FBX was detected in urine at less than 1% of the dose administered for either route, while the highest detected urinary metabolite, M1, was detected at levels of between 2.1 to 2.6% of the dose administered. Intravenous administration of FBX to chimpanzees (Study WSRC##1009) showed greater recovery in urine than faeces. Urinary excretion was also identified as a major excretion route (49% compared to 44% for faecal) in a clinical study using healthy subjects that received FBX at the recommended clinical dose and route.

Biliary excretion was examined in the mouse and rat and was found to be a significant excretion route. Biliary excretion of metabolites was examined in rats (Study 18-K-##006), where 74% of the administered dose of radioactively labelled (^{14}C)-FBX was recovered in bile. Subsequent HPLC analysis found that conjugates of unchanged FBX (glucuronide conjugate) accounted for 68% of recovered radioactivity in bile, 2.6% was unchanged FBX, and 5.8% was M2 (67M-2).

Conclusion

The FBX pharmacokinetic profiles of all tested animal species shared some similarities to humans for the proposed clinical conditions of use. Clinical rates of absorption (as T_{max}) fell within the range of rates observed in animal studies suggesting comparable onsets of action. Protein-binding properties of FBX were similar in human and rat studies (no other animal plasma protein studies were available). Metabolic profiles from mice, rats, dogs and humans are qualitatively similar between the species but quantitatively different. Unchanged FBX was the dominant moiety which was mainly eliminated through faecal route (although the proportion of urinary excretion was equal to that of faecal excretion in humans and chimpanzees). Overall, the tested animal species are adequate for assessing the toxicity profile of FBX.

Pharmacokinetic drug interactions

Dedicated studies examining the pharmacokinetic drug interaction potential of FBX were not provided. Nevertheless, FBX did not show any clinically significant inhibition of most CYP isozymes. Weak inhibition of CYP isoform 2D6 was shown under in vitro conditions, which was confirmed by a clinical drug-drug interaction study with desipramine, a CYP2D6 substrate (Study C##-005). This finding is noted in the proposed PI document.

Although FBX readily binds with albumin and shows high plasma protein binding, it binds to a different binding region to warfarin, thus FBX is unlikely to have a clinically significant interaction with warfarin. While FBX was not found to be a substrate for P-glycoprotein, there was no indication of whether it can inhibit P-gp itself.

Toxicology

Acute toxicity

Single dose oral toxicity studies were performed in rats and dogs.

In the rat, the maximum non-lethal dose was 300 mg/kg, with mortalities in the 600 mg/kg high dose (HD) group (most within the first 24 h) preceded by decreased locomotor activity, increased salivation/lacrimation and irregular respiration. Gross necropsy examinations found distended stomachs/intestinal tissue as well as granular substance in the urinary bladders of HD males.

There were no mortalities in dogs at the highest dose tested (2000 mg/kg PO). Clinical signs included decreased locomotor activity, ptosis, salivation and diarrhoea as well as vomiting in all dose groups. It is uncertain whether vomiting affected correct dosing as the study authors described the presence of capsules and other dosing material in the vomit. Toxicokinetic parameters in this study were not consistent with or proportional to plasma levels measured in dogs from other studies (for example, single dose study at 500 mg/kg = 239 µg.h/mL compared to repeat-dose study at 80 mg/kg on Day 1 = 166 µg.h/mL).

Based on these measures, FBX demonstrated a low to moderate order of acute toxicity, although the reliability of the dog findings is questionable.

Repeat-dose toxicity

Repeat-dose toxicity studies were performed in mice (4 weeks, 3 months), rats (5 weeks, 3 month preliminary carcinogenicity dose-range finding study, 6 months) and dogs (3 and 12 month pivotal study), which used the clinical route of administration (PO). All studies were GLP compliant. Pivotal studies included a 12 month dog study and a 6 month rat study. Toxicokinetic studies were performed for all toxicity studies; however, not all parameters were calculated or easily sourced in the study reports. Nonetheless, the submitted repeat-dose toxicity studies were generally consistent with ICH guideline requirements.

Relative exposure

Exposure ratios are calculated based on animal: human plasma AUC values. Human values are derived from a repeat-dose pharmacokinetic study (Study TMX##001) where the reference AUC value was obtained at the maximum recommended human dose (MRHD) of 120 mg/day on day 14 of treatment. Exposures attained across the toxicity studies ranged from less than 10 to approximately 100. Exposure ratios were quite low (<5) at the NO Observable Adverse Effect Level (NOAEL) (based on kidney toxicity) in all toxicity studies and were less than 1 in the pivotal 12 month dog study.

Table 1. Relative exposure in repeat-dose and carcinogenicity studies

Species	Study duration	Dose mg/kg/day	AUC _{0-24 h} µg·h/mL	Exposure ratio [#]	
Mouse	4 weeks Study: ###-TD00-801 (C57BL/6) – day 28	♂	62.5	113	9.4
			125	284	24
			250	606	51
		♀	62.5	274	23

Species	Study duration	Dose mg/kg/day	AUC _{0-24h} µg·h/mL	Exposure ratio [#]
		125	566	47
		250	916	76
	3 months Study:35##/35## (B6C3F ₁)	♂ 3	3.4	0.3
		♂ 12	19	1.6
		♂ 24	35	2.9
		♂ 48	91	7.6
		♀ 3	13	1.1
		♀ 12	62	5.2
		♀ 24	123	10.3
		♀ 48	317	26.4
	Estimated values for carcinogenicity study based on values from Study:35##/35## (B6C3F ₁)	♂ 3	3.4	0.3
		♂ 7.5	11	0.9
		♂ 18.75	28	2.3
		♀ 3	13.2	1.2
		♀ 7.5	38	3.2
		♀ 18.75	97	8.1
Rat	26 weeks Study: S0##C3R100^ (Slc:SD)	3	14.6	1.2
		12	69.6	5.8
		48	272	23
	3 months Study: S0##S2R10A^ Carcinogenicity study (F344/DuCrj) – day 91	3	17	1.4
		12	73.8	6.2
		24	198	17
	3 months Study: S0##S2R10B^	48	357	30
		75	623	52

Species	Study duration	Dose mg/kg/day	AUC _{0-24h} µg·h/mL	Exposure ratio [#]
	(F344/DuCrj) – day 91	150	1184	99
Dog	3 months Study: S0##S2D100 [^] (HRP Beagle) – day 90	5	2.6	0.2
		20	27	2.3
		80	471	39
	12 months Study: S0##C4D100 [^] (CSK Beagle) – day 365	5	4.6	0.4
		15	35.3	2.9
		45	484	40
Human (healthy subjects)	steady state	[120 mg]	12	–

[#] = animal: human plasma AUC_{0-24h}; [^]Mean male and female AUC values; bolded and shaded = NOAEL.

Major toxicities

Due to its pharmacological action, FBX reduces uric acid formation and increases circulating levels of xanthine. Excretion of xanthine via urinary systems over time results in the formation of calculi and cause urolithiasis. In the repeat-dose toxicity studies, calculi developed in the kidneys, ureters, urinary bladder and urethra and were typically accompanied by gross and histopathological changes to the epithelial cells and local environment indicative of cellular damage and irritation. Functional evidence of adverse changes to kidneys included elevated BUN and creatinine, higher urinary volumes and decreased specific gravity.

The thyroid appeared to be a target organ as shown by its enlargement and increased relative weight seen consistently in high dose treated animals. Haematological tests revealed higher WBC counts, decreased haemoglobin and haematocrit, and high platelet counts (sometimes accompanied by a shortened thromboplastin time).

Kidney

Renal changes were a consistent feature of all toxicity studies. In the mouse, cortical inflammation was seen in males treated with 125 mg/kg for 28 days. Increases in relative kidney weights were noted in all male dose groups in a preliminary 3 month mouse carcinogenicity study; evidence of kidney fibrosis was also seen in the HD groups. Males were clearly more sensitive as females showed less prominent treatment-related kidney effects despite a 3.5 fold higher plasma exposure (AUC).

In the rat, at FBX doses of 24 and 36 mg/kg, kidneys developed a yellow/white appearance, related to deposition of crystalline material. Associated histopathological effects included changes to the basophilic epithelium, cystic dilatation and increased deposits in tubules. At higher doses (> 48 mg/kg/day), presence of calculus coincided with tubular dilatation, cellular infiltration and fibrosis of interstitium and necrosis of the tubular epithelium. In the pivotal six month rat study (3, 12 and 48 mg/kg/day; Study S0##C3R100), deposition of yellow/white crystalline material was noted in kidneys of both male and female rats. This was associated with histopathological changes such as

tubular dilatation, vacuolar degeneration (of tubule epithelium), interstitial fibrosis and presence of hyaline casts. Functional changes included increased blood urea nitrogen (BUN) levels, which did not resolve following a 6 week recovery period. As well, urinary volume increased, while specific gravity decreased in high dose groups, suggesting impairments to tubular reabsorption. Plasma exposures did not differ greatly between male and female rats, with AUC levels showing proportionality at all doses.

Similar effects on the kidney were also seen in the pivotal dog study (Study S0##C4D100). Calculus was noted and kidneys had a hardened surface, suggesting increased crystalline deposition, as well relative kidney weights were higher in the high dose groups. Histological examinations also revealed fibrosis of the interstitium, atrophy of renal tubules cellular infiltration, as well as evidence of hyperplasia. Incidences of basement membrane thickening were also noted in mid dose (MD) and HD male groups. BUN levels increased in both male and female HD groups, which decreased to near vehicle group levels after a 3 month recovery period. However, the presence of calculi, cellular infiltration, interstitial fibrosis, hyperplasia and renal tubule atrophy persisted in the recovery HD cohort.

Urinary bladder

Calculi deposits were also commonly seen in the urinary bladder. In the mouse, bladder stones were noted in the HD male and female groups (48 mg/kg/day) following a three month treatment period (Study 35##-011-022). Histological examination noted the presence of round eosinophilic bodies in the urinary bladders of all treated males in a 4 week dose-range finding study (Study ###-TD00-801). Calculus development and cellular infiltration were also noted in rats, with a yellow granular substance reported in both male and female rats at doses of 75 mg/kg and higher (Study S0##S2R10B). Development of urinary bladder calculi was not as prominent in dogs compared to rodents. Urinary bladder histological changes included reddened mucosa in one male and female each from the HD group and cellular infiltration after a 12 month treatment period (Study S0##C4D100). Sedimentary material and occult blood was detected in urine from dogs in the MD and HD groups, suggesting injury originating in the urinary tract, possibly the urinary bladder.

Thyroid

The thyroid gland of rats was often affected by repeated FBX treatment. In a preliminary dose-range finding carcinogenicity study (Study S0##S2R10B) enlarged thyroids and significantly higher relative thyroid weights were noted in the HD dose (150 mg/kg/day) male groups at the end of a 3 month treatment period. In a 5 week study increased thyroid weight and follicular epithelial hyperplasia were noted in MD and HD males and HD females (3, 15, 75 and 100 mg/kg; Study S0##S1R100). This change coincided with decreases in circulating levels of the hormones, triiodothyronine (T₃) and thyroxine (T₄), which were also monitored in the study; however attempts to elucidate whether this affected thyroid stimulating hormones (TSH) levels were unsuccessful because the study authors did not use a suitable probe/antibody against TSH. Enlarged thyroids were also observed in F₀ dams⁶ from HD group of the pre/postnatal study (3, 12 and 48 mg/kg/day; Study S0##30R100). Some of the F₁ pups⁷ from the MD and HD group dams exhibited exophthalmos, which may be associated with high maternal thyroid weight and aberrant thyroid hormone levels. Further examination of the role of thyroid hormones was provided in a 5 week repeat dose study in which thyroid hormone levels (free T₃, T₄ and TSH) were monitored following treatment of male rats with FBX (150 mg/kg/day) with or without T₄ (Study ###-24-66). FBX reduced T₃ and T₄ levels and increased TSH levels

⁶ F0 dams= the initial parent generation in a multi-generation reproduction study.

⁷ The F1 pups or F1 generation is the generation resulting immediately from a cross of the first set of parents (parental generation or F0 dams and males).

almost six fold. On the other hand, supplementing FBX with exogenous T₄ maintained thyroid hormone levels close to normal (vehicle treated group) and did not bring about the gross pathological changes (that is, enlargement, hyperplasia and hypertrophy of follicular cells) seen in FBX alone treated groups. Rat thyroid is more sensitive to proliferative lesions caused by chronic TSH stimulation than the human thyroid⁸.

Haematological parameters

Changes to haematological parameters were noted in some of the repeat-dose studies although effects were not always consistent. Red blood cell (RBC) counts, haemoglobin and haematocrit levels in rats were significantly lower at doses of 150 mg/kg/day than in vehicle controls, while white blood cell (WBC) counts were significantly higher in males at 75 and 150 mg/kg/day, and in females at 150 mg/kg/day (Study S0##S1R100). No haematological changes were noted at the doses used in a preliminary carcinogenicity study (Study S0##S2R10A: ≤ 36 mg/kg/day); however, in the second preliminary carcinogenicity study in which higher doses were tested (Study S0##S2R10B; 48, 75 & 150 mg/kg/day) similar patterns to those observed in Study S0##S1R100 emerged. Incomplete recovery of these parameters was observed following a 6 week recovery period for both HD groups. Platelet counts, activated partial thromboplastin time (APTT) and partial thromboplastin time (PT) were also significantly higher in male HD rats of this study.

The sponsor's Nonclinical Expert proposed that decreased RBC counts were a consequence of injury to kidney tissue brought on by calculi deposition, which may have affected erythropoietin production. Erythropoietin levels were not measured to confirm this mechanism. Increases in platelet levels and WBC were considered to be a response to increased inflammatory processes caused by injury to kidney tissue; a plausible mechanism considering the cellular infiltration, fibrosis and necrosis of the tubule epithelium observed in HD rats. It is unclear why these observations were confined to the rat, since no haematological changes were seen in the dog study where there was evidence of kidney injury with fibrosis and cellular infiltration. Note also that *in vitro* studies using either human platelets or whole blood found no effect by FBX on platelet aggregation or other coagulation parameters (Study 18-G-##010; Study ###05003665).

Liver

High doses of FBX (corresponding to AUC exposure ratios of 20 to 30) caused enzyme elevations (alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT)) in rats and dogs with no accompanying histological changes in the liver. Elevated liver enzymes (aspartate aminotransferase (AST), lactate dehydrogenase (LDH)) were also noted in chimpanzees receiving FBX for 3 consecutive days (Study WSRC##0109) but these were equivocal due to possible ketamine (anaesthetic) effects. Nevertheless, liver test abnormalities have been reported to occur in 2% to 13% (average approximately 3.5%) of patients receiving FBX⁹ but the levels are generally mild to moderate and self-limited. The mechanism of FBX hepatotoxicity is speculated to be due to its hepatic metabolism, the major pathway being glucuronidation with minor metabolism via the CYP 450 system⁹.

Genotoxicity

FBX was negative in seven of the eight conventional genotoxicity studies submitted: a bacterial reverse mutation assay, a forward mutation test in mouse lymphoma cells (L5178Y), an *in vitro* chromosomal aberration study in human lymphocytes, two *in vivo*

⁸ Hill RN, Crisp TM, Hurley PM, Rosenthal SL, Singh DV. Risk assessment of thyroid follicular cell tumors. Environ Health Perspect. 1998; 106(8):447-457.

⁹ <<http://livertox.nih.gov/Feboxostat.htm>> (accessed 23 Oct 2013).

chromosomal aberration studies in mice and rats and an ex vivo unscheduled deoxyribonucleic acid (DNA) synthesis assay in rats. All studies were appropriately designed and were validated by adequate demonstration of cytotoxicity (in vitro studies), clinical signs (in vivo) and positive control effects.

A weak positive finding was noted in one in vitro chromosomal aberration study (Study S0##W0C900) in the absence and presence of S9¹⁰ in Chinese Hamster Lung fibroblast cells treated with high concentrations (1.336 to 2.0 mM equivalent to 422.68 to 632.76 µg/mL) of FBX. However, given that negative results were obtained in human peripheral blood lymphocytes (in vitro) and in two in vivo bone marrow studies, the weight of evidence suggests that FBX is not of genotoxic concern.

Carcinogenicity

Two life-time (104 weeks) rodent carcinogenicity studies were conducted (Studies 42##-011-025 and 42##-4260).

Dose selection for both studies was based on gross findings from preliminary 13 week repeat-dose studies in which urinary calculi were a common finding. Because calculi readily develop in rodents and eventually lead to nephropathy and urinary obstruction, which may affect the 24 month survival of test animals, doses were selected at levels that did not induce severe calculi development. The sponsor's Nonclinical Expert argued that development of urolithiasis and nephropathy were the consequence of an exaggerated pharmacodynamic effect of FBX and to ensure test animal survival, only limited doses could be used. This approach was considered acceptable in line with ICH guidance S1C(R2).¹¹

Mouse

In the mouse tumour incidences were generally low and were not statistically significant when compared to vehicle-treated groups. Nevertheless, transitional cell papilloma (3/50) and carcinoma (1/50) in the urinary bladder were seen in HD treated females, which coincided with significantly higher incidences of histological changes to the urinary bladder predictive of pre-neoplastic effects such as hyperplasia, fibrosis, hyaline droplet and oedema in tissues from HD females. While historical control data were not available to ascertain if incidences of this tumour type were consistent or above the norm for this strain, it is considered to be an uncommon type of neoplasm in mice. The related histological observations suggest that the development of calculi and ensuing irritant and inflammatory effects are the main cause. Indeed, this incidence of urinary bladder tumours in HD females strongly correlated with urinary bladder calculi, where all animals that had tumours had coexisting calculi in their urinary bladders.

Overall, the No Observable Adverse Effect Level (NOEL) effect for neoplastic effects in mice was 7.5 mg/kg/day (corresponding to relative AUC exposure ratio of 0.9 [M] and 3.2 [F]) whereas the NOAEL for non-neoplastic effects was 3 mg/kg/day (exposure margins 0.3 [M] and 1.2 [F]).

Rat

Plasma exposures for the rat carcinogenicity study were calculated using data from a 13 week preliminary carcinogenicity study in F344/DuCrj rats (Study S0##S2R10A) and were found to be similar in males and females.

¹⁰Rat liver extract or S9 (containing cytochrome P450 isoforms and other enzyme activities) is optionally added to simulate the effect of mammalian metabolism, as some compounds, like benzo[a]pyrene, are not mutagenic themselves but their metabolic products are. Hence, to mimic the metabolism of a medicine that would occur in mammals a S9 fraction is often added to the Ames test.

¹¹ ICH Harmonised Tripartite Guideline: Dose selection for carcinogenicity studies of pharmaceuticals Ss1c(R2)

Neoplastic lesion incidences in the rat were generally low following FBX treatment. The most prevalent tumours were transitional cell papillomas (10/50) and carcinomas (7/50) in urinary bladders of males at the HD of 24 mg/kg/day. The relative exposure margins (AUC) for neoplastic effects (urinary tumours) were 6 at the No Observable Effect Level (NOEL) (12 mg/kg/day) and 17 at the Lowest Observable Effect Level (LOEL) (24 mg/kg/day).

Non-neoplastic lesions were notable in the kidney, where a number of treatment related effects were most likely due to deposition of xanthine crystals and formation of calculi. The latter were observed in the kidney (47/50), urinary bladders (12/50) and urethra (15/50) of all HD treated males and kidney calculi in MD and HD females (MD: 16/20 and HD: 44/50). Fibrosis was frequently observed in kidneys from HD animals (Males: 34/50; Females: 11/50). Transitional cell hyperplasia was common and was closely correlated with calculi formation.

Clinical relevance of rodent findings

Spontaneous development of urinary bladder papillomas and carcinomas are rare in rodents unless epithelial erosion or injury occurs, such as that following the urinary calculi development. Calculi are only weakly associated with bladder carcinogenesis in humans: they form less readily in humans and other primates than in rodents. The higher osmolality of rodent urine (mOsm/kg: mice 2100-3100, rats 300-3800, humans 100-1000) maybe one factor predisposing rodents more to calculi formation than humans. Unless xanthinuria is a common clinical finding with FBX treatment, it is unlikely that urinary bladder neoplasms caused by the xanthine calculi in rodents are relevant to humans, despite the relatively low exposure margins attained in these studies.

Reproductive toxicity

The same dose levels were used for all reproductive toxicity studies in rats and rabbits (3, 12 and 48 mg/kg/day). As toxicokinetic measurements were not made in the rat reproductive toxicity studies values were taken from the 6 month repeat dose toxicity study (S0##C3R100) where identical doses had been used. Relative exposures are tabulated below:

Table 2. Relative exposure (based on AUC comparisons, µg.h/mL):

Species	Gender	Dose (mg/kg/day)	AUC _{0-24h} (µg.h/mL)	Exposure ratio [#]
Rat*	F	3	16.4	1.3
		12	86.2	7
		48	305.2	25
	M	48	238.5	20
Rabbit	F	3	9.3	0.8
		12	59	4.9
		48	395	33
Human (healthy)	M/F	2.4	12	-

Species	Gender	Dose (mg/kg/day)	AUC _{0-24h} (µg·h/mL)	Exposure ratio [#]
subjects)				

[#] = animal:human dose (plasma AUC_{0-24h}); * based on toxicokinetic parameters ascertained in Study S0##C3R100; ^ based on measurements from healthy subjects who received a final daily dose of 120 mg (Study TMX-##-001)

FBX (3, 12 and 48 mg/kg/day) did not impair either male or female fertility or affect early embryonic development in rats. Clinical signs and gross findings were consistent with those noted in other toxicity studies. The NOAEL for both male and female fertility was established at ≥ 48 mg/kg/day, which is more than 20 to 25 times the maximum anticipated clinical exposure at a dose of 120 mg/day (based on AUC). Similarly, the embryofetal development study in rats did not reveal any remarkable effects, with maternal and embryofetal NOAELs also established at ≥ 48 mg/kg/day.

In the rabbit study (Study T-##3) there was no indication of an effect on fetal development by FBX (3, 12 and 48 mg/kg/day), as there were no apparent malformations and abnormalities. Relative exposure at the HD (NOAEL) was more than 33 fold the maximum anticipated clinical exposure.

Maternal mortalities were noted in the HD group of the rat pre-postnatal development study (Study S0##30R100). Moreover, the deposition of xanthine crystals in the kidney and urinary tract was noted in dams at the MD and HD. Bodyweight and survival of the F1 generation was decreased at the HD. While maternal and neonatal levels of FBX were not measured in this study, FBX was shown in other pharmacokinetics (PK) studies to readily pass through the milk and histopathology data showed xanthine crystals in the kidney for new born pups of dams treated at the HD. Tests on the fertility of F1 generation offspring showed a lower mating index in F1 males from the HD group.

Based on these observations the NOAEL for both maternotoxicity and pup development effects is 3 mg/kg/day, based on gross findings and clinical observations, respectively. At this level, relative exposure (1.3) was similar to that anticipated clinically at the maximum daily dose.

Pregnancy classification

The sponsor's proposed Pregnancy Category of **B2**¹² is inappropriate as the reproductive studies in animals are not inadequate or lacking. Given that FBX caused no fetal malformations or abnormalities at more than 20 to 30 fold human exposure (AUC) and that placental transfer was negligible, the category should be changed to **B1**¹³. FBX caused delayed postnatal development, most likely from direct exposure via the milk during the lactation period. The *Use in Lactation* statement in the PI should be amended to reflect the findings (see Product Information section for details).

¹²**Category B2:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

¹³**Category B1:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Local tolerance – antigenicity studies

FBX did not evoke any sensitisation reactions in rats (IP) and did not show systemic reactivity or anaphylaxis in guinea pigs.

Paediatric use

FBX is not proposed for paediatric use and the sponsor did not submit any juvenile toxicity studies to support such a use.

Nonclinical summary

- The content of the nonclinical dossier was adequate. Most studies were conducted according to international guideline requirements and were scientifically sound.
- FBX was shown to inhibit xanthine oxidoreductase and decrease uric acid production both in vitro and in vivo. Selectivity was demonstrated by showing that enzymes involved in purine metabolism were not affected by FBX. Metabolites of FBX also exhibited inhibitory activities against xanthine oxidoreductase. FBX was approximately 2 to 4-fold more potent at lowering plasma/serum uric acid than allopurinol in various rodent models *in vivo*.
- Although receptor screening studies were not performed, potential secondary actions of FBX were investigated in studies not covered by core safety pharmacology studies. FBX did not affect thrombin or time dependent platelet activation or affect the anticoagulant actions of heparin or warfarin, nor did it reduce urate-crystal induced inflammation in rats.
- Most safety pharmacology studies were non-GLP. In the CNS FBX caused decreased locomotor activity. FBX had no effect on a potassium current (I_{Kr}) in a hERG channel assay and no significant effects on cardiac sodium and calcium currents at clinically relevant concentrations. Transient decreases in BP were noted in conscious (but not anaesthetised) dogs and FBX did not affect the hypotensive effects of nifedipine. Increased urinary volume and excretion of K and Cl were seen in a renal study. FBX did not affect intestinal motility.
- FBX had similar onsets of action in rodents and humans (T_{max} : 0.4 to 1 h and 1 h, respectively). Plasma levels were dose proportional for all tested species and there was no evidence of accumulation. Gender differences in mouse AUC were observed, which were approximately 2 fold higher in females. Oral bioavailability was highest in humans (84%) and rats (78%), moderate in dogs (48%) and low in mice (< 20%). Feeding state, particularly in dogs, reduced bioavailability (plasma FBX), an effect also shown in clinical studies.
- High plasma protein binding ($\geq 99\%$) was demonstrated with human and rat plasma samples. FBX was found to bind to the diazepam site of albumin. Metabolites were also highly protein bound (81 to 91%); however, they appeared to bind to a different (and unidentified) region of albumin. FBX exhibited low permeability across the placenta but was readily excreted through milk.
- Unchanged FBX accounted for the highest proportion of reaction product recovered in metabolism studies. FBX undergoes oxidation and glucuronidation, with the glucuronide conjugate of FBX (G2) being the dominant metabolite for all species, followed by the hydroxylation products 67M-1 and 67M-2. Elimination of FBX and its metabolites was predominantly through the faecal route, although urinary excretion was also identified as a significant excretion route in humans. FBX did not cause enzyme induction and had weak inhibitory activity against CYP2D6 (K_i approximately 40 μ M). FBX was not a substrate of P-gp.

- Single dose oral toxicity studies were performed in rats and dogs. High numbers of mortalities in the HD rat groups (600 mg/kg) were preceded by decreased locomotor activity, increased salivation and irregular breathing. There were no mortalities in the dog but decreased locomotor activity, ptosis and increased salivation were seen in all dose groups. Maximum non-lethal doses were 300 and >2000 mg/kg for rats and dogs, respectively, suggesting a low to moderate level of acute toxicity.
- Repeat dose oral toxicity studies were conducted in mice (up to 3 months), rats (up to 6 months) and dogs (up to 12 months). AUC based relative exposure attained in these studies ranged from low to moderate (<1 up to 100), with low exposure ratios evident at the NOAELs for all toxicity studies (<5).
- Major toxicities of FBX were related to its intended pharmacological effect, where inhibition of xanthine oxidoreductase resulted in increased xanthinuria and calculi deposits in urinary tissues. Renal changes were noted in all toxicity studies with calculi deposits, interstitial fibrosis, cortical inflammation, vacuolar degeneration and cellular infiltration seen in all animal models. Functional effects of these changes included increased urinary BUN and creatinine levels, increased urinary volumes and decreased specific gravity. Urinary bladder stones were noted in HD mice, calculus development and cellular infiltration were seen in rats, while reddened urinary bladder mucosa and cellular infiltration were seen in dogs.
- Species specific thyroid changes were seen in rats, including hyperplasia and hypertrophy of follicular cells, and were associated with decreased triiodothyronine (T₃) and thyroxine (T₄) levels and increased thyroid stimulating hormone (TSH) levels. Changes to haematological parameters in rats included reduced RBC counts, haemoglobin and haematocrit levels which were attributed to aberrant erythropoietin production by the kidneys. Increased WBC counts and platelet levels (rat only) were considered to reflect increased local inflammation in the kidney. High doses of FBX (AUC exposure ratios of 20-30) caused enzyme elevations (ALP, ALT, GGT) in rats and dogs with no accompanying histological changes in the liver.
- FBX was negative for genotoxicity in studies of bacterial reverse mutation study, mammalian forward mutation, chromosomal aberration and ex vivo unscheduled DNA synthesis. While FBX was positive for chromosomal aberrations in Chinese Hamster Lung fibroblasts, the weight of evidence suggests that it does not pose a genotoxic risk.
- In a two year carcinogenicity study in male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 17 times human exposure (based on AUC). In mice, these tumour types were only seen in females at approximately 8 times human exposure. Chronic irritation of bladder epithelium by the presence of calculi is believed to elicit pre-neoplastic and neoplastic changes. However, differences in species specific purine metabolism and urine composition mean that xanthine calculi form less readily in humans than in rodents such that urinary bladder tumours are not considered to be of likely clinical significance.
- Reproduction studies in rats up to 48 mg/kg/day (20 to 25 times human exposure at the MRHD, based on AUC) showed no dose dependent adverse effects on male or female fertility or early embryonic development. Embryofetal development studies in rats and rabbits found no evidence of external fetal abnormalities at 25 to 33 times clinical exposure, consistent with the minimal placental transfer of FBX found in pharmacokinetic studies. Rats exposed to FBX during the lactation period at 25 times clinical exposure showed maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring. At the NOAEL for maternal and pup

developmental effects the AUC-based relative exposure was similar to that anticipated clinically at the maximum daily dose.

- FBX did not exhibit antigenic properties when tested in a rodent bioassay test or in guinea pigs.

Conclusions and recommendation

- In vitro and in vivo nonclinical data showed that FBX (and some of its metabolites) can inhibit xanthine oxidoreductase (XOR) and elicit decreases in plasma/serum uric acid. FBX potency in rodents was approximately 2 to 4-fold that of allopurinol.
- The toxicity of FBX following repeated dosing was directly related to its pharmacological activity. Inhibition of XOR led to high circulating levels of xanthine, which deposited in and around tissues associated with urinary systems. This deposition (calculi build-up) led to irritation and injury of urinary epithelial tissue, which brought about a range of adverse gross morphological and histological changes to the kidney, urinary bladder and urethra of test animals. Chronic irritation and injury of these tissues were likely causes for the preneoplastic and neoplastic changes seen in these organs. However, differences in species specific purine metabolism and urine composition mean that xanthine calculi form less readily in humans than in rodents such that urinary bladder tumours are not considered to be of likely clinical significance, despite the relatively low exposure margins attained in these studies.
- The weight of evidence from an extensive test battery suggests that FBX does not pose a genotoxic risk.
- FBX had no effect of fertility in rats and was not teratogenic in rats and rabbits at approximately 20-30-fold clinical exposure (AUC). However, FBX was clearly excreted into the milk, and exposure of rat pups via this route led to impaired development at high maternal doses. At the NOAEL for maternal and pup developmental effects the AUC-based relative exposure was similar to that anticipated clinically at the maximum daily dose. Therefore, a risk to a suckling infant cannot be excluded and FBX should not be used while breastfeeding.
- There are no nonclinical objections to the registration of FBX for the proposed indication.
- Changes to the draft Product Information were recommended but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Hyperuricaemia is defined as a serum or plasma urate concentration greater than 7.0 mg/dL (0.42 mmol/L). This value exceeds the limit of solubility of urate in extracellular fluid (6.8 mg/dL). Hyperuricaemia is usually the result of both increased uric acid production (from either endogenous or exogenous sources) and decreased uric acid excretion due to deficits in renal urate handling. The prevalence of hyperuricaemia in Caucasian males is estimated to be 5 to 8% but it is much higher in people of Polynesian and Chinese ethnicity. There is epidemiological data to suggest that the incidence and

prevalence of symptomatic hyperuricaemia may be rising in developed countries (including Australia) due to several factors such as the increasing incidence of obesity and renal insufficiency, as well as changes in eating habits.

Symptomatic hyperuricaemia is a metabolic disorder in which tissue deposition of monosodium urate crystals from supersaturated body fluids results in attacks of inflammatory arthritis (acute gouty arthritis) and the development of macroscopic crystalline aggregates (tophi), primarily in the connective tissue. The plasma urate concentration is the single most important determinant of the risk of developing gout as there is a strong correlation between the incidence of acute gouty arthritis and mean serum urate concentration. Gout is rare in children and pre-menopausal females. Males are more commonly affected, and the peak age of onset in men is between 40 and 50 years of age. Gouty arthritis may be acute, acute-on-chronic or chronic. It usually begins in one joint (classically, the first metatarsophalangeal joint) but may affect multiple joints. Chronic tophaceous gout is a destructive and incapacitating condition affecting up to 20% of patients with gout. Symptomatic hyperuricaemia may also affect renal function by deposition of urate crystals in the renal interstitial tissue (urate nephropathy) and excretory tracts (nephrolithiasis).

Current approved treatment options in Australia for the management of hyperuricaemia include the XO inhibitor allopurinol and uricosuric drugs (for example probenecid and sulfinpyrazone). However, significant proportions of patients either fail to respond to or are intolerant of these treatment options. In addition, the current approved drugs have dosing limitations in patients with impaired renal function, which limit their optimal utilisation. As such there is an unmet need for additional therapies for management of symptomatic hyperuricaemia.

Guidance

A requirement for applications of new chemical entities of immediate release dosage forms is the provision of an absolute bioavailability study and a study to establish that the proposed formulation is optimal (for example, a study of the proposed commercial versus an oral solution of the drug). In the submission, the sponsor has provided acceptable justification for this variation of application requirement.

There are 2 specific regulatory guidelines pertaining to the requested indication (see *Product background* above).

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- 32 clinical pharmacology studies, all of which provided Pharmacokinetic (PK) data and 11 studies that provided Pharmacodynamic (PD) data.
- 2 population PK-PD analyses using data collected in Studies TMX-##-005 and C##-009.
- 2 pivotal efficacy/safety trials; Studies C##-009 and C##-010.
- 1 dose-finding study (TMX-##-004)
- 3 other efficacy/safety studies; one of which was a Phase III trial (Study F-GT##-153), and the other 2 trials were long-term open-label extension studies (TMX-##-005 and C##-021).
- Integrated Summary of Efficacy and Integrated Summary of Safety.

- The sponsor's Clinical Overview, Summary of Clinical Pharmacology Studies, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All of the studies in the FBX (FBX) clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each PK topic, and the location of each study summary.

Table 3. Submitted Pharmacokinetic Studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	TMX-##-01 and C##-040
	- Multi-dose	TMX-##-001 and C##-023 (USA), as well as
		TMX-##-03 and TMX-##-05 (Japan)
	Bioequivalence† - Multi-dose only	TMX-##-009, TMX-##-010, TMX-##-018, C##-033, C##-034 and C##-044
	Food effect	TMX-##-002 C##-036 C##-054
PK in special populations	Target population § - Multi-dose only	TMX-##-009 and TMX-##-010 (Japan); as well as TMX-##-004 (USA)
	Hepatic impairment	TMX-##-012 (US)
	Renal impairment	TMX-##-008 (US) and TMX-##-08 (Japan)
	Elderly	TMX-##-016 (US)
Gender-related PK	Males versus Females	TMX-##-016 (US)
PK interactions	Colchicine	TMX-##-006 and C##-006
	Indomethacin	TMX-##-017

PK topic	Subtopic	Study ID
	Naproxen	C##-013
	Hydrochlorthiazide	C##-059
	Desipramine	C##-005
	Antacid medication	TMX-##-014
	Rosiglitazone	TMX-##-103
	Theophylline	TMX-##-101
	Warfarin	C##-057 and F-P1##-162
Population PK analyses	Healthy subjects	Nil
	Target population	TMX-##-005 and C##-009 (Sub-study)

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

In this submission, the PK properties of FBX has been assessed in 19 Phase I studies involving otherwise healthy volunteers (some with co-variables of interest such as renal or hepatic impairment, and older age), 11 drug-drug interaction studies, 3 trials involving subjects with hyperuricaemia and gout as well as 2 population PK-PD analyses.

The key PK conclusions identified in the submission are as follows:

- Orally administered FBX is rapidly (T_{max} of 1.0 to 1.5 hours) and well absorbed (at least 84%) from the gastrointestinal tract, but absolute bioavailability has not been determined.
- The proposed commercial formulation and dosage strengths of FBX to be made available in Australia are similar to the 80 mg and 120 mg tablet strengths of the B1 formulation, which have demonstrated bioequivalence when produced at a commercial scale to the preceding formulations.
- Ingestion of multiple oral doses of FBX 80 mg once daily and single FBX doses of 120 mg following a high fat meal compared to drug administration under fasted conditions, results in a decrease in FBX C_{max} by 38 to 49%, a decrease in AUC by 16 to 19%, and a delay in T_{max} by as much as 1 hour.
- The evening administration of FBX results in a slight decrease in C_{max} and a minor delay in T_{max} when compared to morning dose ingestion, however, the total exposure (AUC) to FBX and its metabolites is similar.
- Regarding dose proportionality, the PK parameters of FBX are not time or dose dependent, and remained linear in the dose range of 10 to 120 mg once daily but when the dose of FBX exceeds 120 mg/day, a greater than dose proportional increase in AUC was observed, which is postulated to be due to an increase in the extent of enterohepatic recycling of FBX.

- FBX appears to have a low to medium apparent volume of distribution (approximately 0.7 L/kg).
- FBX is highly bound to human plasma proteins (98 to 99%; and predominately to albumin), and is constant over the concentration range achieved with FBX 40 to 120 mg doses. Plasma protein binding of the active metabolites ranges from 82 to 91%.
- The $t_{1/2}$ of FBX in the plasma ranges from 5 to 8 hours and reaches steady state within 1 week of once daily dosing.
- FBX is predominately eliminated from the blood by liver metabolism (mainly by metabolism to glucuronide conjugates, and to a much lesser degree by oxidative metabolism), and the majority of metabolites that are eliminated in the urine are not active.
- Subjects with renal impairment have higher unbound FBX AUC₂₄ values (approximately 1.8 fold increase) than those with normal renal function, but mean FBX T_{max} (0.93 to 1.33 hours) and unbound C_{max} values are similar. FBX half-life ($t_{1/2}$) also tended to increase with worsening renal function (4.7 hours in those with normal renal function versus 7.0 hours in subjects with moderate renal impairment). The active metabolites (67M-1, 67M-2 and 67-M4) also showed the same statistically significant relationship between mean AUC₂₄ values and worsening creatinine clearance (CrCl).
- The population PK analyses identified baseline CrCl (both studies), body weight and co-administration of fibrate therapy (Study C##-009 only), as well as smoking status (TMX-01-005 only) as statistically significant covariates for determining FBX clearance.
- The PK of FBX does not appear to be substantially affected by age or gender (when adjusted for body weight).
- Compared to subjects with normal hepatic function, total plasma exposure to FBX is higher in subjects with mild or moderate hepatic impairment (mean FBX unbound C_{max} values 24% higher; and mean unbound AUC₂₄ values 24 to 28% greater); but there are no other observed changes in PK parameters in subjects with hepatic impairment.
- The PK characteristics of FBX in relation to C_{max} and AUC demonstrate relatively low intra-subject and inter-subject variability (though moderate variability for T_{max}), with no observed differences related to FBX formulation or dose across the 20 to 120 mg range.
- A total of 11 in vivo drug-drug interaction studies in humans have been performed. The results indicate that many frequent concomitant medications such as colchicine, indomethacin, hydrochlorothiazide, warfarin, CYP2D6 substrates (desipramine) do not have clinically significant effects on the PK of FBX. However, naproxen (glucuronidation inhibitor) increases exposure to FBX (C_{max} increases by 28%, AUC by 41% and $t_{1/2}$ by 26%). In addition, the concomitant ingestion of antacids has shown to delay the absorption of FBX by approximately 1 hour and to cause a decrease in C_{max} of 32% but no significant change in AUC. The sponsor has not submitted any evaluable data on the potential for interaction between FBX and rosiglitazone (Study TMX-##-103).

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4 shows the studies relating to each PD topic.

Table 4. Submitted Pharmacodynamic Studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on serum urate concentration, xanthine and hypoxanthine levels; as well as urine uric acid excretion	Healthy Subjects: C##-023, TMX-##-001, TMX-##-008, TMX-##-012
		Target Population: TMX-##-004
Secondary Pharmacology	Effect on Cardiac QT Interval	C##-023 (Part B) and C##-009 (Sub-study)
Gender and Age-Related Differences in PD Response	Effect of gender	TMX-##-016
	Effect of age	TMX-##-016
PD Interactions	Warfarin	C##-057 and F-P1##-162
	Effect of Food	C##-036
Population PD and PK-PD analyses	Healthy subjects	Nil
	Target population	TMX-##-005 and C##-009 (Sub-study)

One of the PD studies had deficiencies that excluded its results from consideration. Study TMX-##-003 (USA based) was meant to recruit hyperuricaemic subjects with a baseline serum urate level of between 8.0 and 12.0 mg/dL within 6 months of enrolment. However, none of the subjects achieved this target hyperuricaemia level on Day -1. In addition, further protocol violations and study conduct irregularities meant the PD data for this study was excluded as it was considered unreliable.

Evaluator's conclusions on pharmacodynamics

In this submission, the PD properties of FBX have been assessed in at least 6 Phase I studies involving otherwise healthy volunteers (some with co-variables of interest such as renal or hepatic impairment, and older age) as well as 3 trials involving subjects with hyperuricaemia and gout (including 2 population PK-PD analyses).

The key PD conclusions identified in the submission are as follows:

- Following administration of multiple once daily oral doses of FBX 80 and 120 mg for 7 days, mean serum urate concentrations reduce by a mean of 55 to 66% from baseline.
- There is a linear dose-response relationship for FBX doses 10 to 120 mg, which appears to level off for doses > 120 mg.
- When FBX is administered in the fasted versus fed state, there is a slightly greater reduction in serum urate concentrations at 7 days but this difference is unlikely to be of clinical relevance.
- The percentage reduction in serum urate concentrations following ingestion of FBX is unaffected by age or presence of renal impairment.

- The percentage reduction in serum urate concentrations following administration of FBX is greater in females versus male subjects and higher in those with normal liver function versus subjects with mild-moderate hepatic impairment but the changes are of small magnitude and therefore unlikely to be of clinical significance.
- Steady state serum urate concentrations are achieved within the first week of multiple once daily dosing with FBX.
- Mean serum xanthine concentrations increase significantly following multiple daily doses of FBX, especially in subjects with renal impairment, but the concentrations reached are substantially lower than the solubility limit in serum (that is unlikely to form xanthine crystals).
- Consistent with the serum changes, there are decreases in urinary excretion of uric acid and an increase in urinary excretion of xanthine. Serum hypoxanthine levels do not significantly increase due to increased urinary elimination of this compound.
- Two population PD analyses (Studies TMX-##-005 and C##-009) demonstrate moderate inter-individual variability for the concentration of FBX at steady state that would result in a 50% decrease in serum urate concentrations from baseline (IC_{50}), which remains unexplained.
- FBX in doses up to 300 mg/day at steady state does not cause any significant effects on cardiac repolarisation such as prolongation of the QT interval¹⁴ in normal healthy subjects (Part B of Study C##-023), as well as patients with gout (Study C##-009).
- Two drug-drug interaction studies (C##-057 and F-P1##-162) involving healthy subjects have demonstrated that multiple doses of FBX have no clinically significant effects on the PD of concomitantly administered warfarin.

Dosage selection for the pivotal studies

Study TMX-##-004 was a Phase II dose-finding trial, which informed the selection of FBX doses (80 and 120 mg once daily) chosen for examination in the 2 pivotal Phase III studies (C##-009 and C##-010). After 28 days of treatment, the mean percentage reduction in serum urate level (by enzymatic method) was 2.15% for placebo, 36.6% for FBX 40 mg/day, 44.3% for FBX 80 mg/day and 59.1% for FBX 120 mg/day. In addition, the proportion of hyperuricaemic patients achieving a serum urate level of < 6.0 mg/dL (by enzymatic method) in Study TMX-##-004 was greater in each of the FBX treatment groups (55.9% [19/34] in those treated with FBX 40 mg/day, 75.7% [28/37] for FBX 80 mg/day and 94.1% [32/34] for patients receiving FBX 120 mg/day) compared to zero patients who received placebo therapy. In Study C##-009, a FBX 240 mg/day arm was included to provide additional safety information on twice the maximal intended dose of FBX for registration (that is, FBX 120 mg/day). FBX 240 mg/day was administered to healthy volunteers for 14 days in the Phase I Study TMX-##-001 and was generally well tolerated. In Study C##-010, only 2 doses of FBX were investigated (80 and 120 mg/day). The third Phase III trial (Study F-GT##-153 which finished after the 2 pivotal Phase III studies), assessed the lower dose of FBX 40 mg/day at the request of the FDA as this dose had not been investigated in either of the preceding Phase III studies.

The doses of allopurinol used in the Phase III trials as the active treatment comparator for FBX were acceptable. At the time when the 2 pivotal Phase III studies (C##-009 and C##-010) were performed, it was recommended that the dose of allopurinol be reduced from

¹⁴ The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

300 mg/day (in those with normal function) to 100 mg/day in patients with renal impairment. In the subsequent Phase III Study (F-GT##-153) the comparator doses of allopurinol were adjusted to contemporary practice guidelines; a minimum of 300 mg/day for those with CrCl of at least 60 mL/min; and 200 mg/day for patients with CrCl 30-59 mL/min.

The use of non-steroidal anti-inflammatory drugs (NSAID) and colchicine for gout flare prophylaxis and treatment of acute gouty arthritis attacks, is consistent with contemporary clinical practice in Australia. It is also acceptable to use low dose oral prednisone (< 10 mg/day) in selected patients with difficult to control gouty arthritis in the setting of co-morbidities such as renal impairment and/or age > 65 years, which limit alternative treatment options (NSAID and colchicine). However, the exclusion of subjects who were taking concurrent clopidogrel from the Phase III Study F-GT##-153 limits the external validity of the studied populations. Concurrent cardiovascular disease requiring anti-platelet therapy (other than low dose aspirin) is relatively common in the intended target population. The 2 pivotal Phase III studies (C##-009 and C##-010) did not specify in their protocols or report data on whether or not anti-platelet drugs (other than low dose aspirin) were allowed or actually taken.

Efficacy

Studies providing efficacy data

The submission contained the following studies with efficacy data:

- 2 pivotal efficacy/safety trials; Studies C##-009 and C02-010.
- 3 other efficacy/safety studies; one of which was a Phase III trial (Study F-GT##-153), and the other 2 trials were long-term open-label extension studies (TMX-##-005 and C##-021).

Evaluator's conclusions on efficacy

The sponsor has provided the efficacy data from 2 pivotal, randomised, multicentre, double blind trials (C##-009 and C##-010) to support the efficacy of FBX in treating adult patients with hyperuricaemia and gout. Supportive evidence of efficacy is provided by another Phase III study (F-GT##-153) of 6 months duration as well as 2 long-term, open-label extension trials (TMX-##-005 and C##-021) plus a 28 day Phase II dose-finding study (TMX-##-004). In general, the trials were of adequate design to evaluate the proposed indication and they had a clear and appropriate plan of analysis. The biologic rationale for the use of FBX in hyperuricaemia is clear (as a XO inhibitor) and the doses explored in the clinical study program (ranging from 40 to 240 mg/day) were appropriate to define the registered dose. Active comparator therapy (allopurinol 100 to 300 mg/day) was consistent with contemporary literature including international treatment guidelines. In addition, patients received appropriate gout prophylaxis therapy (NSAID or colchicine for most subjects).

In Study C##-009, a total of 1072 subjects were randomised to 5 treatment groups consisting of placebo (n = 134), FBX 80 mg/day (n = 267), FBX 120 mg/day (n = 269), FBX 240 mg/day (n = 134) or allopurinol 100/300 mg/day (n = 258) for 28 weeks of treatment follow-up. In Study C##-010, a total of 760 patients were randomised to receive FBX 80 mg/day (n = 256), FBX 120 mg/day (n = 251) or allopurinol 300 mg/day (n = 253) for 52 weeks of treatment follow-up. The majority of patients (at least 61%) in all treatment groups completed the 28 to 52 weeks of follow-up in both pivotal studies. A relatively low proportion of major protocol violations or deviations (< 10%) occurred in both pivotal Phase III studies, with equal incidence among the treatment groups.

The populations examined in the Phase III studies are similar in demographics to patients that would be treated in Australian clinical practice. The trials were conducted mainly in the USA and mostly recruited overweight, middle-aged Caucasian men. The background treatments (overall, as well as for gout flare prophylaxis) are consistent with Australian treated patients and the incidence and pattern of co-morbid illness was to be expected. The baseline disease characteristics of the study cohorts are consistent with a group of patients with significant hyperuricaemia and evidence of urate deposition, which is congruent with the proposed indication wording. However, the generalisability of the study results to a broader population in Australia has limitations. As stated in the RMP for Australia, the trials have excluded certain patient subgroups at risk of hyperuricaemia such as those with significant over-production of urate and organ transplant recipients, and there is an under-representation of patients with significant renal or hepatic impairment.

The primary efficacy outcome in the 2 pivotal Phase III studies was the proportion of subjects who at the final study visit achieved a consistent reduction in serum urate level to < 6.0 mg/dL. This is an appropriate efficacy measure for determining the utility of a therapy in treating symptomatic hyperuricaemia. There were also several other secondary efficacy endpoints in both studies some of which were dependent on subjective assessments done by either the subject (for example various quality of life instruments). Nonetheless, the efficacy endpoints were appropriate for evaluating the proposed indication for FBX.

The primary efficacy endpoint in the 2 pivotal Phase III trials was achieved. At 28 weeks in Study C##-009 the proportion of subjects whose last 3 serum urate levels were < 6.0 mg/dL were 0% in the placebo group, 48.1% (126/262) in the FBX 80 mg arm, 65.1% (175/269) in the FBX 120 mg group, 68.7% (92/134) in the FBX 240 mg cohort, and 22.4% (60/268) in the allopurinol group. Each of the FBX treatment groups and the allopurinol therapy arm were statistically superior to placebo. The 97.5% confidence intervals (CIs) for the differences in response rates between FBX 80 mg versus allopurinol were 16.7% to 34.7% ($p < 0.001$); and for FBX 120 mg versus allopurinol were 34.0% to 51.3% ($p < 0.001$), thus demonstrating the non-inferiority of both FBX 80 mg/day and 120 mg/day relative to allopurinol 300/100 mg daily. The proportion of subjects in Study C##-010 (52 weeks duration) whose last 3 serum urate levels were < 6.0 mg/dL were 53.3% (136/255) in the FBX 80 mg group, 61.6% (154/250) in the FBX 120 mg arm and 21.1% (53/251) in the allopurinol group. The 97.5% CIs for the differences in response rates for FBX 80 mg versus allopurinol were 23.1% and 41.3%; and for FBX 120 mg versus allopurinol were 31.5% and 49.5%. This result demonstrated the non-inferiority of each FBX dose relative to the allopurinol 300 mg/day. Additionally, the differences between each of the FBX treatment groups (32% difference for FBX 80 mg and 41% difference in proportions for 120 mg) and allopurinol confirmed that each FBX dose was statistically superior to allopurinol ($p < 0.001$ for both comparisons). The difference in response between the FBX 80 mg and 120 mg treatment groups was not statistically significant. Various sensitivity analyses confirmed the robustness of the primary statistical analysis. Exploration of patient factors upon the primary efficacy response was unrevealing apart from showing that patients with very high serum urate levels at baseline (> 10.0 mg/dL) had a slightly lower overall rate of response (regardless of treatment option).

The results for the secondary efficacy endpoints were consistently observed. In the both pivotal Phase III studies, all of the secondary efficacy outcomes associated with changes in serum urate (for example proportion of subjects reaching serum urate level of < 5.0 and < 4.0 mg/dL, and the mean percentage reduction in serum urate from baseline) demonstrated a treatment difference with FBX. However, either inconsistent or no effect with FBX was demonstrated for the percentage reduction in primary tophus size or the total number of tophi. In addition, the percentage of patients requiring treatment for an acute gouty arthritis flare, particularly during the first 8 weeks of therapy, was higher in

the FBX treatment groups compared to allopurinol and placebo. The quality of life measurements demonstrated inconsistent comparative results between the active treatment groups with some parameters appearing to be worse in those receiving FBX versus allopurinol.

Study F-GT##-153 is supportive of the key efficacy findings of the 2 pivotal trials by demonstrating:

A statistically higher proportion of subjects treated with FBX 80 mg/day (67.1%; 507/756) achieving a serum urate level of < 6.0 mg/dL at final study visit (26 weeks) compared to 45.2% (342/757) of patients in the FBX 40 mg/day group, and 42.1% (318/755) of subjects (82%) in the allopurinol group. In addition, FBX 40 mg/day was non-inferior to allopurinol for this primary outcome measure with the absolute treatment difference being 3.1%.

A statistically higher percentage of patients treated with FBX 80 mg/day achieved a serum urate level of < 5.0 and < 4.0 mg/dL at each scheduled visit (bimonthly) compared to those who received treatment with either FBX 40 mg/day or allopurinol 200 to 300 mg/day.

The proportions of subjects with mild to moderate renal impairment who achieved a serum urate level < 6.0 mg/dL at the final visit was 49.7% (238/479) for FBX 40 mg, 71.6% (360/503) for FBX 80 mg, and 42.3% (212/501) in the allopurinol groups. Among the subjects with mild to moderate renal impairment, a statistically significant higher proportion of subjects in the FBX 40 mg group had a final serum urate < 6.0 mg/dL compared to allopurinol ($p = 0.021$). In addition, the proportion of subjects with mild to moderate renal impairment who achieved a serum urate level of < 6.0 mg/dL in the FBX 80 mg group was statistically higher compared to both the FBX 40 mg ($p < 0.001$) and allopurinol treatment groups ($p < 0.001$).

However, a statistically higher percentage of patients in each of the FBX treatment groups required treatment for a gout flare during the 6 month study (31.3% [237/757] for the FBX 40 mg group, and 31.1% [235/756] for the FBX 80 mg arm) compared to 24.6% (186/755) of subjects in the allopurinol arm.

The long-term, open-label extension studies (TMX-##-005 and C##-021) allowed participants who completed the forerunner studies to continue to receive FBX (as per the double blind period) or be switched to FBX from allopurinol. Most of the treatment switch patients (for example 67.1% [55/82] of subjects in Study C##-021) achieved an improvement in their serum urate levels similar to that for the subjects initially treated with FBX, while many of those who continued to take FBX maintained their response (71 to 80% at a further 6 months of follow-up in Study C##-021). In Study TMX-##-005, the ability of FBX to effectively lower and maintain a serum urate level of < 6.0 mg/dL was demonstrated in 77.9% (63/80) of subjects at 1 year, 77% (54/70) of patients at 2 years, 84% (54/64) of subjects at 3 years and 90% (52/58) of subjects at 4 years. The majority of subjects who continued long-term FBX treatment were taking 80 mg/day. After the first year of FBX treatment in Study TMX-##-005, less than 10% of all subjects received treatment for a gout flare. The overall incidence of gout flares gradually declined over 5 years with continued FBX treatment, with the greatest reduction noted in the patient group receiving 80 mg/day.

Study TMX-##-004 was a Phase II, dose-finding trial, which informed the selection of FBX doses (80 and 120 mg once daily) chosen for examination in the 2 pivotal Phase III studies (C##-009 and C##-010). After 28 days of treatment, the mean percentage reduction in serum urate level (by enzymatic method) was 2.15% for placebo, 36.6% for FBX 40 mg/day, 44.3% for FBX 80 mg/day and 59.1% for FBX 120 mg/day. In addition, the proportion of hyperuricaemic patients achieving a serum urate level of < 6.0 mg/dL (by enzymatic method) in Study TMX-##-004 was greater in each of the FBX treatment groups (55.9% [19/34] in those treated with FBX 40 mg/day, 75.7% [28/37] for FBX 80 mg/day

and 94.1% [32/34] for patients receiving FBX 120 mg/day) compared to zero patients who received placebo therapy.

In summary, the data in this submission supports the efficacy of FBX in treating adult patients with hyperuricaemia and gout, particularly with respect to the proportion of patients able to achieve a clinically significant reduction in their serum urate level (< 6.0 mg/dL). The 2 pivotal Phase III studies, as well as an additional Phase III trial (F-GT##-153) have adequately assessed the dose of FBX to be used in clinical practice (40 to 120 mg once daily) over an appropriate time frame of follow-up (26 to 52 weeks) and compared the relative effect of FBX to alternative treatment approaches such as allopurinol and placebo. The long-term, open-label experience provides sufficient information on the durability of response for up to 5 years of FBX treatment.

Safety

Studies providing safety data

The submission contained the following studies with safety data:

- 2 pivotal efficacy/safety trials; Studies C##-009 and C##-010.
- 3 other efficacy/safety studies; one of which was a Phase III trial (Study F-GT##-153), and the other 2 trials were long-term open-label extension studies (TMX-##-005 and C##-021).

Patient exposure

A total of 4072 subjects received at least 1 dose of FBX in the Phase I, II and III clinical studies with the mean duration of FBX dosing being 362 days. Across the Phase I, II and III studies, a total of 2468 subjects were exposed to FBX 80 mg once daily and 1079 subjects were exposed to FBX 120 mg once daily, which are the requested doses in this submission. The duration of dosing (mean + range) in the FBX 80 mg/day treated subjects was 187 (1 to 1274) days and for the patients who received 120 mg/day was 201 (1 to 1675) days.

In the Phase I studies, 811 otherwise healthy subjects received at least 1 dose of FBX (ranging from 10 to 300 mg daily) and 489 of these subjects received FBX for at least 7 days duration.

In the Phase III trials, the overall exposure to study medication was comparable in the FBX 80 mg/day (n = 1279 subjects treated for a mean duration of 184 days) and allopurinol treatment groups (n = 1277 patients treated for a mean duration of 192 days); but lower than in the FBX 120 mg/day (n = 520 patients treated for a mean duration of 214 days). The FBX 240 mg/day (n = 134 subjects treated for a mean duration of 147 days) and placebo arms (n = 134 subjects treated for a mean duration of 163 days) had much lower overall exposure than the 3 preceding active treatment groups as both of those treatment strategies were not included in the 52 week Study C##-010. The exposure to FBX 80 mg and 120 mg once daily in the studies supporting this application exceeds the minimum exposure recommendations provided in the International Conference on Harmonisation (ICH) E1A for the safety evaluation of drugs intended for long-term treatment¹⁵.

In the long-term OLE studies (C##-021 and TMX-##-005) a total of 1143 subjects have received at least 1 dose of FBX for a mean exposure period of 850 days (representing 2661 PY of exposure), which is a much greater exposure than for subjects treated with allopurinol (178 subjects treated for an average of 353 days). This imbalance is primarily a result of study design whereby switching between treatment groups (mainly from

¹⁵ ICH Guideline for Industry: The extent of population exposure to assess clinical safety: For drugs intended for long-term treatment of non-life-threatening conditions.

allopurinol to FBX) was allowed based on satisfactory therapeutic response. In terms of the FBX exposure in the long-term OLE trials by dose: 917 patients took 80 mg/day for a mean of 695 days (1746 PY of exposure), 524 subjects took 120 mg/day for a mean of 612 days (878 PY of exposure) and 12 patients took 40 mg/day for a mean of 1146 days (38 PY of exposure). In total, 909 subjects (579 on 80 mg, 315 on 120 mg and 8 on 40 mg/day) have taken FBX continuously for > 12 months on the OLE trials, 55 of whom (39 on 80 mg, 10 on 120 mg and 6 on 40 mg/day) have taken therapy for > 60 months. In the allopurinol treated patients, 56 of the original 178 cohort (71.8%) took treatment for > 12 months but no subjects continuously took therapy beyond 42 months of follow-up in the OLE studies.

Safety issues with the potential for major regulatory impact

Hepatic toxicity, serious skin reactions and cardiovascular safety have been discussed earlier in this report.

Postmarketing data

The postmarketing experience includes available information as of the eighth Periodic Safety Update Report (PSUR dated June 8, 2012), which contains data with a time lock point of April 20, 2012. The estimated cumulative postmarketing exposure to FBX worldwide (21 April 2008 to 20 April 2012) is 592,238 PY, of which approximately half has occurred in the European Union (EU), 1/3 in North America and 1/6 in Asia. This estimation is based on the drug transfer data between manufacturers and wholesalers. The information will be presented according to identified and potential risks associated with FBX use.

Deaths

Excluding subjects involved in clinical trials, healthcare professionals have reported a total of 38 fatalities in the postmarketing phase. The System Organ Class (SOC) of cardiac disorders is the most common fatal event, including 11 case reports of myocardial infarction. In 8 patients, the exact cause of death was not reported. In the eighth PSUR, there was a fatal case relating to liver disease in a patient taking FBX who had a history of advanced alcoholic cirrhosis.

Cardiovascular events

A total of 125 cardiovascular (CVS) events have been reported in 111 patients in the postmarketing experience and 58 of these CVS events (reported by 50 patients) met the criteria for serious. The postmarketing database contains 32 cases of myocardial infarction. The majority of cases were male, with ages ranging from 35 to 91 years. More than 65% of affected patients reported either previous history of cardiovascular disease or significant risk factors for coronary atherosclerosis (for example diabetes or hyperlipidaemia). In the cases whereby latency between commencement of FBX and the onset of CVS adverse event (AE) was documented (23 of 32 reports), this ranged from 11 days to 9 months, with an average duration of approximately 2 months. Other types of CVS AEs included heart failure (n = 24), stroke and cerebral haemorrhage (n = 18), syncope (n = 15), venous thromboembolism (n = 12) and various types of clinically significant cardiac arrhythmias (n = 10).

Serious skin or hypersensitivity reactions

A total of 675 patients with 785 rash or hypersensitivity reactions have been reported in the postmarketing database over the 4 years dating from 21 April 2008 until 20 April 2012. Of these cases, 109 AEs were rated as serious (that is 13.9% of all rash/hypersensitivity cases were serious). Consistent with the overall treated population, the majority of affected patients were male. The dose of FBX therapy was reported in approximately 70% of cases reports, 40% of which were receiving 40 mg/day, 40% were

taking 80 mg/day, 3% were receiving 120 mg/day and the remainder were taking FBX 10 to 20 mg/day. The most frequent reported individual types of rash or hypersensitivity AE collected during the postmarketing surveillance were eruptions and exanthems (n = 298), pruritus (n = 96), oedema (n = 51) and urticaria (n = 37). No deaths were related to serious skin or hypersensitivity reactions but there are reports of angioedema, anaphylactic shock, leucocytoclastic vasculitis, Stevens-Johnson Syndrome, DRESS and skin necrosis. Most of the postmarketing reports of skin reactions occurred during the first month of FBX therapy, and many of the affected patients reported previous hypersensitivity to allopurinol.

Hepatic effects

Cumulatively, there have been 56 serious AEs involving hepatic effects, classified as either abnormal hepatic investigations (70%) and/or hepatobiliary disorders (30%). Most of the reports relating to abnormal hepatic investigations are classified under a general terminology of increased hepatic enzyme but the most common individual pattern of abnormal liver function tests is elevation in serum transaminases and/or accompanied by increases in serum bilirubin or GGT. The time to event onset ranges from 1 day to 1 year with no particular pattern of latency (that is abnormal liver function tests occur at a similar frequency following drug exposure for periods of up to 300 days). One case of liver disorder was associated with a fatal outcome in a patient with preexisting advanced alcoholic cirrhosis. Another significant reported case involved a patient who developed an elevation of alanine aminotransferase (ALT) to 4485 IU/L and aspartate aminotransferase (AST) to 6825 IU/L 38 days following commencement of FBX. The event resolved 2 days after ceasing treatment. In the postmarketing database, the dose of FBX is not routinely reported but when available does not indicate a higher incidence of abnormal liver function tests in the daily dose range of 40-120 mg.

Renal effects

A total of 234 cases with renal AEs are reported in the postmarketing database, 97 of which were regarded as serious (41.4% of all reports). This includes 1 fatal case with 'renal failure' as the primary cause of death. The serious AEs include azotaemia, renal failure, fluid overload and tubulointerstitial nephritis. Tubulointerstitial nephritis has been proposed for addition to the US label under Immune system disorders SOC. In addition, there have been 13 cases of rhabdomyolysis, 12 of which were considered serious. Seven of the 13 cases were receiving concomitant colchicine and/or a statin drug; and 6 of the 13 patients had a history of renal disease.

Neurological effects

A total of 179 cases (43 rated as serious) of neurological side-effects have been reported in the postmarketing database. The serious AEs include convulsion, encephalopathy, gait disturbance, Guillain-Barre syndrome, loss of consciousness, mental disorder, altered mood, poor quality sleep, syncope and pre-syncope, psychotic behaviour and violence related symptoms. Psychotic behaviour including aggressive thoughts has been inserted into the US label as a potential risk but the observation is not considered to be causal.

Bleeding and haematological effects

A total of 91 cases with significant haematological abnormalities have been recorded in the postmarketing database. Of these, 33 patients reported 40 serious events. The haematological reports include 18 cases of thrombocytopenia (9 serious), 11 cases of pancytopenia (2 subjects received concomitant therapy with azathioprine), 10 reports of anaemia and 2 additional cases of haemolytic anaemia.

Seven cases report bleeding (for example epistaxis, cutaneous haemorrhage and haematuria), all of which were rated as non-serious. Two of the patients were taking concurrent anticoagulant therapy. Latency ranged from 7 to 14 days. Cumulatively, there

have also been 10 reports (5 serious) of increased INR. Oral anticoagulants were being taken by 9 of these affected patients and 3 were also receiving concomitant colchicine as co-suspect medication.

Thyroid effects

Cumulatively, there have been 4 non-serious reports of increased serum thyroid stimulating hormone (TSH) and 1 non-serious report of thyroiditis (outcome unknown).

Drug interactions

A total of 32 potential drug interactions have been reported with FBX in the postmarketing period including 11 reports of azathioprine co-prescription resulting in significant haematological toxicity (various types of cytopenia, usually serious), 9 reports of concomitant vitamin K antagonist therapy resulting in increased INR (2 with bleeding) and 2 reports of concurrent simvastatin therapy associated with rhabdomyolysis. The remainder of the drug interaction reports are single cases of limited clinical relevance apart from 1 report. A patient taking tacrolimus following renal transplant was reported to have developed a serious increase in tacrolimus levels 2 weeks after starting FBX 40 mg/day. FBX was discontinued for 1 week and the patient's tacrolimus level returned to normal. FBX was re-introduced at a dose of 20 mg/day without recurrence of increased blood tacrolimus levels.

Evaluator's conclusions on safety

The total clinical safety dataset from the Phase I, II and III studies consists of 4072 patients in 31 studies of which 2468 subjects were exposed to FBX 80 mg once daily and 1079 subjects were exposed to FBX 120 mg once daily, which are the requested doses in this submission. Across the Phase I, II and III studies, the duration of dosing (mean + range) in the FBX 80 mg/day treated subjects was 187 (1 to 1274) days and for the patients who received 120 mg/day was 201 (1 to 1675) days. In the long-term OLE studies (C##-021 and TMX-##-005) a total of 1143 subjects have received at least 1 dose of FBX for a mean exposure period of 850 days (representing 2661 PY of exposure), including 917 patients taking FBX 80 mg/day for a mean of 695 days (1746 PY of exposure), 524 subjects taking FBX 120 mg/day for a mean of 612 days (878 PY of exposure) and 12 patients taking FBX 40 mg/day for a mean of 1146 days (38 PY of exposure). In addition, to the clinical trial experience, there is an estimated postmarketing exposure to FBX worldwide (21 April 2008 to 20 April 2012) of 592,238 PY, of which approximately half has occurred in the EU, 1/3 in North America and 1/6 in Asia. The current safety dataset provides sufficient information about the short-term risk with FBX in the target population (such as discontinuations due to AEs, abnormalities of liver functions tests, and skin reactions), as well as potential long-term risks such as cardiovascular safety.

In general, the study populations had baseline characteristics, disease activity and concomitant medications indicative of the intended target population for the claimed indication. The majority of subjects in the Phase II and III studies were male (> 90%), Caucasian (76-87%) and middle-aged (56-59% were between the ages of 45 and 65 years). In the pivotal Phase III trials, approximately 14% of all recruited patients were aged > 65 years but the majority of these subjects were < 75 years of age, indicating limited exposure to FBX for patients > 75 years (< 4% of all subjects). The pivotal studies included patients with common medical co-morbidities such as known atherosclerotic disease (13%), hypertension (46%), diabetes mellitus (8%) and hyperlipidaemia (33%). However, few subjects (2%) had cardiac failure at entry, which is more frequent co-morbidity in clinical practice. In addition, there is no or very limited experience in certain patient subgroups of relevance including subjects in whom the rate of urate formation is greatly increased (in particular, those with underlying malignancy), organ transplantation patients, and those with severe renal or hepatic impairment.

The key safety conclusions identified in the 3 Phase III trials are as follows:

- The overall incidence of AEs was similar in the FBX (doses ranging from 40 to 240 mg/day), placebo and allopurinol treatment groups.
- However, the incidence of non-infective diarrhoea was higher in patients who received FBX 240 mg/day compared with all other treatment groups (Study C##-009).
- The most frequent types of AEs in all active treatment groups (all doses of FBX, and allopurinol 100 to 300 mg/day) were upper respiratory tract infections, musculoskeletal pain, joint related symptoms, non-infective diarrhoea, headache, abnormal liver function tests and nausea.
- Overall treatment related AEs were similar between all active treatment groups and placebo, apart from a higher incidence of treatment related AEs being observed in the FBX 240 mg/day arm of Study C##-009, which was primarily accounted for by a greater number of diarrhoea, nausea, gastrointestinal pain and headache AEs.
- In both the FBX and allopurinol treatment groups versus placebo arm in Study C##-009, there was a numerically higher incidence of treatment related, abnormal liver function tests (2-3% for all active treatment groups versus < 1% for placebo).
- Permanent discontinuations from study medication because of AEs were similar in frequency among the active treatment groups (5-8% at 6 to 12 months) and the main AE related reasons for withdrawal were diarrhoea, abnormal liver function tests and skin rashes.
- At 6 to 12 months of follow-up, the overall incidence of SAEs was low (< 4%; or < 0.3 per 100 PY) and similar in frequency between the active treatment groups, with the most frequent type of SAE being various types of adverse cardiovascular events.

The Phase III studies were unable to clearly identify a subset of patients at the highest risk of AEs from FBX. In particular, older patients (aged > 65 years) and those with renal impairment did not experience a higher overall rate or particular type of AEs. Study F-GT##-153 revealed a slightly higher incidence of abnormal liver function tests in those taking naproxen versus colchicine for gout flare prophylaxis (regardless of whether FBX or allopurinol was used as ULT).

In the long-term OLE studies, the incidence of treatment emergent and treatment related AEs (overall, and for each type of frequent or special interest AE) was lower compared to the controlled trial experience. In the Phase II, dose-finding study (TMX-##-004) of 28 days duration, patients who received FBX (40-120 mg/day) versus placebo experienced more diarrhoea and abnormalities of liver function tests.

There is an association between patients with hyperuricaemia and gout, and a greater risk of cardiovascular disease. Study F-GT##-153 specifically examined the rate of adverse cardiovascular outcomes over 6 months of follow-up in patients receiving FBX 40 or 80 mg/day versus allopurinol, as the 2 preceding Phase III studies (C##-009 and C##-010) observed a higher incidence of CVS related AEs in the FBX treatment groups compared to allopurinol and placebo. In particular, the proportion of subjects with primary Antiplatelet Trialists' Collaboration (APTC) events in the 2 pivotal Phase III studies (C##-009 and C##-010) were numerically higher in the FBX 80 mg (0.8%; 4/523) and FBX 120 mg (1.0%; 5/520) groups compared to the allopurinol treated cohorts (0.2%; 1/521) but this observation did not reach statistical significance. In Study F-GT##-153, at least 1 cardiovascular AE was reported by the site investigators in 5.2% (39/757) of subjects in the FBX 40 mg group, 5.4% (41/756) of patients in the FBX 80 mg group, and 5.8% (44/756) of subjects in the allopurinol group. There was no difference between the treatments groups in any specific type of cardiovascular AE detected. Pre-specified adjudication of all deaths and cardiovascular AEs identified 6 subjects experiencing an

adjudicated APTC event: 3 in the FBX 80 mg group (rate 0.40; 95% CI 0.082, 1.155) and 3 in the allopurinol group (rate 0.40; 95% CI 0.082, 1.155). In addition, a total of 26 patients suffered non-APTC cardiovascular events: 10 in the FBX 40 mg group (rate 1.32; 95% CI 0.635, 2.416), 9 in the FBX 80 mg arm (rate 1.19; 95% CI 0.546, 2.248) and 7 in the allopurinol group (rate 0.93; 95% CI 0.373, 1.898). No statistically significant difference in the overall rates of adjudicated non-APTC cardiovascular events between the treatment groups was concluded.

Death has been reported in 14 subjects exposed to FBX (8 receiving 80 mg/day, 5 taking 120 mg/day and 1 receiving 40 mg/day) in the Phase III and long-term OLE studies (6 patients in the controlled trials, and 8 in OLE studies). At least 4 of the deaths were related to myocardial infarction and another 2 suffered cardiac failure. In the postmarketing period, a total of 38 deaths have been recorded; 11 of which are attributable to myocardial infarction. However, the mortality rates and types of deaths observed in the clinical studies and postmarketing database is consistent with those expected in the target population. A total of 6 malignancies were recorded in the 3 Phase III studies and there were a few deaths related to sepsis. Again, this result is within expectations for the target population.

Rash and hypersensitivity reactions are an AE of special interest in drugs with an effect on XO (FBX and allopurinol). In Study C##-009, the incidence of rash AEs was similar in the placebo (2%), all FBX treatment groups (2 to 3%) and allopurinol treatment groups (2%). However, in Study C##-010 7.6-10.9% of subjects in all 3 treatment groups (FBX 80 and 120 mg/day, and allopurinol) reported at least 1 rash AE. In Study TMX-##-004, 8.7% (10/115) of subjects treated with FBX developed rash or allergy related AEs, including 1 subject who experienced angioedema of the upper lip and prematurely discontinued from the study. Overall, the majority of rash AEs observed in the clinical trials resolve while continuing treatment and were graded as either mild or moderate in severity. The risk of skin or hypersensitivity reaction does not appear to be related to FBX dose. No deaths related to serious skin or hypersensitivity reactions have been reported in either the clinical trials or postmarketing database but there are reports of serious and major reactions (such as angioedema, Stevens-Johnson Syndrome and skin necrosis). Most of the postmarketing reports of skin reactions occurred during the first month of FBX therapy, and many of the affected patients reported previous hypersensitivity to allopurinol indicating a general predisposition to allergic reactions.

In the 3 Phase III studies, a higher frequency of abnormal liver function tests (mainly, elevated serum transaminases and/or minor increases in bilirubin) was observed in all of the active treatment groups (3 to 5% in FBX and allopurinol treatment groups) versus placebo (< 1%). The incidence of abnormal liver function tests did not increase with time in the long-term trials. Study F-GT##-153 suggested that when NSAID was used for gout flare prophylaxis (versus colchicine) there was a slightly higher incidence of abnormal liver function tests. The majority of patients who developed elevations in liver function tests were regular consumers of alcohol, had body mass index (BMI) > 30 kg/m² or had additional hepatic risk factors (such as pre-existing hepatic steatosis). Nonetheless, there have been postmarketing reports of severe hepatic reactions in association with FBX therapy, including fatality. The risk of abnormal liver function tests is not related to FBX dose.

The safety dataset also reveals a low incidence of renal and haematological (including bleeding) AEs. Although the nonclinical studies raised the possibility of abnormalities of thyroid function, the clinical trial dataset did not reveal any significant pattern of thyroid dysfunction in association with FBX use in humans. When FBX is administered at doses of 40 to 240 mg/day, no clinically relevant effects upon resting 12-lead electrocardiograms (ECGs) and vital signs is observed. As demonstrated in the postmarketing experience there

is a low but serious risk of major toxicity (haematological) when FBX is co-prescribed with azathioprine.

In summary, the safety data indicates that FBX has an acceptable and comparable safety profile to the current standard of care (allopurinol) in patients with hyperuricaemia and gout. There are some significant associated safety concerns including the risk of liver function test abnormalities, skin and hypersensitivity reactions, and major adverse cardiovascular events. If approval were granted for FBX in the management of hyperuricaemia in patients with gout, ongoing pharmacovigilance for the above types of AEs (as well as all-cause mortality, renal effects and potential drug interactions) would be advised.

First round benefit-risk assessment

First round assessment of benefits

The benefits of FBX in the proposed usage are:

- Higher proportion of subjects treated with FBX 80 and 120 mg/day achieving a desirable target serum urate level of < 6.0 mg/dL after 26 to 52 weeks of treatment compared to placebo and allopurinol.
- Study F-GT##-153 demonstrates that FBX 80 mg/day is more efficacious than dose adjusted allopurinol in lowering serum urate levels to < 6.0 mg/dL in those with mild or moderate renal impairment.
- Long-term, open-label studies (TMX-##-005 and C##-021) support the maintenance of treatment effect with FBX for up to 5 years of therapy.
- Availability of an alternative urate lowering therapy in a patient group that is relatively common and with an unmet need for additional effective therapies.

First round assessment of risks

The risks of FBX in the proposed usage are:

- Risk of non-infective diarrhoea, headache and nausea
- Possible increased rate of thromboembolic cardiovascular events (versus allopurinol in the 2 pivotal Phase III studies, but similar in a 3rd and subsequent Phase III study),
- Increased risk of skin and hypersensitivity reactions (versus placebo; but similar incidence to allopurinol),
- Increased risk of abnormal liver function tests (versus placebo; but similar incidence to allopurinol).
- Potential for serious drug interaction if co-prescribed with azathioprine and increased INR vigilance when added to vitamin K antagonist treatment,
- Risk of gout flares, particularly during the initiation of therapy, and the need for the co-prescription of gout prophylaxis treatment (either NSAID or colchicine) for 6 months after the initiation of FBX, and
- Insufficient information in certain patient subgroups such as those who have high rates of urate production, organ transplantation and patients with severe renal or hepatic impairment.

First round assessment of benefit-risk balance

The overall benefit-risk balance of FBX, given the proposed usage, is favourable. The current submission has provided robust evidence that FBX therapy in patients with hyperuricaemia and gout results in a clinically meaningful effect in the appropriate disease related outcomes (for example significant lowering of serum urate levels) at an acceptable risk profile (short and long-term). There is a substantial unmet need for additional urate lowering drug therapies in patients with hyperuricaemia and gout. The benefits of FBX therapy for the claimed indication are statistically significant and also of clinical relevance and magnitude. The current dataset for use of FBX in patients with hyperuricaemia and gout is extensive and has been replicated in several well conducted clinical studies in the target population. There are some significant potential risks associated with FBX therapy, including abnormal liver function tests, a possible association with major adverse cardiac events and severe skin and hypersensitivity reactions. The population assessed in the Phase II and III study program had external validity to the needed patient groups in Australian clinical practice. On balance, the known and potential benefits of FBX therapy outweigh the currently identified risks when used appropriately in the target population.

First round recommendation regarding authorisation

This evaluator would recommend acceptance of the sponsor's proposed registration of FBX for the indication of treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation). Consistent with the approved EU posology, the evaluator would recommend the sponsor proposed dose of FBX to be 80 mg taken once daily, with or without food. If the serum uric acid is > 6 mg/dL (357 µmol/L) after 2 to 4 weeks, FBX 120 mg once daily may be considered. No dose adjustment is recommended in patients with mild or moderate renal insufficiency, mild hepatic impairment or in the elderly. Gout flare prophylaxis of at least 6 months is recommended.

Clinical questions

Pharmacokinetics

Question one:

Could the sponsor provide information demonstrating that the proposed commercial presentation of FBX has been optimally formulated? In particular, has the bioavailability of the proposed FBX formulation been compared relative to an oral solution? This is a TGA recommendation for licensing of new immediate release oral dose forms.

Question two:

Could the sponsor provide the final study report with results of Study TMX-##-103, which was a Phase I crossover trial, which examined the effect of multiple doses of FBX on the pharmacokinetics of a single oral dose of rosiglitazone and its metabolite? Only the protocol of Study TMX-##-103 was provided.

Pharmacodynamics

Question three:

Could the sponsor elaborate on the possible reasons for moderate inter-individual variability for the relationship between the concentration of FBX at steady state and 50% decrease in serum urate concentrations from baseline?

Question four:

Could the sponsor provide information and comment on whether it is anticipated that FBX may have a potential pharmacodynamic interaction (increased bleeding risk) with new oral anticoagulants, in particular rivaroxaban, dabigatrin and apixaban?

Safety**Question five:**

In Study F-GT##-153, concomitant clopidogrel therapy was an exclusion criterion at baseline. The sponsor should be asked to clarify if anti-platelet drugs (other than low dose aspirin) were an exclusion criterion for the 2 other Phase III Studies (C##-009 and C##-010). In addition, does the exclusion of patients taking concurrent clopidogrel limit the external validity of the study's findings?

Second round evaluation of clinical data submitted in response to questions

The sponsor's responses to the *Clinical questions* and the evaluator's review of these responses are provided in Attachment 2 of this AusPAR.

Second round benefit-risk assessment**Second round assessment of benefits**

No new clinical information regarding efficacy and benefits was requested by the evaluator or provided by the sponsor in the second round evaluation. Accordingly, the benefits of FBX are unchanged from those identified in the first round.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of FBX in the proposed usage are unchanged from those identified in the first round.

Second round assessment of benefit-risk balance

The benefit-risk balance of FBX, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

This evaluator would recommend acceptance of the sponsor's proposed registration of FBX for the indication of treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation). The clinical evaluator would also recommend acceptance of the sponsor proposed posology of FBX 80 mg daily (with or without food), and if the serum uric acid remains > 6 mg/dL (357 µmol/L) after 2 to 4 weeks of therapy, then the daily dose of FBX may be increased to 120 mg. In addition, gout flare prophylaxis for at least 6 months is recommended.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU RMP, version 3.3, dated 1 June 2012, data lock point 20 October 2012 and an Australian Specific Annex (ASA) to the EU RMP

version 3.3, dated December 2012 which were reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the nonclinical and clinical aspects of the Safety Specification (SS) by the TGA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Table 5. Summary of ongoing safety concerns

Important identified risks:	• Serious skin / hypersensitivity reactions
Important potential risks:	• Cardiovascular effects • Hepatic effects • Renal effects • Neurological effects (including psychiatric effects) • Haematological effects • Thyroid effects
Important missing information:	No experience in: • Children and adolescents • Subjects in whom the rate of serum urate formation is greatly increased (eg. malignant disease and its treatment, Lesch-Nyhan syndrome) • Organ transplantation • Severe hepatic impairment • Pregnancy and lactation Limited experience in: • Female patients • Elderly patients • Severe renal impairment • Moderate hepatic impairment

The sponsor states 'As stated in Sect 1.5.2.7, based on final safety results from combined Phase III and LTE studies and available postmarketing experience, thyroid effects are no longer considered as a potential risk. Based on final safety results from Phase III and postmarketing surveillance, FBX is no longer expected to pose a potential risk to thyroid.'

Contents of the RMP submission

Routine and additional pharmacovigilance activities are proposed by the sponsor for the important potential risk of cardiovascular effects. Routine pharmacovigilance and routine risk minimisation activities are proposed by the sponsor to address all other ongoing safety concerns.

The sponsor refers to a Direct Healthcare Professional Communication (DHPC) which has been implemented in Europe as additional routine pharmacovigilance activity. Of note a DHPC is considered risk minimisation and therefore, will be further discussed in the risk minimisation plan. The sponsor does not specify in the ASA if this DHPC will be implemented in Australia and recommendations to amend the ASA to include this detail have been made the TGA evaluator. The DHPC has not been included in the submission.

A post marketing safety study (PASS) is proposed to monitor the important potential risk of cardiovascular events. The provided study synopsis for the PASS specifies a study starting date of 1 January 2012 and an enrolment completion date of 31 March 2013. No interim results of data collected during this study were provided with the evaluated RMP. Recommendations to provide interim results are by the TGA evaluator. Moreover, the ASA does not refer to the post marketing study and recommendations to amend the ASA to refer to this detail were also made by the TAB evaluator.

The provided EU RMP was not considered to be of a satisfactory standard (see Table 6 *Reconciliation of issues outlined in the RMP report* below for details).

Reconciliation of issues outlined in the RMP report

Table 6 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's comments on the sponsor's responses.

Table 6. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Extracts of sponsor's response	OPR evaluator's comment
It is recommended that the sponsor amends the EU RMP to correct the following shortcomings. Links to tables listed in the table of content are linked to the wrong sections in the document. Tables are numbered out of order. A tabular summary of risk minimisation activities is not provided in section 3.1 as per EU RMP guidelines, Reference is made to a section which is not included in the RMP.	The sponsor acknowledges the evaluator's request. At this time, version 3.3 cannot be updated as it is approved by the EMA, however these comments are noted for future versions of the RMP.	The sponsor's response has been noted. However, content of section 3.1 is required for a RMP evaluation. Consequently, it is recommended that the sponsor submits a summary table as attachment to the ASA, detailing how risk minimisation is carried out in Australia. In particular wording should be provided pertaining to routine risk minimisation in the Australian PI/CMI.
It is recommended that the sponsor revises the ASA to include the implementation of the appropriate regulatory guidelines: Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines (Version 1.1, December 2012) and any future updates of these guidelines.	The Australian Specific Annex has been updated to include the Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines (Version 1.2, August 2013). Please refer to section 2 Pharmacovigilance practice which has been updated in line with this request.	This is considered acceptable.

Recommendation in RMP evaluation report	Extracts of sponsor's response	OPR evaluator's comment
The final study protocol for the post marketing safety study to monitor cardiovascular effects has not been provided, and it is recommended that the sponsor provides this to the TGA. In addition, this study should be referenced in the ASA in section "Studies referenced in the RMP".	Please find enclosed in Attachment 1 to the ASA the final protocol for the post marketing safety study (PASS) for the FAST study. In addition, the study details have been included in the ASA in the section "Studies referenced in the RMP" as requested.	This is considered acceptable.
It is recommended that the sponsor submits interim results of the PASS for review, and that future study reports are submitted to the TGA at the same time as reports are submitted to other regulatory agencies.	Please find enclosed the interim results of the PASS, known as the FAST study, in Attachment 2 of the ASA. In addition, the sponsor give the commitment that future study reports are submitted to the TGA at the same time as reports are submitted to other regulatory agencies.	The interim results have been reviewed by the RMP evaluator and there appears to be no safety concern. However, the RMP evaluator would like to draw the Delegate's attention to the availability of these interim results for review by the clinical evaluation unit.
It is recommended that the sponsor clarifies whether the DHPC will be implemented in Australia. Moreover, it is recommended that the sponsor amends the ASA to clarify this point and provides the DHPC for review.	The DHCP letter was requested by the CHMP in Europe as part of a response to review of the EU RMP version 3.2 (previous version) and Periodic Safety Update Report (PSUR) #7 submitted to the EMA on 20 December 2011. Review of the PSUR and EU RMP resulted in an upgraded risk profile of 'potential risk' to an 'identified risk' for serious skin and hypersensitivity and allergic reactions. The CHMP requested the Marketing Authorisation Holder (MAH) to communicate the changed safety profile of the medicinal product to Healthcare professionals. In addition, information was included in the Summary of Product Characteristics (SmPC). As the precautionary information is already included in the Australian PI and will be available upon approval, the	This is considered acceptable. <i>The commitment "to include such precautionary information about serious skin and hypersensitivity and allergic reactions in external communication materials directed at Health Care Professionals such as sales aids and presentations about the use of FBX" is noted, and it is recommended this to be implemented as a condition of registration.</i>

Recommendation in RMP evaluation report	Extracts of sponsor's response	OPR evaluator's comment
	sponsor feels that it is not necessary to issue a DHCP letter upon approval of the product. The reason behind the DHCP letter in Europe was to inform Health Care Professionals of the change observed in adverse event profile post-marketing in Europe since the European approval. In Australia, as the product is not currently marketed, there is no recent change in the risk profile and hence no change to be communicated. As stated above, the approved PI will include this information about serious skin and hypersensitivity and allergic reactions. The sponsor can commit to including such precautionary information about serious skin and hypersensitivity and allergic reactions in external communication materials directed at Health Care Professionals such as sales aids and presentations about the use of FBX. Communication of the risk via these means will ensure that Health Care Professionals are aware of the possible risks to patients. As the PI clearly indicates, <i>"Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions"</i>.	
It is recommended that the sponsor amends the PI/CMI as recommended in section 10.1: It is recommended that the sponsor amends the PI to include routine risk minimisation for the missing information of	The company has already included information in the SmPC and also in the proposed Australian PI with regards to females and elderly, in line with the EU RMP. The sponsor does not propose to add any further information at this time and prefers to keep the SmPC	Limited information in female and elderly is listed as missing information in the table of ongoing safety concerns and therefore, it is considered not appropriate to make dose recommendations about these patient groups

Recommendation in RMP evaluation report	Extracts of sponsor's response	OPR evaluator's comment
females and elderly. It is recommended that the sponsor amends the PI to reflect that dose recommendations for females and elderly are based on missing information. It is recommended that any amendments to the PI will be reflected in the CMI as appropriate.	and the Australian PI consistent in relation to these aspects of the label.	without stating that these recommendations are based on limited experience. It is brought to the Delegate's attention that dose recommendations for females and elderly are based on limited information, without this being reflected in the currently proposed PI statements. It is recommended to the Delegate to evaluate the appropriateness of these statements and to consider amendments to the PI to address these points.

Summary of recommendations

It was considered that the sponsor's response has not adequately addressed all of the issues identified in the RMP evaluation report (see *Outstanding* issues below).

Outstanding issues

Issues in relation to the RMP

- The issues raised by the clinical and nonclinical evaluator should be addressed by the sponsor.
- It is recommended that the sponsor submits a summary table as attachment to the ASA, detailing how risk minimisation is carried out in Australia. In particular wording should be provided pertaining to routine risk minimisation in the Australian PI/CMI.
- The sponsor has submitted interim results of the PASS, known as the FAST study. The RMP evaluator would like to draw the Delegate's attention to the availability of these interim results for review by the clinical evaluation unit.
- It is brought to the Delegate's attention that dose recommendations for females and elderly are based on limited information, without this being reflected in the currently proposed PI statements. It is recommended to the Delegate to evaluate the appropriateness of these statements and to consider amendments to the PI to address these points.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA request for further information the sponsor provided an updated Australian Specific Annex to EU RMP version 3.3, dated 26 September 2013.

Minor changes were made by the sponsor as a consequence of recommendations made in the First Round RMP evaluation. The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented (see below).

Suggested wording for conditions of registration

RMP

- Implement EU RMP, version 3.3, dated 1 June 2012, data lock point 20 October 2012; Australian Specific Annex to EU-RMP version 3.3, dated September 2013, and any future updates as a condition of registration.
- Precautionary information about serious skin and hypersensitivity and allergic reactions should be included in external communication materials directed at Health Care Professionals such as sales aids and presentations about the use of FBX.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator has no objections to the registration of FBX.

FBX is manufactured by chemical synthesis into immediate release, unscored, film coated tablets using conventional manufacturing techniques. It has a shelf life of 36 months when stored below 30°C.

No absolute bioavailability study was provided which was considered acceptable by the quality and clinical evaluators. The submission included 9 biopharmaceutic studies. These showed a high fat meal reduced the peak and exposure of FBX by 38% and 16% respectively on average with bioequivalence not established between fed and fasted which was also seen in two other food effect studies. However one of the studies showed that this did not lead to a significant change in uric acid levels with similar levels observed in fed and fasted subjects. Therefore the dosing advice that FBX can be taken with or without food appears acceptable, which is also consistent with the advice in USA and Europe.

Nonclinical

The nonclinical evaluator has no objections to the registration of FBX.

FBX demonstrated in vitro and in vivo inhibition of xanthine oxidoreductase and decreased uric acid production which did not affect enzymes involved in purine metabolism and was 2 to 4 fold more potent than allopurinol at lowering uric acid. FBX did not affect thrombin or platelet activation or affect the action of heparin, warfarin or nifedipine. It had no significant effect in a potassium (hERG) channel assay, nor cardiac sodium or calcium currents. Transient decreases in blood pressure were seen in animals. Toxicity studies suggested a low to moderate level of acute toxicity with decreased locomotor activity at high doses, increased salivation, ptosis and irregular breathing. Major toxicities included xanthinuria and calculi deposits in urinary tissues, renal changes, thyroid changes, haematological changes and raised liver transaminases. FBX was not genotoxic overall although there were some chromosomal aberrations.

The carcinogenicity studies showed a significant increase in urinary bladder tumours associated with xanthine calculi at 8 to 17 times human exposure. This was thought to be due to the chronic irritation from xanthine calculi which form less readily in humans than in rodents and therefore is unlikely to be a clinically significant finding. There was no

effect on fertility or teratogenicity seen however exposure occurred from lactation that led to reduced development of offspring and therefore use during lactation is not recommended.

The recommended Pregnancy Category by the evaluator is B1.

Clinical

The clinical evaluator has recommended approval for FBX with a revised indication of '*treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation).*'

The clinical evaluator has recommended acceptance of the sponsor's dosage of 80 to 120 mg daily.

For details of the clinical data submitted see *Clinical findings, Scope of the dossier* above and Attachment 2 of this AusPAR.

Pharmacology

The pharmacology studies noted the following findings:

- T_{max} is 1 to 1.5 h; at least 84% is absorbed; the volume of distribution is about 0.7 L/kg; 98-99% of the drug is protein bound (mainly to albumin); $t_{1/2}$ is 5 to 8 hours; steady state is reached within 1 week.
- Low intra-subject and inter-subject variability in pharmacokinetics.
- A high fat meal reduced C_{max} by 38 to 49% and AUC by 16 to 19% and delayed T_{max} by up to 1 h.
- Evening dosing led to a slight decrease in C_{max} and delayed T_{max} compared to morning dosing but total exposure was similar.
- Linear pharmacokinetics was seen in the range 10 to 120 mg daily but not beyond 120 mg daily.
- Elimination is mainly by liver metabolism (mainly glucuronide conjugates) to inactive metabolites in the urine and to a lesser extent by CYP450 enzymes. Only 4% of unchanged drug is excreted in the urine.
- Renal impairment led to a 1.8 fold increase in exposure in the severe group compared to normal renal function but C_{max} and T_{max} remained similar.
- Hepatic impairment led to a 24 to 28% increase in exposure in mild to moderate groups compared to normal hepatic function and a 24% increase in C_{max} . There is no data in severe hepatic impairment.
- Age showed a 10% increase in exposure in those ≥ 65 years compared to younger and gender showed a 16% increase in exposure (33% increase in C_{max}) in females compared to males which appeared to be related to body weight.
- Population PK analyses indicated body weight, creatinine clearance, fibrate therapy and smoking status as affecting FBX clearance.
- Drug interaction studies showed that colchicine, indomethacin, hydrochlorothiazide, warfarin, CYP2D6 substrates (desipramine) do not have clinically significant effects on the pharmacokinetics of FBX. FBX did not have clinically significant effects on the pharmacokinetics of indomethacin, colchicine or warfarin (including pharmacodynamics). Naproxen led to a 41% increase in FBX, antacids delayed FBX absorption by 1 h. Theophylline's clearance and $t_{1/2}$ life were not affected by FBX.

- Urate concentration was reduced by 55 to 66% following 7 days of 80 to 120 mg daily which was unaffected by age or renal impairment but was greater in females than males and higher in normal hepatic function but the changes were small.
- Xanthine concentrations increased, especially in renal impairment, but were below the solubility limit in serum and unlikely to form crystals.
- Urinary excretion of uric acid decreased and xanthine excretion increased.
- No significant effects on cardiac repolarisation such as QT prolongation were seen in healthy subjects and patients with gout.
- A Phase II dose finding study indicated that serum urate levels were reduced by 37% on 40 mg daily, 44% on 80 mg daily and 59% on 120 mg daily after 28 days treatment.

Efficacy

Study C##-009

This was a Phase III, USA, multi-centre, randomised, double blind, placebo and allopurinol controlled, parallel group, superiority and non-inferiority study of 80, 120 and 240 mg daily FBX versus placebo and allopurinol 300 mg daily (100 mg daily if baseline serum creatinine 1.5 to 2 mg/dL) in 1072 subjects with hyperuricaemia (serum urate of $\geq$ 8mg/dL) and a history or presence of gout¹⁶ for 28 weeks. Patients were excluded if they had xanthinuria, secondary hyperuricaemia, alcohol abuse, taking concomitant treatments such as thiazides, oral prednisolone >10 mg/day or urate lowering therapy along with other conditions. Uricosuric drugs were ceased prior to the study and all subjects began prophylaxis with naproxen (40 to 49%) or colchicine (50 to 60%) for 8 weeks only. Acute gout attacks were treated with additional doses of naproxen or colchicine as needed. The 240 mg FBX group was mainly included for safety. Premature discontinuations occurred in 28% (mainly loss to follow up (24%), adverse events (23%), personal reasons (20%), other (12%) and gout flare (9% [9% on 120 mg, 14% on 80 mg and 0% on placebo])). Baseline demographic and disease characteristics were similar across the groups (94% male, mean 52 years, 15% $\geq$ 65 years, 62% body mass index $\geq$ 30, 66% alcohol use, 20% smokers, 47% hypertension, 33% hyperlipidaemia, mean serum urate at baseline 9.85 mg/dL, mean 10 years with gout, 89% had <1 year since last gout flare, 20% with a primary palpable tophus at screening) and concomitant medications were also comparable except low dose aspirin was higher in the placebo and 240 mg groups. The study had 95% power to detect a 45% difference between FBX and placebo and 80% power to determine non-inferiority with allopurinol. The study assessed superiority to

¹⁶Definition of gout: Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum.* 1977;20(3):895-900. TAP-0 1-1 01454. Subject had a history or presence of gout as defined below:

- the presence of characteristic urate crystals in the joint fluid and/or
- a tophus proven to contain urate crystals by chemical or polarized light microscopic means and/or
- the presence of at least 6 of the following clinical, laboratory, and x-ray phenomena:
 - more than 1 attack of acute arthritis
 - maximum inflammation developed within 1 day
 - monoarticular arthritis
 - redness observed over joints
 - first metatarsophalangeal joint painful or swollen
 - unilateral first metatarsophalangeal joint attack
 - unilateral tarsal joint attack
 - tophus (proven or suspected)
 - hyperuricemia
 - asymmetric swelling within a joint on x-ray
 - subcortical cysts without erosions on x-ray
 - joint fluid culture negative for organisms during attack

placebo first, then non-inferiority to allopurinol (if absolute value of the lower bound of the 97.5% confidence interval did not exceed 10%) and then superiority of FBX to allopurinol, providing each of the previous steps was statistically significant.

The primary efficacy endpoint of proportion of subjects whose last three serum urate levels were < 6 mg/dL in the Intent-to-Treat (ITT) analysis was:

- 0% placebo
- 48% on 80 mg FBX ($p \leq 0.05$ versus placebo, $p < 0.001$ versus allopurinol)
- 65% on 120 mg FBX ($p \leq 0.05$ versus placebo, $p < 0.001$ versus allopurinol)
- 69% on 240 mg FBX ($p \leq 0.05$ versus placebo)
- 22% on allopurinol ($p \leq 0.05$ versus placebo)

Each FBX dose and allopurinol were superior to placebo. Both 80 mg and 120 mg FBX were non-inferior and superior to allopurinol (80 mg: 26% difference, 97.5% CI 16.7-34.7%; 120 mg: 43% difference, 97.5% CI 34-51%). The 80 mg group was also statistically significantly different to the 120 mg and 240 mg dose groups but there was no significant difference between the 120 mg and 240 mg groups. A sensitivity analysis using prematurely discontinued subjects based on 1-2 serum urate levels indicated statistically significant superiority for the FBX groups compared to placebo and allopurinol. Subgroup analyses were supportive. Secondary efficacy endpoints were supportive for serum urate levels <6 mg/dL at each visit (seen from Week 2 onwards), serum urate levels <5 mg/dL at Week 28, serum urate levels <4 mg/dL at Week 28, percentage reduction in serum urate levels and most quality of life measurements. However there was no significant difference between any of the 5 treatment groups for the change in primary tophus size despite the tophus reducing in size in all groups, no significant difference between groups in the change in the number of tophi (except the 120 mg dose) and a significantly greater proportion of subjects on 120 mg (36%) and 240 mg (46%) requiring treatment for gout flares compared to placebo (20%), allopurinol (23%) and 80 mg (28%) during the first 8 weeks (after this there was no significant difference between the groups).

Study C##-010

This was a Phase III, North American, multi-centre, randomised, double blind, allopurinol controlled, parallel group, superiority and non-inferiority study of 80 and 120 mg daily FBX versus allopurinol 300 mg daily in 760 subjects with hyperuricaemia (serum urate of ≥ 8 mg/dL) and a history or presence of gout¹⁶ for 52 weeks. Patients were excluded as per the previous study. Uricosuric drugs were ceased prior to the study and all subjects began prophylaxis with naproxen (42-49%) or colchicine (50-58%) for 8 weeks. Acute gout attacks were treated with additional doses of naproxen or colchicine as needed. Premature discontinuations occurred in 33% (mainly loss to follow up (25%)), with discontinuations higher on 120 mg (39%) than 80 mg (34%) or allopurinol (26%), more discontinuing in the first 12 weeks on 120 mg (53%) compared to 80 mg (40%) and allopurinol (35%) and more discontinuing due to gout flares and adverse events on 120 mg (29% and 24% respectively) compared to 80 mg (11% and 18% respectively) and allopurinol (14% and 12% respectively). Baseline demographic and disease characteristics were similar across the groups (96% male, mean 52 years, 62% body mass index ≥ 30 , 66% alcohol use, 17% smokers, 44% hypertension, 34% hyperlipidaemia, mean serum urate at baseline 9.8 to 9.9 mg/dL, mean 12 years with gout, 87% had <1 year since last gout flare, 20% with a primary palpable tophus at screening). The study had 80% power to determine non-inferiority with allopurinol and 90% power to detect a 15% difference between FBX and allopurinol. The study assessed non-inferiority to allopurinol first (if absolute value of the lower bound of the 97.5% confidence interval did not exceed 10%) and then superiority of FBX to allopurinol, providing the previous step was statistically significant.

The primary efficacy endpoint of proportion of subjects whose last three serum urate levels were <6mg/dL in the ITT analysis was:

- 53% on 80 mg FBX ($p < 0.001$ versus allopurinol)
- 62% on 120 mg FBX ($p < 0.001$ versus allopurinol)
- 21% on allopurinol

Both 80 mg and 120 mg FBX were non-inferior and superior to allopurinol (80 mg: 32% difference, 97.5% CI 23.1-41.3%; 120 mg: 41% difference, 97.5% CI 31.5-49.5%). The 80 mg group was not statistically significantly different from the 120 mg group. Subgroup analyses were generally supportive. A sensitivity analysis using prematurely discontinued subjects based on 1 to 2 serum urate levels indicated statistically significant superiority for the FBX groups compared to allopurinol. Secondary efficacy endpoints were supportive for serum urate levels <6 mg/dL at each visit, serum urate levels <5 mg/dL at Weeks 28 and 52, serum urate levels <4 mg/dL at Weeks 28 and 52, percentage reduction in serum urate levels and most quality of life measurements. However there was no significant difference between any of the treatment groups for the change in primary tophus size at Week 52, despite the tophus reducing in size in all groups, no significant difference between groups in the change in the number of tophi at Weeks 28 and 52 and a significantly greater proportion of subjects on 120 mg (36%) requiring treatment for gout flares compared to allopurinol (21%) and 80 mg (22%) during the first 8 weeks (after this there was no significant difference between the groups to Week 52).

Studies TMX-##-004 and TMX-##-005

These were a Phase II dose response study for 4 weeks in 153 patients assessing placebo, 40 mg, 80 mg and 120 mg daily and its extension study up to 5 years (interim analysis provided). The primary efficacy results for serum urate <6 mg/dL at Day 28 was statistically significant on 40 mg (56%), 80 mg (76%) and 120 mg (94%) compared to placebo (0%). Gout flares were higher on the 120 mg dose (56%) compared to placebo (37%), 40 mg (35%) and 80 mg (41%). The extension study indicated a maintenance of serum urate to <6 mg/dL (84% at 3 years and 90% at 4 years) with the majority of patients taking the 80 mg dose and the incidence of gout flares declining over the 5 years.

Study C##-021

This was an open label extension study in 1086 subjects for 24 months who completed the two pivotal studies. Subjects could take 80 mg, 120 mg or allopurinol 300 mg (100 mg if serum creatinine was 1.5 to 2mg/dL). Subjects could switch treatment (5% did to allopurinol and 59% did to FBX) or increase their FBX dose if serum urate levels were >6 mg/dL during the first 6 months of treatment. Both FBX doses (70.8% on 80 mg and 82 % on 120 mg) maintained serum urate levels to <6 mg/dL at final visit. Gout flares at 6 months was 10.4% on 80 mg, 21.16% on 120 mg and 8.9% on allopurinol.

Study F-GT##-153

This was a Phase III, randomised, double blind, allopurinol controlled, superiority and non-inferiority study of 40 mg and 80 mg FBX versus 300 mg allopurinol (200 mg if CrCl 30-59 mL/min) in 2269 subjects with hyperuricaemia (serum urate $\geq$ 8 mg/dL) and gout¹⁶ for 6 months. At least 35% of patients were to have mild or moderate renal impairment. Due to a safety signal seen in the preceding Phase III studies of an higher incidence of cardiovascular events on FBX compared to allopurinol, the FDA requested this study be conducted to examine a 40 mg daily dose and the most common dose of 80 mg. Patients ceased urate lowering therapy and all commenced gout prophylaxis with naproxen (15%) or colchicine (80%). Premature discontinuations occurred in 18% (17% on 40 mg, 21% on 80 mg and 18% on allopurinol; mainly adverse events (7.7%), loss to follow up (3.9%); 29% discontinued during the first month). Baseline demographic and disease

characteristics were similar across the groups (94% male, mean 53 years, 64% body mass index ≥ 30 , 68% alcohol use, 18% smokers, 65% mild-moderate renal impairment, 53% hypertension, 42% hyperlipidaemia, 14% diabetes, mean serum urate at baseline 9.5 to 9.6 mg/dL, mean 12 years with gout, 54% had < 2 months since last gout flare). The study had 90% power to determine non-inferiority of 40 mg with allopurinol, 90% power to detect a 10% difference between 40 mg FBX and allopurinol and 90% power to detect a 10% difference between 40 mg and 80 mg. The study assessed non-inferiority of 40 mg to allopurinol first then superiority of 40 mg to allopurinol, providing the previous step was statistically significant.

The primary efficacy endpoint of proportion of subjects whose serum urate level at 6 months was < 6 mg/dL in the ITT analysis was:

- 45% on 40 mg FBX
- 67% on 80 mg FBX ($p \leq 0.05$ versus allopurinol and 40 mg FBX)
- 42% on allopurinol

FBX 40 mg was non-inferior to allopurinol but not superior. The 80 mg dose was superior to the 40 mg dose and allopurinol. Subgroup analyses were consistent with the overall analysis. Results by renal function showed a greater percentage of patients with serum urate < 6 mg/dL in those with mild and moderate impairment compared to normal renal function on FBX, with those with mild renal impairment having the greatest response. Secondary endpoints were supportive however treatment for gout flares was similar between the FBX groups (31% for both dose groups) but higher than for allopurinol (25%). This reduction in gout flares is thought to be due to continuation of gout flare prophylaxis for 6 months unlike the higher rates seen in the two pivotal studies which had prophylaxis for 8 weeks.

Safety

A total 4072 patients (2468 on 80 mg and 1079 on 120 mg) received at least one dose of FBX with 674 patients for ≥ 12 months on 80 mg and 437 patients for ≥ 12 months on 120 mg. TEAEs in the three pivotal studies occurred in NA/NA/57% on 40 mg, 68%/80%/54% on 80 mg, 68%/75%/NA on 120 mg, 73%/NA/NA on 240 mg, 75%/85%/57% on allopurinol and 73%/NA/NA on placebo. The most common TEAEs in the first pivotal study were mild to moderate and for placebo/80 mg/120 mg/allopurinol were: Upper respiratory tract infections (URTI) (16/15/19/19%), non-infective diarrhoea (8/6/7/6%), musculoskeletal pain (10/9/9/10%), joint related (5/6/9/7%), headache (5/5/5/7%), increased liver function tests (LFTs) (2/6/4/6%), influenza (4/4/5/4%), nausea and vomiting (4/4/4/2%) and hypertension (6/5/2/1%). Hypertension was significantly higher on 80 mg than allopurinol.

Skin rash was similar in the placebo, FBX and allopurinol groups. The second pivotal trial (80 mg/120 mg/allopurinol) showed higher event rates but a similar profile to the first trial except diarrhoea was higher on FBX than allopurinol (11/10/6%), nausea and vomiting (7/5/3%), oedema (7/3/3%) and neurological (7/4/3%). Hypertension was higher on allopurinol in this study (6%) than 80 mg (3%) or 120 mg (4%). Rash occurred in 11% of patients on 80 mg, 8% of patients on 120 mg and 10% of patients on allopurinol. The third Phase III trial showed similar rates of AEs amongst the 40 mg, 80 mg and allopurinol groups with URTI, LFT changes, diarrhoea, musculoskeletal symptoms being the most common. Rash occurred in 5.6-5.8% of patients on FBX compared to 7.3% of patients on allopurinol. Significantly more subjects had gastrointestinal upset, muscle symptoms and nasal congestion on allopurinol than 40 mg FBX whereas the opposite occurred for neurological events. The dose response study showed similar rates of AEs between the groups except for diarrhoea which was more common on 80 mg (20%) than

placebo (11%), 40 mg (3%) or 120 mg (11%) and one patient developed angioedema on 120 mg. The long term extension studies showed TEAEs were higher on 40 mg (92%), 80 mg (74%) and 120 mg (69%) than allopurinol (57%) but were closer when adjusted for exposure duration.

Adverse drug reactions were slightly higher on FBX than allopurinol in the two pivotal studies with the most common being diarrhoea, nausea, headache, abdominal pain, dizziness and abnormal LFTs. The 240 mg dose showed statistically significantly higher rates of diarrhoea, nausea, vomiting, gastrointestinal/abdominal pain and neurological signs and symptoms. The third Phase III study showed abnormal LFTs and diarrhoea were the most common reactions and that abnormal LFTs were higher in those on colchicine than naproxen. The long term studies showed abnormal LFTs, diarrhoea, raised renal function tests, hyperlipidaemia and nephrolithiasis were the most common.

Deaths occurred in no patients in the first pivotal trial, 4 patients in the second trial all on FBX but all considered unrelated and 5 patients in the third Phase III trial (3 on allopurinol and 2 on FBX) all considered unrelated. The long term studies had 8 deaths with all on FBX of which 4 were due to myocardial infarction, 1 congestive cardiac failure following myocardial infarction and 3 sepsis related.

Serious adverse events in the first study were considered unrelated except for one patient given 240 mg. Cardiovascular events were the most common serious adverse events (SAEs) in the first study and mostly occurred on FBX (3 chest pain, 3 coronary artery disease, 2 myocardial infarction, 2 atrial fibrillation) compared with one event on allopurinol of chest pain, with all subjects having underlying cardiovascular disease or risk factors. SAEs in the second pivotal trial were more mixed and all considered unlikely to be related (11 on 80 mg, 19 on 120 mg and 18 on allopurinol, excluding gout flares).

Cardiovascular events occurred in 4 patients on each FBX dose and 6 patients on allopurinol. In the third study, SAEs were more common on allopurinol than FBX. The long term studies had more SAEs on FBX (10.5%) than allopurinol (7.3%) which were lower on FBX when adjusted for exposure duration and the most common were coronary artery disease and lower respiratory tract infection. Discontinuations due to AEs were similar amongst the active treatment groups (5 to 8% at 6 to 12 months) with the main reasons being diarrhoea, abnormal liver function tests and skin rashes and during the long term studies, discontinuation due to AEs was higher on FBX than allopurinol and mainly due to abnormal liver function tests.

Laboratory tests showed liver function test abnormalities were seen on active treatment at 3-5% compared to placebo (<1%) but these didn't increase with time but appeared higher with non-steroidal anti-inflammatory drugs use and postmarketing reports indicated severe hepatic reactions, including fatalities. Liver function testing is recommended in the PI. Renal function and haematological AEs were seen along with thyroid function test abnormalities (increased TSH values) but clinically evident thyroid AEs were low. No clinically relevant changes in ECGs or vital signs were seen. Elderly patients and those with renal impairment did not appear to have a higher overall rate of AEs.

Cardiovascular events (primary Anti-Platelet Trialists' Collaboration (APTCC)) were higher in the two pivotal studies on FBX 80 mg (0.8%) and 120 mg (1%) compared to allopurinol (0.2%) but this was not statistically significant. This higher rate included a higher rate of cardiovascular death (0.4% and 0.2% versus 0%) and myocardial infarction (0.4% and 0.6% versus 0.2%). The third Phase III trial showed at least one cardiovascular AE in 5.2% on 40 mg, 5.4% on 80 mg and 5.8% on allopurinol with no difference between the groups for any specific type. Non-APTCC events were similar to slightly higher on FBX (1.32% on 40 mg, 1.19% on 80 mg and 0.93% on allopurinol). The long term studies did not show any difference in the overall incidence or type of cardiovascular event between FBX and allopurinol however most patients were on 80 mg.

Postmarketing data (592,238 patient years from April 2008 to April 2012) reported 38 deaths (11 due to myocardial infarction), 125 cardiovascular events with 32 myocardial infarctions and a latency of 11 days to 9 months until event, 675 rash or hypersensitivity reactions (14% serious including angioedema, anaphylactic shock, Stevens Johnson Syndrome) including eruptions and exanthemas (298), pruritus (96), oedema (51) and urticaria (37) with most occurring during the first month, 56 hepatic effects (70% abnormal LFTs), 234 renal effects (41% serious), 179 neurological, 91 haematological including 7 reports of non-serious bleeding, 5 thyroid (4 increased TSH) and 32 potential drug interactions (11 reports with azathioprine).

Risk management plan

The TGA's OPR has accepted the EU Risk Management Plan for Adenuric (FBX), version 3.3, dated 1 June 2012 (data lock point 20 October 2012), with the Australian Specific Annex (ASA), dated September 2013.

The following were outstanding matters and should be followed up with OPR and in the sponsor's Pre Advisory Committee on Prescription Medicines (ACPM) response:

- Limited information is available to support the statement that no dose adjustment in the elderly is required and a PK study has indicated an increase in females although this may be related to body weight differences. It is recommended that the PI statements in the *Pharmacology* sections be updated to those in the US PI for age and gender and to also note in the *Precautions* that only 14% of patients were aged >65 years and only <4% were >75 years. The sponsor should clarify how the RMP addresses use in the elderly.
- Following review of the safety in Europe, a Dear Healthcare Professional letter was distributed regarding serious skin, hypersensitivity and allergic reactions along with changes to their PI. The precautionary information has been included in the PI here and the sponsor has committed to including such information in external communications with healthcare professionals. It is recommended this be a condition of registration.
- The sponsor is to maintain ongoing pharmacovigilance in relation to hepatic safety, skin and hypersensitivity reactions, all-cause mortality, renal effects, potential drug interactions and adverse cardiovascular events.

Risk-benefit analysis

Delegate's considerations

Efficacy

The efficacy of FBX in treating hyperuricaemia and gout was demonstrated in three adequately designed Phase III studies for 26 to 52 weeks, a Phase II dose response study and two long term extension studies for up to 2 to 5 years. The studies compared FBX with placebo and allopurinol at an appropriate dose in a population that is generalisable to the Australian population except that some groups were excluded (for example organ transplant recipients) or under-represented (for example renal impairment). These studies showed that FBX treatment at 80 mg and 120 mg was superior to placebo and superior to 300 mg allopurinol with one pivotal study showing a difference between the two FBX doses and the other pivotal study not showing a difference between the doses. A third Phase III study that assessed a 40 mg dose showed it was non-inferior to 300 mg allopurinol but not superior and that the 80 mg dose was superior to the 40 mg dose and to 300 mg allopurinol. Results by renal function showed a greater percentage of patients with serum urate <6 mg/dL in those with mild and moderate impairment compared to

normal renal function on FBX. Secondary efficacy endpoints were generally supportive except that there was no significant difference between placebo, FBX doses and allopurinol in the change in the size of the primary tophus or the number of tophi in the two pivotal studies. Patients requiring treatment for acute gouty flares were higher on FBX 120 mg compared to 80 mg, allopurinol and placebo during the first 8 weeks of treatment when they were on gout flare prophylaxis. However the rates of gouty flares increased when the prophylaxis ceased in the two pivotal studies, for example, 80 mg: 28% (Weeks 1 to 8) to 55% (Weeks 8-28) in the first study and 22% (Weeks 1 to 8) to 64% (Weeks 8 to 52) in the second study. However the other Phase III study which had patients continue their prophylaxis for 6 months showed a gout flare rate of 31% at 6 months, thus supporting continuation of prophylaxis for at least 6 months whilst on FBX. The long term extension studies showed a maintenance of effect with the majority on 80 mg daily and gout flares declining with time.

Safety and RMP

FBX had adequate exposure in a number of studies for an acceptable duration but with some adverse events of concern. There appeared to be an increased risk of diarrhoea, headache and nausea, possible signal for cardiovascular events, increased skin and hypersensitivity reactions (compared to placebo but similar to allopurinol), increased abnormal liver function tests (compared to placebo but similar to allopurinol), potential for drug interaction with azathioprine (precaution in PI) and a risk of gout flares during initiation of therapy with the need for co-administration with gout prophylaxis treatments (NSAID or colchicine) for 6 months. Postmarket reports have shown cardiovascular events, rash or hypersensitivity reactions, hepatic (including fatal) events, renal events and haematological events to be reported. An acceptable RMP has been provided.

Cardiovascular events

The two pivotal trials indicated a signal for cardiovascular events on FBX compared with allopurinol and placebo. Although this signal was not statistically significant, such safety signals are of concern for a medicine which is to be used chronically, in a population at risk of cardiovascular events and for an indication that is not life threatening such as gout. Following this signal, a third Phase III study (Study F-GT##-153) that investigated a lower dose was undertaken that examined APTC criteria and non-APTC cardiovascular events which did not show an increase in APTC events for 40 mg or 80 mg compared with allopurinol and a similar to slight increase in non-APTC events. Exposure to FBX in the elderly, who are more likely to be at risk of cardiovascular events was 14% of the trial database but only <4% of these were >75 years indicating a limited exposure for this higher risk population. Cardiovascular safety is a concern and the PI includes a precaution that FBX is not recommended in patients with ischemic heart disease or congestive heart failure. A long term cardiovascular outcome study is currently being conducted which will be a condition of registration for submission to the TGA.

Dose

The efficacy data from the first pivotal study showed a significant difference between 80 mg and 120 mg in the proportion of subjects whose last three serum urate levels were <6 mg/dL however there were significantly more subjects on 120 mg who required treatment for gout flares (36%) compared to 80 mg (28%) during the first 8 weeks of treatment. The second pivotal study showed premature discontinuations were higher on 120 mg (39%) than 80 mg (34%), more discontinued in the first 12 weeks on 120 mg (53%) compared to 80 mg (40%) and more discontinued due to gout flares and adverse events on 120 mg (29% and 24% respectively) compared to 80 mg (11% and 18% respectively). The second study showed no significant difference in the primary efficacy endpoint between the 80 mg and 120 mg groups and again more subjects on 120 mg who required treatment for gout flares (36%) compared to 80 mg (22%) during the first 8

weeks of treatment. The dose response study showed significant efficacy at 40 mg dose compared to placebo and that the 120 mg dose again had more gout flares than the 40 mg or 80 mg dose. The third Phase III study examining the 40 mg showed it was non-inferior to allopurinol and therefore could be reasonable to commence dosing. If a higher dose is needed then patients could progress to the 80 mg dose which showed it was superior to the 40 mg dose and to allopurinol. Given that gout is not a life threatening condition, then the lowest effective dose should be used. Considering that a possible cardiovascular signal was observed in the two pivotal trials on 80 mg and 120 mg but the third Phase III trial did not show this signal on 40 mg and 80 mg (120 mg was not assessed and therefore it is unclear if this dose would again have shown a signal or not), then until further data becomes available from the cardiovascular outcomes trial currently underway, it is recommended that the lowest effective dose be used, which is a starting dose of 40 mg (non-inferior to allopurinol) with the possibility of titration to a maximum dose of 80 mg (superior to 40 mg and allopurinol). The 120 mg tablet should therefore not be registered at this time. This would be consistent with the dosing in the US PI (40 to 80 mg) and Canada (80 mg only) but differ to the proposed dose here by the sponsor and approved in Europe and New Zealand (starting dose of 80 mg and adjust up to 120 mg). A potential issue is that the sponsor has not proposed a 40 mg tablet for registration and the 80 mg tablet is not scored so that it can be broken in half to provide a 40 mg dose. The sponsor will be asked if there is acceptable data available to support breaking an 80 mg tablet in half to allow for a 40 mg dose and their intentions with registering a 40 mg tablet. ACPM's advice is requested on the proposed dose.

Indication

The clinical evaluator recommended the indication be modified to 'treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation).' However noting the wording used in New Zealand, USA and Canada and that the inclusion criteria required hyperuricaemia and gout, then a modified indication is suggested that includes symptomatic disease since efficacy and safety has not been established in asymptomatic people. A suggested wording is:

Treatment of chronic symptomatic hyperuricaemia in adults with gout.

Data deficiencies

There are no data in severe hepatic impairment and other patient groups such as those in whom the rate of urate formation is greatly increased (that is, malignancy) and organ transplant recipients. There is limited data in those >75 years.

Conditions of registration

The following are proposed as conditions of registration:

1. The implementation in Australia of the EU Risk Management Plan for Adenuric (FBX), version 3.3, dated 1 June 2012 (data lock point 20 October 2012), with the Australian Specific Annex (ASA), dated September 2013 and sponsor's email of 3 December 2013 and the RMP agreements from the Pre-ACPM Response, included with submission PM-2012-03425-1-3, and any subsequent revisions, as agreed with the TGA.
2. Precautionary information about serious skin, hypersensitivity and allergic reactions should be included in external communication materials (such as sales aids and presentations about the use of FBX) directed at healthcare professionals.
3. The following studies/reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
 - a. The final clinical study report for the trial evaluating the cardiovascular safety of FBX in comparison with allopurinol and any interim reports if a potential cardiovascular safety signal is observed.

Summary of the Delegate's issues

The primary issues with this submission are as follows:

1. The dose of FBX and whether it should be limited to a maximum 80 mg once daily rather than the proposed 120 mg daily and include a starting dose of 40 mg.
2. The safety concerns with increased cardiovascular events observed in two pivotal studies on 80 mg and 120 mg FBX compared with allopurinol but not in a third Phase III trial that used 40 mg and 80 mg FBX

Delegate's proposed action

The Delegate had no reason to say, at this time, that the application for Adenuric 80 mg should not be approved for registration. However the Delegate is not in a position to say, at this time, that the application for Adenuric 120 mg should be approved for registration.

The Delegate's suggested indication is as follows:

Treatment of chronic symptomatic hyperuricaemia in adults with gout.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Please include a summary of the interim results from the clinical outcome study investigating cardiovascular safety of FBX, including the doses being investigated, and provide a timeframe for when the final study report and any interim reports will be available.
2. The nonclinical evaluator was concerned that prolonged use of FBX may lead to xanthinuria in certain patient populations given the potential for prolonged usage, active metabolites and high potency. Please discuss this potential risk in humans and consider if PI changes are needed to advise monitoring for xanthinuria in patients on prolonged treatment.
3. The clinical evaluator was concerned about the potential for a pharmacodynamic interaction with new oral anticoagulants in terms of bleeding risk and recommended post-marketing pharmacovigilance of this potential issue. Please discuss the sponsor's plans in this regard.
4. Given the concerns with the appropriate dose, please advise of the sponsor's intentions regarding registering a 40 mg tablet and whether there is acceptable breakability data available for the 80 mg tablet to allow a half dose to be administered?

Delegate's request for ACPM advice

The Committee is requested to provide advice on the following specific issues:

1. Whether the definition of gout used in the pivotal studies is currently acceptable to support the validity of the clinical trials?
2. Whether the indication should be modified to chronic symptomatic hyperuricaemia in adults with gout only?
3. Whether the dose of FBX should be limited to a maximum of 80 mg daily, rather than the proposed 120 mg daily, and whether it should include a starting dose of 40 mg daily rather than the proposed 80 mg daily? Has sufficient safety data been submitted to support a 120 mg dose at this time?

4. Whether the safety concerns in relation to potential cardiovascular events, liver function test abnormalities and skin and hypersensitivity reactions are acceptable given the efficacy of FBX, whether they are adequately addressed in the PI or whether further data is required?

The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Overall recommendation and indication

The sponsor agrees with the Delegate to recommend approval of the 80 mg dose of FBX but disagrees with the recommendation that the 120 mg dose should not be registered at this time. The sponsor believes that the 120 mg dose is a valuable therapeutic option for those patients who are not achieving target serum urate levels with the 80 mg dose. In LTE Study C##-021, dose switching from one dose to another was permitted; out of 102 subjects who did not achieve serum urate levels < 6.0 mg/dL on FBX 80 mg, 62 (61%) achieved serum urate levels < 6.0 mg/dL after switching to FBX 120 mg. In addition, based on usage data in the EU and proposed similarity in Australia, it is expected that only approximately 10% of patients will require the 120 mg dose which is a small but yet significant percentage.

The sponsor believes that the 120 mg dose has a favourable risk-benefit profile and the sponsor has substantial amount of safety information from the clinical trial program as well as from postmarketing safety data from Europe and New Zealand for this dosage. In addition, the sponsor is monitoring cardiovascular events rate also at this dose level in the FAST study and in ongoing postmarketing surveillance.

In regards to the indication, the sponsor disagrees with the changes proposed by the Delegate but agrees with the TGA clinical evaluator's recommendation. The sponsor believes that the indication wording of

'Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation). Adenuric is indicated in adults.'

represents the data contained within the application and aligns with the patient inclusion criteria of the pivotal studies (those with gouty arthritis and/or tophus formation). In particular this proposed indication aligns with the patient populations in the APEX and FACT studies where inclusion criteria included the presence of characteristic urate crystals in the joint fluid and/or a tophus proven to contain urate crystals¹⁶. Furthermore, the indication wording is based upon the European League Against Rheumatism (EULAR) guidelines for management of gout¹⁷, whereby the treatment algorithm defines an appropriate patient with gouty arthritis, having presence of tophi and frequent attacks of gouty arthritis. Also, the sponsor is concerned that the Delegate's proposed wording of the indication in terms of the word '*symptomatic*' could be associated with gout flare by prescribers, rather than the presence of urate deposition and associated ongoing symptoms.

Dose of FBX 40 mg, 80 mg and 120 mg

Issue raised: The dose of FBX and whether it should be limited to a maximum 80 mg once daily dose rather than the proposed 120 mg daily and include a starting dose of 40 mg. Given the concerns with the appropriate dose, please advise of the sponsor's intentions

¹⁷Zhang W et. al. (2006) EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee For International Clinical Studies Including Therapeutics (ESCISIT) Ann Rheum Dis 2006;65:1312-1324

regarding registering a 40 mg tablet and whether there is acceptable breakability data available for the 80 mg tablet to allow a half dose to be administered?

Sponsor comment:

At this time, the intention by the sponsor is not to register a 40 mg dose in Australia due to several reasons. From a clinical standpoint, the sponsor believes that the 80 mg dose is a more appropriate starting dose than the 40 mg on the basis of the submitted clinical results. In particular, the Phase III study (F-GT##-153, CONFIRMS) demonstrated that the 80 mg dose significantly decreased serum urate levels (sUA) < 6.0 , < 5.0 and < 4.0 mg/dL to a larger extent than the 40 mg. The decrease in sUA levels to less than 6 mg/dL is more readily attained with 80 mg as compared to 40 mg. However, in terms of safety, both the 40 mg and 80 mg showed a similar profile. In this respect it is important to note that the use of a 40 mg starting dose was not associated with a smaller number of gout flares compared to the 80 mg during the CONFIRMS study. According to the results, rates of flare requiring treatment occurred in 10% to 15% of subjects in all treatment groups during each of the first two months of treatment but declined slowly over the subsequent course of the trial. In summary, given that the use of a 40 mg dose does not reduce the incidence of gout flares compared to the 80 mg but has demonstrated to be less effective with almost 50% of patients not achieving the therapeutic target of sUA less than 6 mg/dL it is therefore considered that the 40 mg dose is not the best option as an appropriate starting dose. On the contrary, the 80 mg dose is a valuable option with a superior clinical benefit over the existing therapies. From a technical standpoint it should be noted out that the current 80 mg film-coated tablet formulation is not scored and is not designed to be broken.

Cardiovascular events

Issue raised: The safety concerns with increased cardiovascular events observed in two pivotal studies on 80 mg and 120 mg FBX compared with allopurinol but not in a third Phase III trial that used 40 mg and 80 mg FBX.

Sponsor comment:

The efficacy of FBX is dose-dependent and there is a percentage of patients who do not achieve target serum urate levels with the 80 mg dose and would benefit from the 120 mg dosage strength. In the clinical development of FBX (three large Phase III and two long term extension studies), the 120 mg dose has showed to be more effective than the 80 mg dose. In particular in the long term extension study C##-021 (EXCEL), where switches from one dose to another were permitted, 54 (18%) out of 299 subjects were switched from the 80 mg to 120 mg FBX dose due to therapeutic failure. Among these 57% reached a serum urate level < 6.0 mg/dL. In addition, the 120 mg dose was found to be significantly superior to the 80 mg dose with regard to the proportion of subjects whose sUA level decreased to < 5 mg/dL and < 4 mg/dL.

The tolerability profile of the 80 and 120 mg doses was similar, looking at the data collected in the clinical development. In particular, the cardiovascular tolerability was evaluated through 2 strategies: i) the first strategy was based on search criteria including appropriate Standardised MedDRA¹⁸ Queries (SMQs) and Preferred Terms (PTs); ii) the second strategy was based on the search of APTC events (or Major Cardiovascular Events, MACEs, for the postmarketing surveillance).

When the evaluation was performed according to the first strategy, in the Phase III studies, similar proportions of subjects experienced treatment-emergent cardiovascular events across the treatment groups (5.2%, 6.3%, 6.3%, 6.0% and 6.0% in the FBX 40 mg, 80 mg,

¹⁸ **MedDRA** is a clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry.

120 mg, 240 mg, and allopurinol groups, respectively), compared to 3.0% in the placebo group. Likewise, in the LTE studies, the incidences of cardiovascular events per 100 patient-years (PY) were similar across treatment groups (5.3, 6.6, 7.2 and 6.6 subjects for the FBX 40 mg, 80 mg, 120 mg and FBX total groups, respectively, and 8.1 subjects for the allopurinol group). These incidences were lower than those reported in the Phase III studies per 100 PY (12.4, 10.8, and 11.5 subjects in the FBX 80 mg, 120 mg and allopurinol groups, respectively). When the evaluation was performed looking at APTC events, in the Phase III studies, the proportions of subjects with treatment-emergent adjudicated APTC events were 0.5%, and 0.6% in the FBX 80 mg and 120 mg groups, respectively, and 0.3% in the placebo and allopurinol groups, respectively. Likewise, in the LTE studies, the overall incidences of adjudicated APTC events were 1.0, 1.0, and 0.6 events per 100 PY of exposure in the FBX 80 mg and 120 mg groups, and allopurinol group, respectively. One subject experienced an adjudicated APTC event while receiving FBX 40 mg (rate=2.7 per 100 PY based on only N=12 subjects).

Similar conclusions were drawn when the cardiovascular tolerability in the postmarketing setting was analysed through the above mentioned strategies. At 20 April 2012, a total of 300 (138 Serious and 162 Non-serious) medically confirmed cases were retrieved by performing the below mentioned search strategy based on SMQs and PTs. These 300 cases rendered 312 adverse drug reactions (ADRs): 163 Serious ADRs and 149 Non-serious. The dose was known in 99 serious cases: 3 cases occurred at 10 mg, 1 case at 20 mg, 38 cases at 40 mg, 52 cases at 80 mg and 5 cases at 120 mg. When the exposure by dose is considered, the reporting rate per 1000 PY by dose was the following: 0.18 at 40 mg, 0.17 at 80 mg and 0.26 at 120 mg. Similar data were retrieved when considering MACEs (64 cases over 592,238 PY). The dose was known in 45 cases: 1 case occurred at 10 mg, 1 case at 20 mg, 22 cases at 40 mg, 19 cases at 80 mg and 2 cases at 120 mg. The reporting rate per 1000 PY by dose was the following: 0.011 at 40 mg, 0.006 at 80 mg, 0.010 at 120 mg. Therefore, no trend for dose relationship was noted in MACEs associated to FBX treatment.

These results indicate that these cardiovascular events can be attributed at the background of the cardiovascular co-morbidities accompanying gout and that the cardiovascular safety of the 120 mg dose is not different from that recorded at lower doses (40 mg and 80 mg).

The sponsor would like to point out that cardiovascular safety is considered to be of the utmost importance and therefore particularly monitored and investigated. In this regard the sponsor is also performing a cardiovascular (CV) outcome trial (the FAST study), which includes both the 80 mg and 120 mg dosage strengths compared to allopurinol. Furthermore in addition to US label, the proposed Australian Production Information (PI) includes the precautionary statement '*Treatment with FBX in patients with ischaemic heart disease or congestive heart failure is not recommended.*'

Risk management plan

1. Limited information is available to support the statement that no dose adjustment in elderly is required and a PK study has indicated an increase in females although this may be related to body weight differences. It is recommended that PI statements in the Pharmacology sections be updated. The sponsor should clarify how the RMP addresses use in the elderly.

Sponsor comment: In line with the clinical evaluator and the Delegate's recommendation, the proposed PI has been updated to include information about the elderly and gender in line with the US PI. Of the 2,690 subjects treated with FBX in the combined Phase III studies, 436 (16%) of subjects were aged ≥ 65 years and 139 (5%) were female. If it is considered that patients aged > 85 year old were excluded from these studies, then this percentage of elderly and female patients is similar to what is described in papers by Zhu

et al. 2011¹⁹ and Dirken-Heukensfeldt et al (2010)²⁰, where patients aged between 60 and 80 years represented 17% and females varied from 23 to 7% of the gout population, respectively. The safety of FBX in elderly and female patients is being monitored through routine pharmacovigilance. Sub-analyses of Phase III studies summarised in PSUR#8 indicated that in both elderly and female patients FBX was effective and well tolerated (Becker et al 2011, Jackson et al., 2012).^{21,22} An updated analysis of safety data in the postmarketing setting concluded that the safety profile of FBX in these populations was similar to that of the overall population.

2. Following review in EU, a DHPC letter was distributed regarding serious skin, hypersensitivity and allergic reactions along with changes to their PI. The precautionary information has been included in the PI here and the sponsor has committed to including such external communications with healthcare professionals. It is recommended this be a condition of registration.

Sponsor comment: The sponsor accepts the Delegate's comment and agrees to the condition of registration.

3. The sponsor is to maintain ongoing pharmacovigilance in relation to hepatic safety, skin and hypersensitivity reactions, all-cause mortality, renal effects, potential drug interactions and adverse CV events.

Sponsor comment: The sponsor agrees to maintain ongoing pharmacovigilance.

Conditions of registration

Sponsor comment:

The sponsor commits to fulfilling the three items addressed as a condition of registration for Adenuric (FBX).

Questions for the sponsor:

1. Please include a summary of the interim results from the clinical outcome study investigating cardiovascular safety of FBX, including the doses being investigated, and provide a time frame for when the final study report and any interim results will be available.

Sponsor comment:

The sponsor provided the first interim update on the FAST study conducted in Europe and investigating CV safety of both 80 and 120 mg doses as part of the response OPR's RMP questions. The interim update, dated 30 January 2013, summarised that patient recruitment was not met at that time. The next update is due on 31 January 2014 with yearly updates until the final study report will be available in September 2016, according to the current due dates agreed at European level. So far, although it is still too early to make any statement about the actual event rate in FAST, up until 30 November 2013 at least 30 potential primary endpoints have been reported which seems in line with what could be expected. The Independent Data Monitoring Committee (IDMC) for the study has recently met (November 2013) and reported that the study should continue as there were no safety issues.

¹⁹ Zhu Y, Pandya BJ, Choi HK. (2011). Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum* 63(10):3136-41.

²⁰ KJM Jansen Dirken-Heukensfeldt & TAM Teunissen, EH van de Lisdonk and ALM Lagro-Janssen (2010). Clinical features of women with gout arthritis. A systematic review. *Clin Rheumatol* 29:575-582

²¹ Jackson, B. Hunt, P.A. Macdonald (2012) The efficacy and safety of febuxostat for urate lowering in gout patients [greater than or equal to] 65 years of age. *BMC Geriatrics* 12:11.

²² Becker MA, MacDonald PA, Hunt B and Gunawardhana L. (2011). Treating hyperuricemia of Gout: Safety and Efficacy of Febuxostat and Allopurinol in Older Versus Younger Subjects. *Nucleosides, Nucleotides and Nucleic Acids*, 30:12, 1011-1017

2. The nonclinical evaluator was concerned that prolonged use of FBX may lead to xanthinuria in certain patient populations given the potential for prolonged usage, active metabolites and high potency. Please discuss this potential risk in humans and consider PI changes are needed to advise monitoring of xanthinuria in patients on prolonged treatment.

Sponsor comment: Xanthinuria and xanthine calculi are very unlikely to occur in humans, due to species dependent differences in purine metabolism and urine composition/pH. Xanthinuria and crystalluria were not reported in any clinical trials, even in those with long duration of treatment. The proposed Australian PI of FBX (and allopurinol, which has the same mechanism of action), recognises that the use of urate lowering medicinal products in patients with a greatly increased rate of urate formation (for example, malignant disease and its treatment, Lesch-Nyhan syndrome) could in rare cases increase the urinary concentration of xanthine and hypoxanthine with crystal deposition in the urinary tract. However, it is worth mentioning that currently, FBX is not recommended in such patient populations. Moreover, the Australian PI for allopurinol (Zyloprim PI dated 17 September 2008) recommends only an adequate hydration in such patients without any need for the monitoring of xanthinuria.

3. The clinical evaluation was concerned about the potential for a pharmacodynamic interaction with new oral anticoagulants in terms of bleeding risk and recommended post-marketing pharmacovigilance of this potential issue. Please discuss the sponsor's plan in this regard.

Sponsor comment: The anticoagulant effects of new anticoagulants such as rivaroxaban or dabigatran can be reversed by administering recombinant Factor VII. As FBX does not affect International Normalised Ratio (INR)²³ or Factor VII (F-P-##7-162 study on the interaction with warfarin), no pharmacodynamic interactions between FBX and rivaroxaban, dabigatran or other anticoagulants are normally expected. An enhancement of the anticoagulant effect of these drugs could occur in the rare cases when FBX prolongs thromboplastin time (this is a rare ADR to FBX).

This rare theoretical interaction between FBX and anticoagulants can be monitored through routine pharmacovigilance, as drug interactions are routinely described in PSURs and haematological/bleeding (including changes in INR) events is a potential risk summarised in each PSUR.

To date, no cases of interaction between FBX and rivaroxaban or dabigatran have been collected, whereas in 2 cases recorded, these drugs were considered co-suspect: case TPA2013A01313 (epistaxis) with rivaroxaban as co-suspect, and case TPA2011A07599 (rash) with dabigatran as co-suspect. Overall, the safety data do not indicate a major concern in the co-administration of FBX with new anticoagulants.

4. See above for the Sponsor's comment.

Review of product information

The sponsor provided comment on the recommendations by the Delegate for amendments of the PI but these are beyond the scope of this AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

²³The INR provides a standardised method of reporting the effects of an oral anticoagulant such as warfarin on blood clotting.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Adenuric tablet containing 80 mg of FBX to have an overall positive benefit–risk profile for the amended indication;

Treatment of chronic symptomatic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation) in adults with gout.

In making this recommendation the ACPM

- Expressed concern at the lack of flexibility in dosing
- Advised that standard clinical care recommended starting urate lowering agents at low dose
- Advised that the data supports a starting dose of 40 mg
- Noted the lack of paediatric data submitted and requested information of the sponsor relating to any completed or in-progress studies
- Noted lack of data regarding prophylaxis of tumour lysis syndrome and uric acid nephrolithiasis, and use in Asian populations.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration, particularly the need for submission of reports from the cardiac safety study underway.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the following:

- A statement in the *Dosage and Administration/Clinical Trials/Precautions* sections of the PI and relevant sections of the CMI on data available relating to use in Asian populations
- The table in the PI comparing the 80, 120 and 240 mg doses of Adenuric compared to 300 mg of allopurinol should be amended. The 240 mg dose should be removed since this is not recommended and the 40 mg dose should be added as this is available in another jurisdiction and is recommended here.
- A statement in the *Dosage and Administration/Precautions/Contraindications* sections of the PI and relevant sections of the CMI on the evidence for an increase in exposure in renal/hepatic impairment but there are no clinical data in severe hepatic impairment.
- A statement in the *Dosage and Administration/Precautions* sections of the PI and relevant sections of the CMI on dose reduction in moderate renal impairment.
- The terminology for Chronic Kidney Disease stages should be included in the PI when referring to degrees of renal impairment

Specific advice:

1. Whether the definition of gout used in the pivotal studies is currently acceptable to support the validity of the clinical trials?

The ACPM advised the definition was current and suitable.

2. Whether the indication should be modified to chronic symptomatic hyperuricaemia in adults with gout only?

The ACPM advised that the indication, as proposed by the sponsor in the Pre-ACPM response was suitable.

3. Whether the dose of FBX should be limited to a maximum of 80 mg daily, rather than the proposed 120 mg daily, and whether it should include a starting dose of 40 mg daily rather than the proposed 80 mg daily? Has sufficient safety data been submitted to support a 120 mg dose at this time?

The ACPM advised that its preference was for a 40 mg and the 80 mg doses to allow for lowest possible doses which provided efficacy with minimal safety problems. As the 40 mg is not currently proposed by the sponsor the evidence of safety and efficacy for the 80 mg dose is adequate. However, the ACPM was unconvinced of the benefit: risk profile of the 120 mg dose and agreed with the Delegate this should not be registered without further safety data.

4. Whether the safety concerns in relation to potential cardiovascular events, liver function test abnormalities and skin and hypersensitivity reactions are acceptable given FBX's efficacy, whether they are adequately addressed in the PI or whether further data is required

The ACPM was of the view that the amendments proposed by the Delegate now adequately covered the safety concerns for the 80 mg dose. However, the use of Standard International (SI) units is required.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Adenuric tablet containing 120 mg of FBX. The ACPM considered this product to have an overall negative benefit-risk profile.

In making this recommendation the ACPM

- Expressed concern that despite no significant difference in cardiovascular AEs between FBX doses a signal was evident over allopurinol and placebo in the pivotal trial. This was not seen in the FDA-requested trial at the lower doses.
- Noted gout flares were more common with higher doses
- Were of the view that a suitable population had not yet been adequately defined for this dose.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Adenuric FBX 80 mg tablets blister pack for oral administration, indicated for:

Treatment of chronic symptomatic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation) in adults with gout.

Specific conditions of registration applying to these goods

1. The Adenuric FBX EU Risk Management Plan (RMP), version 3.3, dated 1 June 2012 (data lock point 20 October 2010), with the Australian Specific Annex (ASA), dated September 2013 and sponsor's email of 3 Dec 2013 and the RMP agreements from the Pre-ACPM Response of 27 January 2014, included with submission PM-2012-03425-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

2. An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required.
3. Precautionary information about serious skin, hypersensitivity and allergic reactions are to be included in external communication materials (e.g. sales aids and presentations about the use of FBX) directed at healthcare professionals.
4. The following studies/reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
 - a. The final clinical study report for the trial evaluating the cardiovascular safety of FBX in comparison with allopurinol and any interim reports if a potential cardiovascular safety signal is observed.
 - b. Study TMX-##-203 in patients with moderate to severe renal failure.

Attachment 1. Product Information

The Product Information approved for main Adenuric at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

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