WARNING - Cardiovascular Death **-** Gout patients with established cardiovascular (CV) disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study. Treatment with febuxostat in patients with pre-existing major CV disease is not recommended. Prescribers should consider patients' CV risk factors before initiating febuxostat (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Cardiovascular disorders).

AUSTRALIAN PRODUCT INFORMATION

ADENURIC® febuxostat tablets

1. NAME OF THE MEDICINE

Febuxostat

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of febuxostat.

Excipients with known effect: Contains lactose. For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

ADENURIC 80 mg tablets are pale yellow to yellow, film-coated, rectangular shaped tablets, with a break line on one side and "80" engraved on the other side. They are immediate-release tablets containing 80 mg of febuxostat as the active substance.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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 357 micromole/L (6 mg/dL) after 2-4 weeks, ADENURIC 80 mg once daily is recommended. The 80 mg tablet can be split into two equal halves in order to provide a 40 mg dose. Prescribers should advise patients on how to break the tablets in half.

Testing for the target serum uric acid level of less than 357 micromole/L (6 mg/dL) may be performed as early as two weeks after initiating ADENURIC therapy.

Gout flare prophylaxis of up to 6 months is recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Acute Gouty Attacks (gout flares)).

Elderly

No dose adjustment is required in the elderly.

Renal impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment (Cl_{cr} 30 to 89 mL/min, Stages 2-3 CKD).

Caution should be exercised in patients with severe renal impairment (creatinine clearance < 30 ml/ min, Stage 4 CKD, see Section 5.2 PHARMACOKINETIC PROPERTIES). The efficacy and safety has not been fully evaluated in these patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The maximum recommended dose of ADENURIC in patients with severe renal impairment is 40 mg once daily.

Hepatic impairment

The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C). Caution should be exercised in these patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Limited information is available in patients with moderate hepatic impairment. No dosage adjustment is necessary in patients with mild hepatic impairment.

4.3 CONTRAINDICATIONS

Hypersensitivity to febuxostat or to any other ingredients in the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiovascular disorders

Treatment with febuxostat in patients with pre-existing major cardiovascular (CV) disease (e.g. myocardial infarction, stroke or unstable angina) is not recommended.

A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials, for detailed characteristics of the studies). The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.

In a post-marketing CV outcome study (CARES study) (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials), the rate of major adverse cardiovascular events (MACE) in patients with gout and a history of major CV disease including MI, hospitalisation for unstable angina, coronary or cerebral revascularisation procedure, stroke, hospitalised transient ischaemic attack, peripheral vascular disease, or diabetes mellitus with evidence of microvascular or macrovascular disease was similar in febuxostat versus allopurinol treated patients (hazard ratio [HR] 1.03; two-sided repeated 95% confidence interval [CI] 0.89-1.21), but a statistically significantly higher rate of CV deaths was observed with febuxostat (134 [1.5 per 100 patient years]) compared to patients treated with allopurinol (100 [1.1 per 100 patient years]) (HR 1.34; 95% CI 1.03-1.73). Sudden cardiac death was the most common cause of adjudicated CV death in the febuxostat group (83 of 3,098; 2.7%) as compared to the allopurinol group (56 of 3,092; 1.8%) (see Table 1).

Table 1: Patients with MACE in CARES (Cardiovascular Outcomes Study in Patients with Gout and a History of Major Cardiovascular Disease)

	Febuxostat (N=3,098)		Allopurinol (N=3,092)		Hazard Ratio
	Number of Patients with Events (%)	Rate per 100 PY*	Number of Patients with Events (%)	Rate per 100 PY*	95% CI
Composite of primary endpoint MACE	**335 (10.8)**	**3.8**	**321 (10.4)**	**3.7**	**1.03 (0.89, 1.21)**
Cardiovascular Death	134 (4.3)	1.5	100 (3.2)	1.1	1.34 (1.03, 1.73)
Nonfatal MI	111 (3.6)	1.2	118 (3.8)	1.3	0.93 (0.72, 1.21)
Nonfatal stroke	71 (2.3)	0.8	70 (2.3)	0.8	1.01 (0.73, 1.41)
Unstable angina with urgent coronary revascularisation	49 (1.6)	0.5	56 (1.8)	0.6	0.86 (0.59, 1.26)

* Patient Years (PY)

In a Phase IV post-authorisation CV safety study (FAST study) (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials), the CV safety profile of febuxostat versus allopurinol in patients with chronic hyperuricaemia (in conditions where urate deposition had already occurred) and CV risk factors (i.e. patients 60 years or older and with at least one other CV risk factor) was investigated. In contrast to the CARES study where 100% of patients had a history of MACE, in the FAST study 66.6% of patients had no history of MACE.

In the primary on-treatment (OT) analysis, febuxostat was non-inferior to allopurinol in the incidence of the primary endpoint (time to the first occurrence of any event included in the Antiplatelet Trialists' Collaborative (APTC) composite endpoint), which occurred in 172 patients (1.72/100 patient years) on febuxostat compared to 241 patients (2.05/100 patient years) on allopurinol, with an adjusted HR 0.85 (95% CI: 0.70, 1.03), p<0.001.

No increase in CV death or all-cause death was observed with febuxostat in the overall population. Overall, there were fewer deaths in the febuxostat group (62 of 3,063 CV deaths [0.61 per 100 patient years] and 108 of 3,063 all-cause deaths [1.06 per 100 patient years]), than in the allopurinol group (82 of 3,065 CV deaths [0.68 per 100 patient years] and 174 of 3,065 all-cause deaths [1.44 per 100 patient years]). In the subgroup of patients with a baseline history of MI, stroke or ACS, treatment with febuxostat was not associated with any increase in the primary composite endpoint (MI, stroke, ACS or cardiovascular death). See Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials.

Prescribers should consider patients' cardiovascular risk factors before initiating febuxostat. Prescribers should monitor for and counsel patients on the signs and symptoms of MI, stroke and cardiac failure.

Medicinal product allergy / hypersensitivity

Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) reactions were associated with fever, haematological, renal or hepatic involvement in some cases.

Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions (see Section 4.8 ADVERSE EFFECTS

(UNDESIRABLE EFFECTS)). Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson Syndrome, occur since early withdrawal is associated with a better prognosis. If a patient has developed allergic/hypersensitivity reactions including Stevens-Johnson Syndrome and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time.

Acute gouty attacks (gout flares)

Febuxostat treatment should not be started until an acute attack of gout has completely subsided. After initiation of febuxostat, an increase in gout flares is frequently observed. This increase is due to changing serum uric acid levels resulting in mobilisation of urate from tissue deposits. In order to prevent gout flares when febuxostat is initiated, concurrent prophylaxis for up to 6 months with an NSAID or colchicine is recommended.

If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

Populations with markedly increased urate production

In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

Mercaptopurine/azathioprine

Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine as inhibition of xanthine oxidase (XO) by febuxostat may cause substantially increased plasma concentrations of mercaptopurine/azathioprine leading to severe toxicity. Where the combination cannot be avoided patients should be closely monitored. A reduction of the dose of mercaptopurine/azathioprine is recommended in order to reduce the risk of possible haematological effects. Data are insufficient to support a specific dose reduction of mercaptopurine/azathioprine when used concomitantly with febuxostat (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Pharmacokinetic modelling and simulation of rat data suggests that concomitant administration of oral mercaptopurine/azathioprine and febuxostat results in a ~80% decrease in the predicted population clearance, which corresponds to a ~500% increase in mercaptopurine/azathioprine AUC in humans (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS & 5.3 PRECLINICAL SAFETY DATA).

Organ transplant recipients

As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended.

Theophylline

No dose adjustment is necessary for theophylline when co-administered with febuxostat. Co-administration of febuxostat 80 mg and theophylline in healthy participants showed no statistically significant interaction (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by febuxostat. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to co-administer febuxostat and theophylline.

Liver disorders

During the combined Phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (see Table 5). Liver function tests are recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement.

There have been post-marketing reports of fatal and non-fatal hepatic failure in patients taking ADENURIC, although the reports contain insufficient information necessary to establish the probable cause. During randomised controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ADENURIC and allopurinol-treated patients, respectively).

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), ADENURIC treatment should be interrupted and an investigation done to establish the probable cause. ADENURIC should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative aetiologies are at risk for severe drug-induced liver injury and should not be restarted on ADENURIC. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with ADENURIC can be used with caution.

Thyroid disorders

Increased TSH values (> 5.5 microIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%) in the long-term open-label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function.

Lactose

Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Identified precautions

Use in Asian Populations

About 3% of patients enrolled in Phase 3 studies were of Asian ethnicity. Although the clinical experience is limited, the overall incidence rates of treatment-emergent adverse events were not significantly different between races within each of the treatment groups. There have been post-marketing reports of serious skin/hypersensitivity reactions in some Asian populations.

Use in hepatic impairment

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore caution should be exercised in these patients.

Use in renal impairment

ADENURIC should be used with caution in patients with severe renal impairment (CL_{cr} less than 30 mL/min, Stage 4 CKD) as its efficacy and safety has not been fully evaluated in these patients (see Section 5.2 PHARMACOKINETIC PROPERTIES). There are no data in end-stage renal impairment patients who are on dialysis.

The recommended maximum dose of ADENURIC in patients with severe renal impairment is 40 mg once daily (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in the elderly

No dose adjustment is required in the elderly. Of the total number of participants in clinical studies of ADENURIC, 16% were 65 and over, while 4% were 75 and over. Comparing subjects in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ADENURIC in geriatric subjects (≥ 65 years) were similar to those in younger subjects (18 to 40 years) (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric use

The safety and efficacy of ADENURIC in children aged below the age of 18 years have not been established. No data are available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Mercaptopurine/azathioprine

On the basis of the mechanism of action of febuxostat on xanthine oxidase (XO) inhibition, concomitant use is not recommended. Inhibition of XO by febuxostat may cause substantially increased plasma concentrations of these drugs leading to severe toxicity.

Pharmacokinetic modelling and simulation of rat data suggests that concomitant administration of oral mercaptopurine/azathioprine and febuxostat results in a ~80% decrease in the predicted population clearance, which corresponds to a ~500% increase in mercaptopurine/azathioprine AUC in humans. This was further confirmed by the results of a clinical drug-drug interaction study in healthy volunteers, receiving azathioprine 100 mg alone and a reduced dose of azathioprine (25 mg) in combination with febuxostat (40 or 120 mg). In this study, C_{max} and $AUC_{(0-t)}$ of 6-mercaptopurine were approximately 1.5-fold higher when azathioprine 25 mg was taken in combination with febuxostat than when azathioprine 100 mg was administered as single agent. Irrespective of febuxostat dose, the extent of the interaction was essentially the same (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE & 5.3 PRECLINICAL SAFETY DATA).

A reduction of the dose of mercaptopurine/azathioprine is recommended in order to reduce the risk of possible haematological effect (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Data are insufficient to support a specific dose reduction of mercaptopurine/azathioprine when used concomitantly with febuxostat.

Drug interaction studies of febuxostat with other cytotoxic chemotherapeutic agents have not been conducted. No data are available regarding the safety of febuxostat during other cytotoxic therapy.

Rosiglitazone/CYP2C8 substrates

Febuxostat was shown to be a weak inhibitor of CYP2C8 *in vitro*. In a study in healthy subjects, co-administration of 120 mg febuxostat daily with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor

in vivo. Thus, co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.

Theophylline

No dose adjustment is necessary for theophylline when co-administered with febuxostat. Administration of febuxostat (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by febuxostat. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to co-administer febuxostat and theophylline.

Naproxen and other inhibitors of glucuronidation

Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (UGT) enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250 mg twice daily was associated with an increase in febuxostat exposure (C_{max} 28%, AUC 41% and $t_{1/2}$ 26%). In clinical studies the use of naproxen or other NSAIDs/COX-2 inhibitors was not related to any clinically significant increase in adverse events.

Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxen being necessary.

Inducers of glucuronidation

Potent inducers of UGT enzymes such as phenytoin might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

Colchicine/ indomethacin/ hydrochlorothiazide/ warfarin

Febuxostat can be co-administered with colchicine or indomethacin with no dose adjustment of febuxostat or the co-administered active substance being necessary.

No dose adjustment is necessary for febuxostat when administered with hydrochlorothiazide.

No dose adjustment is necessary for warfarin when administered with febuxostat. Administration of febuxostat (80 mg or 120 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the co-administration of febuxostat.

Desipramine/CYP2D6 substrates

Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro*. In a study in healthy subjects, 120 mg ADENURIC daily resulted in a mean 22% increase in AUC of desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme *in vivo*. Thus, co-administration of febuxostat with other CYP2D6 substrates is not expected to require any dose adjustment for those compounds.

Antacids

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32% decrease in C_{max}, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

Tacrolimus

Attention should be paid when introducing febuxostat in patients taking tacrolimus: although no specific interaction study between tacrolimus and febuxostat has been performed, a documented increase in tacrolimus plasma levels has been reported after febuxostat administration in some post-marketing cases concerning renal transplanted patients.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In rats, reproduction studies up to 48 mg/kg/day (20 to 25 times human exposure at the maximum recommended human dose [MRHD] based on AUC) showed no dose-dependent adverse effects on male or female fertility. The effect of ADENURIC on human fertility is unknown.

Use in pregnancy (Category B1)

Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/newborn child. Studies in rats and rabbits found no evidence of foetal abnormalities at doses up to 48 mg/kg/day (25 to 33 times the clinical exposure at the MRHD based on AUC), consistent with the minimal placental transfer of febuxostat found in pharmacokinetic studies. As the potential risk of foetal harm in humans is unknown, febuxostat is not recommended for use during pregnancy.

Use in lactation

It is unknown whether febuxostat is excreted in human breast milk. Febuxostat is readily excreted in breast milk in rats (milk:plasma ratio of 7.9 at 4 h post-maternal dose). Rats exposed to febuxostat during the lactation period at 48 mg/kg/day (25 times the clinical exposure at the MRHD based on AUC) showed maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring. At the no-observed-adverse-effect-level [NOAEL] for maternal and pup developmental effects of 3 mg/kg/day the AUC-based relative exposure was similar to that anticipated clinically at the maximum daily dose. A risk to a breastfeeding infant cannot be excluded. Febuxostat should not be used while breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Somnolence, dizziness, paraesthesia and blurred vision have been reported with the use of febuxostat. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that ADENURIC does not adversely affect performance.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

A total of 2757 subjects with hyperuricaemia and gout were treated with febuxostat 40 mg or 80 mg daily in clinical studies. For febuxostat 40 mg, 559 patients were treated for ≥ 6 months. For febuxostat 80 mg, 1377 subjects were treated for ≥ 6 months, 674 patients were treated for ≥ 1 year and 515 patients were treated for ≥ 2 years.

The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg), post- authorisation safety studies (FAST study: 3,001 subjects treated at least with a dose from 80 mg to 120 mg) and post-marketing experience are gout flares, liver function abnormalities, diarrhoea, nausea, headache, dizziness, dyspnoea, rash, pruritus, arthralgia, myalgia, pain in extremity, oedema and fatigue. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, and rare events of sudden cardiac death, have occurred in the post-marketing experience.

Table 2 summarises the adverse events from the three placebo-controlled clinical trials that occurred with a frequency of ≥ 1% in the febuxostat, placebo and allopurinol groups.

Table 2: Adverse effects (% Patients) in Phase 3 Clinical Trials

System Organ Class Adverse Effect	Placebo (N=134)	febuxostat 40 mg (N=757)	febuxostat 80 mg (N=1279)	allopurinol (N=1277)
Metabolism and nutrition disorders				
Gout flares*	55.2%	31.3%	43.1%	38.2%
Nervous system disorders				
Headaches	5.2%	2.8%	4.1%	4.9%
Gastrointestinal disorders				
Diarrhoea**	9.0%	5.9%	7.3%	7.1%
Nausea	2.2%	2.6%	3.0%	1.6%
Hepato-biliary disorders				
Liver function abnormalities**	2.2%	8.3%	6.4%	6.0%
Skin and subcutaneous tissue disorders				
Rash	2.2%	1.7%	2.0%	1.3%
General disorders and administration site conditions				
Oedema	0.7%	1.3%	2.7%	2.5%

* See Clinical Trials for incidences of gout flares in the individual Phase 3 randomised controlled studies.
** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of febuxostat 40 mg, 1.2% of febuxostat 80 mg and in 0.9% of allopurinol-treated subjects.

Tabulated list of adverse reactions:

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000) adverse reactions occurring in patients treated with febuxostat are listed in Table 3 and Table 4 below.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse reactions in combined Phase 3, long-term extension studies and post-authorisation safety studies

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia, anaemia[#]
Endocrine disorders	Uncommon Blood thyroid stimulating hormone increased, hypothyroidism[#]
Eye disorders	Uncommon Blurred vision Rare Retinal artery occlusion[#]
Metabolism and nutrition disorders	Common Gout flares* Uncommon Diabetes mellitus, hyperlipidaemia, decrease appetite, weight increase Rare Weight decrease, increase appetite, anorexia
Psychiatric disorders	Uncommon Libido decreased, insomnia Rare Nervousness, depressed mood[#], sleep disorder[#]
Nervous system disorders	Common Headache, dizziness Uncommon Paraesthesia, hemiparesis, somnolence, lethargy[#], altered taste, hypoaesthesia, hyposmia Rare Ageusia[#], burning sensation[#]

Ear and labyrinth disorders	Uncommon Tinnitus Rare Vertigo[#]
Cardiac disorders	Uncommon Atrial fibrillation, palpitations, ECG abnormal, arrhythmia[#]
Vascular disorders	Uncommon Hypertension, flushing, hot flush Rare Circulatory collapse[#]
Respiratory system disorders	Common Dyspnoea Uncommon Bronchitis, upper respiratory tract infection, lower respiratory tract infection[#], cough, rhinorrhoea[#] Rare Pneumonia[#]
Gastrointestinal disorders	Common Diarrhoea**, nausea Uncommon Abdominal pain, abdominal pain upper[#], abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort, pancreatitis, mouth ulceration, lip swelling[#] Rare Gastrointestinal perforation[#], stomatitis[#]
Hepato-biliary disorders	Common Liver function abnormalities** Uncommon Cholelithiasis Rare Hepatitis, cholecystitis[#]
Skin and subcutaneous tissue disorders	Common Rash (including various types of rash reported with lower frequencies, see below), pruritus Uncommon Dermatitis, urticaria, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular, hyperhidrosis, alopecia, eczema[#], erythema, night sweats[#], psoriasis[#], rash pruritic[#] Rare Exfoliative rash, rash follicular, rash vesicular, rash pustular, rash erythematous, rash morbillifom
Musculoskeletal and connective tissue disorders	Common Arthralgia, myalgia, pain in extremity[#] Uncommon Arthritis, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis, joint swelling[#], back pain[#], musculoskeletal stiffness, joint stiffness Rare Rotator cuff syndrome[#], polymyalgia rheumatica[#]
Renal and urinary disorders	Uncommon Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria, micturition urgency, urinary tract infection[#]
Reproductive system and breast disorder	Uncommon Erectile dysfunction
General disorders and administration site conditions	Common Oedema, fatigue Uncommon Chest pain, chest discomfort, pain[#], malaise[#] Rare Thirst, feeling hot[#]

Investigations	Uncommon Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase, INR increased[#] Rare Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase
Injury, poisoning and procedural complications	Uncommon Contusion[#]

* See Clinical Trials for incidences of gout flares in the individual Phase 3 randomised controlled studies.
** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine.
# Adverse reactions from post-authorisation studies.

Post-marketing experience

Table 4: Adverse reactions post-marketing

Blood and lymphatic system disorders	Rare Agranulocytosis
Immune system disorders	Rare Anaphylactic reaction, drug hypersensitivity
Cardiac disorders	Rare Sudden cardiac death
Hepato-biliary disorders	Rare Jaundice, liver injury
Skin and subcutaneous tissue disorders	Rare Toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, drug reaction with eosinophilia and systemic symptoms, generalised rash (serious)
Musculoskeletal and connective tissue disorders	Rare Rhabdomyolysis*
Renal and urinary disorders	Rare Tubulointerstitial nephritis
Investigations	Rare Blood creatine phosphokinase increase

* The majority of these patients were receiving a statin and colchicine as concomitant medications. Also, some patients had renal impairment or failure.

Description of selected adverse reactions

Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated with the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis).

Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended.

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomised, controlled and long-term extension studies. In the Phase 3 randomised, controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI

0.00-6.16), febuxostat 40 mg 0 (95% CI 0.00 – 1.08), febuxostat 80 mg 1.09 (95% CI 0.44-2.24) and allopurinol 0.60 (95% CI 0.16-1.53).

In the long-term extension studies, the incidence of adjudicated APTC events were: febuxostat 80 mg 0.97 (95% CI 0.57-1.56) and allopurinol 0.58 (95% CI 0.02-3.24).

In the long-term post-marketing study (FAST), the incidence of adjusted APTC events were lower in febuxostat than in allopurinol, which occurred in 172 patients (1.72/100 patient years) on febuxostat compared to 241 patients (2.05/100 patient years) on allopurinol, with an adjusted HR 0.85 (95% CI: 0.70, 1.03), p<0.001 non-inferiority.

Overall, a higher rate of APTC events was observed in febuxostat than in allopurinol-treated patients in pre-registration trials; however in post-marketing studies, febuxostat was observed to be non-inferior to allopurinol. A causal relationship with febuxostat has not been established. Monitor for signs and symptoms of myocardial infarction and stroke (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Abnormal Haematologic and Clinical Chemistry Findings

During the 3 randomised, controlled studies, transaminase elevations greater than 3 times the upper limit of normal were observed. The clinically important abnormalities in liver function tests reported in the controlled studies are shown in Table 5.

Table 5: Incidence of Clinically Important Laboratory Abnormalities Reported in Controlled Studies

		Treatment Group (%)			
Laboratory Abnormality	**Normal Values***	Placebo (N=134)	febuxostat 40 mg (N=757)	febuxostat 80 mg (N=1279)	Allopurinol† (N=1277)
Alkaline phosphatase ≥ 2xULN	Males: 31-131 U/L Females: 31-135 U/L	0.0% (0/129)	0.0% (0/711)	0.4% (5/1204)	0.0% (0/1200)
ALT ≥ 3xULN	Males: 6-43 U/L Females: 6-34 U/L	0.8% (1/129)	3.2% (23/711)	3.2% (39/1204)	1.9% (23/1200)
AST ≥ 3xULN	Males: 11-36 U/L Females: 9-34 U/L	0.8% (1/129)	1.4% (10/710)	1.3% (16/1204)	2.0% (24/1200)
Total bilirubin ≥ 2.0 mg/dL	Both genders: 0.2-1.2 mg/dL	0.8% (1/129)	0.3% (2/711)	0.5% (6/1204)	1.0% (12/1200)

Percentages are based on the number of patients with post-baseline laboratory data.
* Normal values across age groups as reported by the central laboratory. ULN = upper limit of normal.
† Of the patients who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg based on the level of renal impairment.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia). Patients with an overdose should be managed by symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

Febuxostat belongs to the pharmacotherapeutic group: Antigout preparation, preparations inhibiting uric acid production (ATC code: M04AA03).

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the above transformations are catalysed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a non-purine selective inhibitor of XO which inhibits human xanthine oxidase under *in vitro* conditions with a dissociation constant (K_i) of 10 nM. Febuxostat has been shown to inhibit both the oxidised and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

Effect on QTc interval

The effect of febuxostat on cardiac repolarisation as assessed by the QTc interval was evaluated in normal healthy participants and in patients with gout. ADENURIC in doses up to 300 mg daily, at steady-state, did not demonstrate an effect on the QTc interval.

Clinical Trials

The efficacy of ADENURIC was demonstrated in one Phase 2 clinical trial (TMX-00-004) and subsequently confirmed in three Phase 3 pivotal studies (APEX, FACT and CONFIRMS studies). Studies were conducted in 4101 patients with hyperuricaemia and gout. Hyperuricaemia was defined as a baseline serum uric acid level (sUA) ≥ 476 micromole/L (8 mg/dL).

Subjects who completed the APEX and FACT studies were eligible to enrol in the EXCEL trial, a long-term extension study in which patients received treatment with ADENURIC for a 3-year period.

<u>TMX-00-004 and FOCUS (TMX-01-005) Studies</u>

The efficacy of ADENURIC was evaluated in a four-week dose-ranging study which randomised patients to: placebo, febuxostat 40 mg daily, 80 mg daily, or 120 mg daily. At the end of treatment (Day 28), the proportion of participants who achieved sUA < 357 micromole/L (6 mg/dL) was 0%, 56% and 76% in the placebo, febuxostat 40 mg and 80 mg groups, respectively.

Subjects who completed this study were eligible to enrol in the FOCUS study (TMX-01-005), a long-term extension study in which subjects received treatment with ADENURIC for up to five years. The proportion of patients with sUA of < 357 micromole/L (6.0 mg/dL) at the final visit was greater than 80% (81-100%) at each febuxostat dose.

<u>CONFIRMS, APEX and FACT Studies</u>

The primary efficacy endpoint in the APEX and FACT studies was the proportion of patients whose last 3-monthly serum uric acid levels were < 357 micromole/L (6.0 mg/dL). In the Phase 3 CONFIRMS study, the primary efficacy endpoint was the proportion of patients whose serum urate level was < 357 micromole/L (6.0 mg/dL) at the final visit. No patients with organ transplant have been included in these studies. Patients were excluded if they had secondary hyperuricaemia, history of excessive alcohol intake, malignancy within the last 5 years, severe renal or hepatic impairment, active peptic ulcer disease, history of myocardial infarction or stroke, paediatric patients, pregnant and nursing women. Non-inferiority of febuxostat to the active control allopurinol specified a 10 percentage point margin (the lower limit of the confidence interval for the difference) of non-inferiority for differences in response rates.

In all three studies, subjects received naproxen 250 mg twice daily or colchicine 0.6 mg once or twice daily for gout flare prophylaxis. In the APEX and FACT studies the duration of prophylaxis was eight weeks. In the CONFIRMS study the duration of prophylaxis was six months.

CONFIRMS Study

The CONFIRMS study was a Phase 3, randomised, controlled, 26-week study to evaluate the safety and efficacy of febuxostat 40 mg and 80 mg, in comparison with allopurinol 300 mg or 200 mg, in patients with gout and hyperuricaemia. Two thousand and two hundred-sixty nine (2269) patients were randomised: ADENURIC 40 mg daily (n=757), ADENURIC 80 mg daily (n=756), or allopurinol 300/200 mg daily (n=756). At least 65% of the patients had mild-moderate renal impairment (with creatinine clearance of 30-89 mL/min, Stages 2-3 CKD). Prophylaxis against gout flares was obligatory over the 26-week period.

The proportion of patients with sUA < 357 micromole/L (6.0 mg/dL) at the final visit, was 45% for 40 mg febuxostat, 67% for febuxostat 80 mg and 42% for allopurinol 300/200 mg, respectively.

APEX Study

The Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX) was a Phase 3, randomised, double-blind, multicenter, 28-week study. One thousand and seventy-two (1072) patients were randomised: placebo (n=134), ADENURIC 80 mg daily (n=267), ADENURIC 120 mg daily (n=269), ADENURIC 240 mg daily (n=134) or allopurinol (300 mg daily [n=258] for patients with a baseline serum creatinine ≤1.5 mg/dL or 100 mg daily [n=10] for patients with a baseline serum creatinine >1.5 mg/dL and ≤ 2.0 mg/dL). Two hundred and forty mg febuxostat (2 times the recommended highest dose) was used as a safety evaluation dose.

The APEX study showed statistically significant superiority of the ADENURIC 80 mg daily treatment arm versus the conventionally used doses of allopurinol 300 mg (n=258) /100 mg (n=10) treatment arm in reducing the sUA below 357 micromole/L (6 mg/dL). See Table 6.

FACT Study

The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomised, double-blind, multicenter, 52-week study. Seven hundred and sixty (760) patients were randomised: ADENURIC 80 mg daily (n=256), ADENURIC 120 mg daily (n=251), or allopurinol 300 mg daily (n=253).

The FACT study showed the statistically significant superiority of the ADENURIC 80 mg daily treatment arm versus the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 357 micromole/L (6 mg/dL).

Patients in all 3 studies (CONFIRMS, APEX and FACT) were representative of the patient population for which ADENURIC use is intended. Table 6 summarises the demographics and baseline characteristics for the subjects enrolled in the studies.

Table 6: Patient Demographics and Baseline Characteristics in CONFIRMS, APEX and FACT studies

Male	95%
Race: Caucasian African American	 80% 10%
Ethnicity: Hispanic or Latino	 7%
Alcohol user	67%
Mild to Moderate Renal Insufficiency; Stages 2-3 CKD (percent estimated Cl_{Cr} less than 90 mL/min)	59%
History of Hypertension	49%
History of Hyperlipidaemia	38%
BMI ≥ 30 kg/m^2	63%
Mean BMI	33 kg/m^2
Baseline sUA ≥ 595 micromole/L (10 mg/dL)	36%
Mean baseline sUA	577 micromole/L (9.7 mg/dL)
Experienced a gout flare in previous year	85%

Table 7 summarises the efficacy endpoint results in all 3 studies:

Table 7: Proportion of Patients with Serum Uric Acid Levels < 357 micromole/L (6.0 mg/dL) at Last Three-Monthly Visits and Final Visit

STUDY	**Treatment Group**				**Difference in Proportion (95% CI)**	
	ADENURIC 40 mg daily	ADENURIC 80 mg daily	Allopurinol 300 mg daily [1, 2]	Placebo	ADENURIC 40 mg vs allopurinol	ADENURIC 80 mg vs allopurinol
LAST THREE-MONTHLY VISITS						
APEX (6 months)		48%* (126/262)	22% (60/268)	0% (0/134)		26% (18%-34%)
FACT (12 months)		53%* (136/255)	21% (53/251)			32% (24%-40%)
FINAL VISIT						
CONFIRMS (6 months)	45% (342/757)	67%* (507/756)	42% (318/755)		3% (-2%, 8%)	25% (20%, 30%)
APEX (6 months)		72% (183/253)	39% (102/263)	1% (1/127)		33% (26%, 42%)
FACT (12 months)		74% (185/249)	36% (88/242)			38% (30%, 46%)

[1] Allopurinol was administered at reduced doses of 200 mg (CONFIRMS study) and 100 mg (APEX / FACT studies) depending on renal function.
[2] Results from subjects receiving either 100 mg daily (n=10: patients with serum creatinine > 1.5 and ≤ 2.0 mg/dL) or 300 mg daily (n=509) were pooled for analyses.
* $p < 0.001$ vs allopurinol

The ability of ADENURIC to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to < 357 micromole/L (6.0 mg/dL) was noted by the Week 2 visit and was maintained throughout treatment.

Primary endpoint in the sub-group of patients with renal impairment

An analysis in patients with gout who had mild to moderate renal impairment (Clcr 30 to 89 mL/min, Stages 2-3 CKD) was prospectively defined in the CONFIRMS study. As shown in Table 8, febuxostat 80 mg was significantly more effective in lowering sUA to < 357 micromole/L (6 mg/dL) compared to allopurinol 300 mg/200 mg or febuxostat 40mg.

Table 8: Proportion of subjects with Serum Urate Level < 357 micromole/L (6 mg/ dL) at Final Visit by Renal Function in CONFIRMS Study

Renal Function	Number (%) Subjects			
	Febuxostat 40 mg daily	Febuxostat 80 mg daily	Allopurinol 300 mg	Allopurinol 200 mg
Normal CL_{cr} > 90mL/min	104/278 (37%)[a]	147/253 (58%)[b]	106/254 (42%)	NA
Mildly impaired (Stage 2 CKD) CL_{cr} 60- 89 mL/min	182/349 (52%)[a]	263/367 (72%)[b]	169/365 (46%)	NA
Moderately impaired (Stage 3 CKD) CL_{cr} 30- 59 mL/min	56/130 (43%)[a]	97/136 (71%)[b]	NA	43/136 (32%)

Note: Allopurinol dose was adjusted to renal function
a. p< 0.01 Febuxostat 40 mg vs febuxostat 80 mg
b. p< 0.001 Febuxostat 80 mg vs allopurinol 300/200 mg

Primary endpoint in the subgroup of patients with sUA ≥ 595 micromole/L (10 mg/dL)

Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of ≥ 595 micromole/L (10 mg/dL). In this subgroup ADENURIC achieved the primary efficacy endpoint (sUA < 357 micromole/L [6.0 mg/dL] at the last 3 visits) in 41% (80 mg daily) of patients compared to 9% in the allopurinol 300 mg/100 mg daily and 0 % in the placebo groups.

In the CONFIRMS study, the proportion of patients achieving the primary efficacy endpoint (sUA < 357 micromole/L [6.0 mg/dL] at the final visit) for patients with a baseline serum urate level of ≥ 595 micromole/L (10 mg/dL) treated with febuxostat 40 mg daily was 27% (66/249), with febuxostat 80 mg daily 49% (125/254) and with allopurinol 300 mg/200 mg daily 31% (72/230), respectively.

Clinical Outcomes: proportion of patients requiring treatment for a gout flare

APEX study: During the 8-week prophylaxis period, the proportion of subjects who required treatment for gout flare was 28% -febuxostat 80 mg, 23% -allopurinol 300 mg, and 20%-placebo treatment groups. Flares increased following the prophylaxis period and gradually decreased over time. Between 46% and 55% of subjects received treatment for gout flares from Week 8 and Week 28. Gout flares during the last 4 weeks of the study (Weeks 24-28) were observed in 15% (febuxostat 80 mg), 14% (allopurinol 300 mg) and 20% (placebo) of subjects.

FACT study: During the 8-week prophylaxis period, the proportion of subjects who required treatment for a gout flare was 22% and 21% for febuxostat 80 mg and allopurinol 300 mg treatment groups respectively. After the 8-week prophylaxis period, the incidence of flares increased and gradually decreased over time (64% and 70% of subjects received treatment for gout flares from Week 8-52). Gout flares during the last 4 weeks of the study (Weeks 49-52) were observed in 6% (febuxostat 80 mg), and 11% (allopurinol 300 mg) of subjects.

The proportion of subjects requiring treatment for a gout flare (APEX and FACT studies) was numerically lower in the groups that achieved an average post-baseline serum urate level < 357 micromole/L, < 297 micromole/L, or < 238 micromole/L compared to the group that achieved an average post-baseline serum urate level ≥ 357 micromole/L during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 49-52 intervals).

CONFIRMS study: The percentage of patients who required treatment for gout flares (Day 1 through Month 6) were 31% and 25% for the febuxostat 80 mg and allopurinol groups, respectively. No difference in the proportion of patients requiring treatment for gout flares was observed between the febuxostat 80 mg and 40 mg groups.

Post Marketing Long Term Studies

CARES Study

The Cardiovascular Safety of Febuxostat and Allopurinol in Participants With Gout and Cardiovascular Comorbidities (CARES) study was a multicentre, randomised, double-blind, allopurinol-controlled, non-inferiority trial comparing CV outcomes with febuxostat versus allopurinol in patients with gout and a history of major CV disease including MI, hospitalisation for unstable angina, coronary or cerebral revascularisation procedure, stroke, hospitalised transient ischemic attack, peripheral vascular disease, or diabetes mellitus with evidence of microvascular or macrovascular disease. To achieve sUA less than 357 micromole/L (6 mg/dL), the dose of febuxostat was titrated from 40 mg up to 80 mg (regardless of renal function) and the dose of allopurinol was titrated in 100 mg increments from 300 to 600 mg in patients with normal renal function and mild renal impairment and from 200 to 400 mg in patients with moderate renal impairment.

The primary endpoint in CARES was the time to first occurrence of MACE; a composite of non-fatal MI, non-fatal stroke, CV death and unstable angina with urgent coronary revascularisation.

The endpoints (primary and secondary) were analysed according to the intention-to-treat (ITT) analysis including all subjects who were randomised and received at least one dose of double-blind study medication.

Overall 56.6% of patients discontinued trial treatment prematurely and 45% of patients did not complete all trial visits.

In total, 6,190 patients were followed for a median of 32 months and the median duration of exposure was 728 days for patients in febuxostat group (n = 3,098) and 719 days in allopurinol group (n = 3,092).

Febuxostat was non-inferior to allopurinol for the primary endpoint of MACE (10.8% vs. 10.4% of patients, respectively; HR 1.03; two-sided repeated 95% CI 0.89-1.21).

In the analysis of the individual components of MACE, the rate of CV deaths was statistically significantly higher with febuxostat (134 [1.5 per 100 patient years]) than allopurinol (100 [1.1 per 100 patient years]) (HR 1.34; 95% CI 1.03-1.73). The rate of all-cause mortality was also higher with febuxostat than allopurinol (7.8% vs. 6.4% of patients; HR 1.22; 95% CI 1.01-1.47), which was mainly driven by the higher rate of CV deaths in that group (4.3% vs 3.2%). Sudden cardiac death was the most common cause of adjudicated CV deaths in the febuxostat group (83 of 3,098; 2.7%) as compared to the allopurinol (56 of 3,092; 1.8%). The rates of the other MACE events were similar in the febuxostat and allopurinol groups, i.e. non-fatal MI (3.6% vs. 3.8% of patients; HR 0.93; 95% CI 0.72-1.21), non-fatal stroke (2.3% vs. 2.3% of patients; HR 1.01; 95% CI 0.73-1.41) and urgent coronary revascularisation due to unstable angina (1.6% vs. 1.8% of patients; HR 0.86; 95% CI 0.59-1.26).

Rates of adjudicated hospitalisation for heart failure, hospital admissions for arrhythmias not associated with ischemia, venous thromboembolic events and hospitalisation for transient ischemic attacks were comparable for febuxostat and allopurinol.

FAST study

The FAST study was a prospective, randomised, open-label, blinded-endpoint Phase IV post-authorisation safety study comparing the cardiovascular (CV) safety profile of febuxostat versus allopurinol in patients with chronic hyperuricaemia (in conditions where urate deposition had already occurred) and CV risk factors (i.e. patients 60 years or older and with at least one other CV risk factor). Eligible patients received allopurinol treatment prior to randomisation, and dose adjustments were required when needed, according to clinical judgement, European Alliance of Associations for Rheumatology (EULAR) recommendations and the approved posology. At the end of the allopurinol lead-in phase,

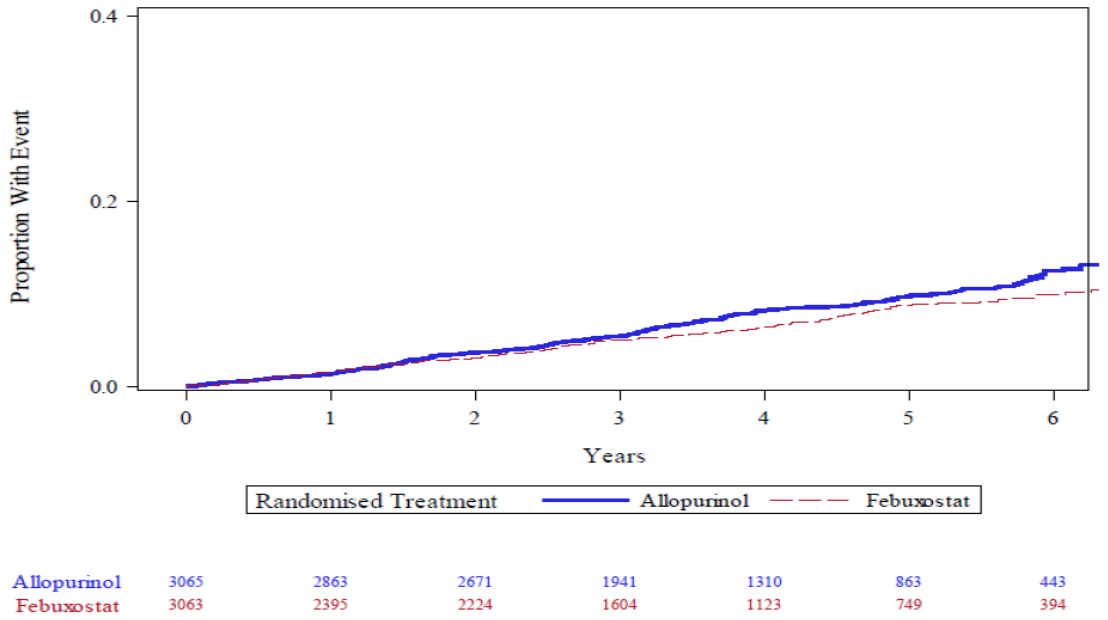
patients with a serum uric acid (sUA) level of <0.36 mmol/L (<6 mg/dL) or receiving the maximum tolerated dose or the maximum licensed dose of allopurinol were randomised in a 1:1 ratio to receive either febuxostat or allopurinol treatment.

The primary endpoint of the FAST study was the time to the first occurrence of any event included in the Antiplatelet Trialists' Collaborative (APTC) composite endpoint, which included: i) hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome (ACS); ii) non-fatal stroke; iii) death due to a CV event. The primary analysis was based on the on-treatment (OT) approach.

Overall, 6,128 patients were randomised, 3,063 to febuxostat and 3,065 to allopurinol. Median time on-treatment was shorter in the febuxostat group compared with the allopurinol group (1227 days vs. 1393 days).

In the primary OT analysis, febuxostat was non-inferior to allopurinol in the incidence of the primary endpoint, which occurred in 172 patients (1.72/100 patient years) on febuxostat compared to 241 patients (2.05/100 patient years) on allopurinol, with an adjusted HR 0.85 (95% CI: 0.70, 1.03), p<0.001. The OT Kaplan-Meier Plot of time to the primary endpoint is show below (Figure 1). There were fewer subjects at risk at each year interval in the febuxostat treatment group, compared with the allopurinol treatment group.

Figure 1 – On-Treatment Kaplan-Meier Plot of Time to the Primary Outcome



Overall, there were fewer deaths in the febuxostat group (62 of 3,063 CV deaths [0.61 per 100 patient years] and 108 of 3,063 all-cause deaths [1.06 per 100 patient years]), than in the allopurinol group (82 of 3,065 CV deaths [0.68 per 100 patient years] and 174 of 3,065 all-cause deaths [1.44 per 100 patient years]) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The OT analysis for the primary endpoint in the subgroup of patients with a history of MI, stroke or ACS showed no significant difference between treatment groups: there were 65 (9.5%) patients with events in the febuxostat group and 83 (11.8%) patients with events in the allopurinol group; adjusted HR 1.02 (95% CI: 0.74-1.42); p=0.202.

5.2 PHARMACOKINETIC PROPERTIES

General

In healthy subjects, maximum plasma concentrations (C_{max}) and area under the concentration time curve (AUC) of febuxostat increased in a dose-proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricaemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy subjects.

Absorption

Febuxostat is rapidly (t_{max} of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.5-1.6 microgram/mL, and 2.5 – 2.6 microgram/mL, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs. 51% fasting). Thus, ADENURIC may be taken with or without food.

Distribution

The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2% (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism

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

Excretion

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

Pharmacokinetics in special patient groups

Renal impairment

In a dedicated Phase 1 pharmacokinetics study, following multiple doses of 80 mg of ADENURIC in patients with mild (Cl_{cr} 60-89 mL/min, Stage 2 Chronic Kidney Disease (CKD)), moderate (Cl_{cr} 30 to 59 mL/min, Stage 3 CKD) or severe renal impairment (Cl_{cr} 10 to 29 mL/min, Stage 4 CKD), the C_{max} of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 microgram·h/mL in the normal renal function group to

13.2 microgram·h/mL in the severe renal dysfunction group. The C_{max} and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment (Cl_{cr} 30-89 mL/min, Stages 2-3 CKD). Based on population pharmacokinetic analysis, following multiple 40 mg or 80 mg doses of ADENURIC, the mean oral clearance (CL/F) values of febuxostat in patients with gout and mild (n=334), moderate (n=232) or severe (n=34) renal impairment were decreased by 14%, 34%, and 48%, respectively, compared to patients with normal (n=89) renal function. The corresponding median AUC values of febuxostat at steady-state in patients with renal impairment were increased by 18%, 49%, and 96% after 40 mg dose, and 7%, 45% and 98% after 80 mg dose, respectively, compared to patients with normal renal function.

There are insufficient data in patients with severe renal impairment (Cl_{cr} 10 to 29 mL/min, Stage 4 CKD), therefore caution should be exercised in these patients (see section 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). There are no data in end-stage renal impairment patients who are on dialysis.

Hepatic impairment

Following multiple 80 mg doses of ADENURIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20% to 30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to subjects with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in subjects with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients.

Age

There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of ADENURIC in elderly as compared to younger healthy subjects. The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of ADENURIC in geriatric participants (≥ 65 years) were similar to those in younger participants (18 to 40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger participants. No dose adjustment is necessary in geriatric patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Gender

Following multiple oral doses of ADENURIC, the C_{max} and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is needed based on gender.

5.3 PRECLINICAL SAFETY DATA

Pharmacokinetic modelling and simulation of rat data suggests that concomitant administration of oral mercaptopurine/azathioprine and febuxostat results in a ~80% decrease in the predicted population clearance, which corresponds to a ~500% increase in mercaptopurine/azathioprine AUC in humans. In addition, this was further confirmed by the results of a clinical drug-drug interaction study in healthy volunteers. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Therefore, when orally co-administered with febuxostat, a reduction of

the dose of mercaptopurine/azathioprine is recommended in order to reduce the risk of possible haematological effects.

Genotoxicity

Febuxostat was not genotoxic in a bacterial reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, two *in vivo* chromosomal aberration tests in mice and rats, and an *ex vivo* unscheduled DNA synthesis assay in rats. While febuxostat was positive for chromosomal aberrations in Chinese Hamster Lung fibroblasts, the weight of evidence suggests that it does not pose a genotoxic risk.

Carcinogenicity

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, magnesium stearate, hyprolose, croscarmellose sodium and silicon dioxide. Core tablets are coated with Opadry II, Yellow, 85F42129 containing: polyvinyl alcohol, titanium dioxide, macrogol 3350, purified talc and iron oxide yellow.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE OF CONTENTS OF CONTAINER

ADENURIC tablets are packed in clear (Aclar/PVC/Aluminium or PVC/PE/PVDC/Al) blisters of 14 film-coated tablets. Two blisters are available in each pack of 28 tablets. Packs of 4 or 8 tablets contain either one or two blisters of 4 tablets, respectively.

ADENURIC 80 mg tablets are available in packs of 4, 8 or 28 film-coated tablets*.

*Not all pack sizes may be marketed.

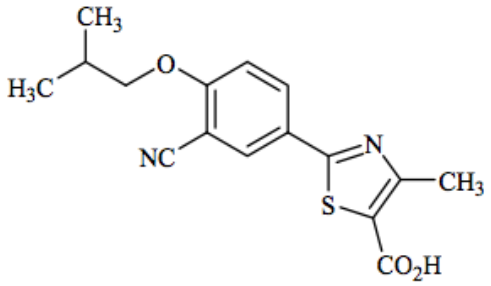
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

ADENURIC tablet is a potent, non-purine, selective inhibitor of Xanthine Oxidase (XO) that prevents the normal oxidation of purines to uric acid. The active ingredient in ADENURIC is febuxostat, a 2-arylthiazole derivative.

Chemical Structure



Chemical name

2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid

Molecular formula

$C_{16}H_{16}N_2O_3S$

Molecular weight

316.37

CAS number

144060-53-7

Febuxostat is a white, crystalline powder with a pH of 5.0 in febuxostat solution (1 in 20,000 w/v). It is practically insoluble in water, slightly soluble in methanol, freely soluble in N, N-dimethylformamide and sparingly soluble in ethanol. The solubility of febuxostat is pH dependent in a wide-ranged buffer solution (i.e. Britton-Robinson buffer): at range pH 2.0 – 6.0 febuxostat is practically insoluble and its solubility slightly increases at range pH 8.0 – 10.0. Febuxostat has an aqueous pKa of 3.3 and a LogD of 1.6 at pH 7.0 in a solution of octanol/aqueous potassium chloride. Several polymorphic forms of febuxostat have been identified; however, ADENURIC tablets contain febuxostat as polymorphic form A.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

A. Menarini Australia Pty Ltd

Level 8, 67 Albert Ave,

Chatswood NSW 2067

Australia

Phone: 1800 644 542

9. DATE OF FIRST APPROVAL

18 December 2014

10. DATE OF REVISION

02 November 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 Special Warnings and Precautions for Use	Cardiovascular disorders – Primary efficacy outcome and cardiovascular deaths from the FAST study are included Mercaptopurine/azathioprine – Removal of the statement that no interaction studies have been performed in humans
4.5 Interactions with Other Medicines and Other Forms of Interactions	Mercaptopurine/azathioprine – Amendment of text based on the clinical drug-drug interaction outcomes.
4.8 Adverse effects (undesirable effects)	Changes to frequency category and addition of adverse reactions from post-authorisation safety study (FAST study).
5.1 Clinical Trials	Inclusion of clinical study outcomes from FAST study.

ADENURIC® is a trademark of Teijin Limited, Tokyo, Japan.