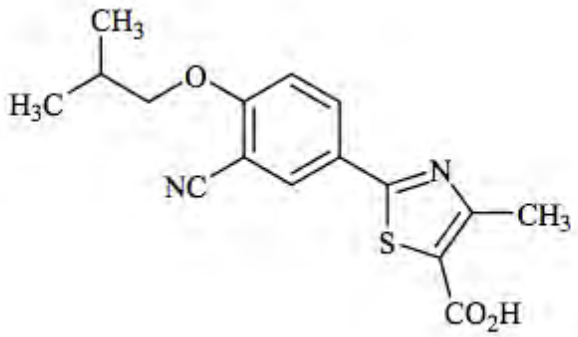
ADENURIC®

(febuxostat)

NAME OF THE MEDICINE

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. Its chemical name is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, and the chemical structure is:



CAS number: 144060-53-7

Molecular formula: $C_{16}H_{16}N_2O_3S$

Molecular weight: 316.37

DESCRIPTION

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.

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.

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

PHARMACOLOGY

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

Pharmacodynamics

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 repolarization 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.

Pharmacokinetics

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 40mg and 80mg once daily doses, C_{max} is approximately 1.5-1.6 µg/mL, and 2.5 – 2.6 µg/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 Cmax 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 without regard to food.

Distribution:

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

Elimination:

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

Pharmacokinetics in special patient groups:

Renal impairment

Following multiple doses of 80 mg of ADENURIC in patients with mild (Clcr 60-89 mL/min, Stage 2 Chronic Kidney Disease (CKD)), moderate (Clcr 30 to 59 mL/min, Stage 3 CKD) or severe renal impairment (Clcr 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 μg·h/mL in the normal renal function group to 13.2 μg.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 (Clcr 30-89 mL/min, Stages 2 -3 CKD). There are insufficient data in patients with severe renal impairment (Clcr 10 to 29 mL/min, Stage 4 CKD), therefore caution should be exercised in these patients. 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 Cmax 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 **PRECAUTIONS**).

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.

CLINICAL TRIALS

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

TMX-00-004 and FOCUS (TMX-01-005) Studies

The efficacy of ADENURIC was evaluated in a four week dose ranging study which randomized 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 µmol/L (6 mg/dL) was 0%, 56%, 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 µmol/L (6.0 mg/dL) at the final visit was greater than 80% (81-100%) at each febuxostat dose.

CONFIRMS, APEX and FACTS Studies

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 µmol/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 µmol/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 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, randomized, 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 µmol/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, randomized, double-blind, multicenter, 28-week study. One thousand and seventy-two (1072) patients were randomized: 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 ADENURIC 80 mg daily treatment arm versus the conventionally used doses of allopurinol 300mg (n = 258) /100mg (n = 10) treatment arm in reducing the sUA below 357 µmol/L (6mg/dL). See **Table 2**.

FACT Study

The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomized, double-blind, multicenter, 52-week study. Seven hundred sixty (760) patients were randomized: 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 ADENURIC 80 mg daily treatment arm versus the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 357 µmol/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 1** summarizes the demographics and baseline characteristics for the subjects enrolled in the studies.

Table 1: 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 Hyperlipidemia	38%
BMI ≥ 30 kg/m^2	63%
Mean BMI	33 kg/m^2
Baseline sUA ≥ 595 µmol/L (10 mg/dL)	36%
Mean baseline sUA	577 µmol/L (9.7 mg/dL)

Experienced a gout flare in previous year	85%

Table 2 summarises the efficacy endpoint results in all 3 studies:

Table 2: Proportion of Patients with Serum Uric Acid Levels < 357µmol/L (6.0 mg/dL) at Last Three Monthly Visits and Final Visit

STUDY	Treatment Group				Difference in Proportion (95% CI)	
	ADENURIC 40mg daily	ADENURIC 80 mg daily	Allopurinol 300mg daily [1, 2]	Placebo	ADENURIC 40mg vs allopurinol	ADENURIC 80mg vs allopurinol
LAST THREE MONTHLY VISITS						
APEX (6 months)		48%* (126/262)	22% (60/268)	0% (0/134)		26% (19%-37%)
FACT (12 months)		53%* (136/255)	21% (53/251)			32% (25%-43%)
FINAL VISIT						
CONFIRMS (6 months)	45% (345/757)	67%* (507/756)	42% (318/755)		3% (-2%, 8%)	25% (20%, 30%)
APEX (6 months)		72% (183/253)	39% (102/263)	1% (1/134)		33% (26%, 42%)
FACT (12 months)		74% (185/249)	36% (88/242)			38% (30%, 46%)

[1] Allopurinol was administered at reduced doses of 200mg (CONFIRMS study) and 100mg (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 µmol/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 3**, febuxostat 80mg was significantly more effective in lowering sUA to < 357 µmol/L (6 mg/dL) compared to allopurinol 300 mg/200 mg or febuxostat 40mg.

Table 3: Proportion of subjects with Serum Urate Level < 357 µmol/L (6mg/ dL) at Final Visit by Renal Function in CONFIRMS Study

Renal Function	Number (%) Subjects			
	Febuxostat 40mg daily	Febuxostat 80mg daily	Allopurinol 300mg	Allopurinol 200mg
Normal CL_{cr} > 90mL/min	104/278 (37%)[a]	147/253 (58%)[b]	106/254 (42%)	NA
Mildly impaired	182/349	263/367	169/365	NA

(Stage 2 CKD) CL_{cr} 60- 89 mL/min	(52%)[a]	(72%)[b]	(46%)	
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 40mg vs febuxostat 80mg
b. p< 0.001 Febuxostat 80mg vs allopurinol 300/200mg

Primary endpoint in the sub group of patients with sUA ≥ 595 µmol/L (10 mg/dL)

Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of ≥ 595 µol/L (10 mg/dL). In this subgroup ADENURIC achieved the primary efficacy endpoint (sUA < 357µmol/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 µmol/L [6.0 mg/dL] at the final visit) for patients with a baseline serum urate level of ≥ 595 µmol/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 80mg), 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 incidences 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 Study) was numerically lower in the groups that achieved an average post-baseline serum urate level < 357 µmol/L, < 297 µmol/L, or < 238 µmol/L compared to the group that achieved an average post-baseline serum urate level ≥ 357µmol/L during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 49 - 52 intervals).

CONFIRMS study: the percentages 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.

INDICATIONS

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

CONTRAINDICATIONS

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

PRECAUTIONS

Cardio-vascular disorders

Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure 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 **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. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

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. 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 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 flare)

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 mobilization 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. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects (see **INTERACTIONS WITH OTHER MEDICINES**).

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 coadministered with febuxostat. Co-administration of febuxostat 80 mg and theophylline in healthy participants showed no statisitically significant interaction (see **INTERACTIONS WITH OTHER MEDICINES**). 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 coadminister 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 7). Liver function test is 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 randomized 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 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 etiologies 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 µIU/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.

Effects on fertility

In rats, reproduction studies 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. 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 fetus/new born child. Studies in rats and rabbits found no evidence of fetal 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 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.

Paediatric use

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

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 **Pharmacokinetics**).

Use in Renal impairment

There are insufficient data in patients with severe renal impairment (Clcr less than 30 mL/min, Stage 4 CKD); therefore caution should be exercised in these patients.

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 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.

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.

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.

INTERACTIONS WITH OTHER MEDICINES

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 substantially increase plasma concentrations of these drugs leading to severe toxicity (see **PRECAUTIONS**). Drug interaction studies of febuxostat with drugs that are metabolized by XO have not been performed.

Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during cytotoxic therapy.

Rosiglitazone/CYP2C8 substrates

Febuxostat was shown to be a weak inhibitor of CYP2C8 *in vitro*. In a study in healthy subjects, coadministration 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 coadministered with febuxostat. Administration of febuxostat (80 mg once daily) with theophylline resulted in an increase of 6% in Cmax 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 coadminister 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.

ADVERSE 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) and post-marketing experience are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post-marketing experience.

Table 4 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 4: Adverse effects (% Patients) in Phase III 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** Nausea	9.0% 2.2%	5.9% 2.6%	7.3% 3.0%	7.1% 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 randomized 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 80mg and in 0.9% of allopurinol-treated subjects.

Tabulated list of adverse reactions:

Uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1000) adverse reactions occurring in patients treated with febuxostat are listed in **Tables 5** and **6** below.

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

Table 5: Adverse reactions in combined Phase 3, long-term extension studies (≤ 1%)

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia
Endocrine disorders	Uncommon Blood thyroid stimulating hormone increased
Eye disorders	Rare Blurred vision
Metabolism and nutrition disorders	Uncommon Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase Rare Weight decrease, increase appetite, anorexia
Psychiatric disorders	Uncommon Libido decreased, insomnia Rare Nervousness
Nervous system disorders	Uncommon Dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia
Ear and labyrinth disorders	Rare Tinnitus
Cardiac disorders	Uncommon Atrial fibrillation, palpitations, ECG abnormal
Vascular disorders	Uncommon Hypertension, flushing, hot flush
Respiratory system disorders	Uncommon Dyspnoea, bronchitis, upper respiratory tract infection, cough
Gastrointestinal disorders	Uncommon Abdominal pain, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort Rare Pancreatitis, mouth ulceration
Hepato-biliary disorders	Uncommon Cholelithiasis Rare Hepatitis
Skin and subcutaneous tissue disorders	Uncommon Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular Rare Erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash erythematous, rash morbillifom, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis Rare Joint stiffness, musculoskeletal stiffness
Renal and urinary disorders	Uncommon Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria Rare Micturition urgency
Reproductive system and breast disorder	Uncommon Erectile dysfunction

General disorders and administration site conditions	Uncommon Fatigue, chest pain, chest discomfort Rare Thirst
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 Rare Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase

Post marketing experience

Table 6: Adverse reactions post-marketing

Immune system disorders	Rare Anaphylactic reaction, drug hypersensitivity
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, generalized rash (serious), rash pruritic
Musculoskeletal and connective tissue disorders	Rare Rhabdomyolysis*
Renal and urinary disorders	Rare Tubulointerstitial nephritis

*The majority of these patients were receiving a statin and colchicines 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 to 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 randomized controlled and long-term extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI 0.00-6.16), febuxostat 40mg 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 incidences 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).

Overall, a higher rate of APTC events was observed in febuxostat than in allopurinol-treated patients. A causal relationship with febuxostat has not been established. Monitor for signs and symptoms of myocardial infarction and stroke (see **PRECAUTIONS**).

Abnormal Hematologic and Clinical Chemistry Findings

During the 3 randomized 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 7.**

Table 7: 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.

DOSAGE AND ADMINISTRATION

The recommended oral dose of ADENURIC is 40mg or 80mg 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. The 80mg tablet can be split into two equal halves in order to provide a 40mg dose. Prescribers should advise patients on how to break the tablets in half.

Testing for the target serum uric acid level of less than 357µmol/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 Precautions, 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 (Clcr 30 to 89 mL/min, Stages 2-3 CKD).

Caution should be exercised in patients with severe renal impairment (creatinine clearance < 30ml/ min, Stage 4 CKD, see **Pharmacokinetics**). The efficacy and safety has not been fully evaluated in these patients (see **Precautions**).

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 **Precautions**).

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

OVERDOSAGE

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for advice. Patients with an overdose should be managed by symptomatic and supportive care.

PRESENTATION AND STORAGE CONDITIONS

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.

Shelf life: 3 years

Store below 30°C.

ADENURIC tablets are packed in clear (Aclar/PVC/Aluminium) 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.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

DD Month YYYY

DATE OF MOST RECENT AMENDMENT

DD Month YYYY

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