

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of febuxostat.

Excipients: Each tablet contains 76.50 mg of lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale yellow to yellow, film-coated, capsule shaped tablets, engraved with "80" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The recommended oral dose of ADENURIC is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dl (357 µmol/l) after 2-4 weeks, ADENURIC 120 mg once daily may be considered.

ADENURIC works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dl (357 µmol/l).

Gout flare prophylaxis of at least 6 months is recommended (see section 4.4).

Special populations

Renal insufficiency

No dosage adjustment is necessary in patients with mild or moderate renal impairment. The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 ml/min, see section 5.2).

Hepatic impairment

The recommended dosage in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment. The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).

Elderly

No dose adjustment is required in the elderly (see section 5.2).

Children and adolescents

As there has been no experience in children and adolescents, the use of febuxostat in such patients is not recommended.

Organ transplant recipients

As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.8).

4.4 Special warnings and precautions for use

Cardio-vascular disorders

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

Acute gouty attacks (gout flare)

Febuxostat treatment should not be started until an acute attack of gout has completely subsided. As with other urate lowering medicinal products, gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 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.

Xanthine deposition

As with other urate lowering medicinal products, 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 (see section 4.5).

Theophylline

Febuxostat should be used with caution in patients concomitantly treated with theophylline and theophylline levels should be monitored in patients starting febuxostat therapy (see section 4.5).

Liver disorders

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement (see section 5.1).

Thyroid disorders

Increased TSH values (>5.5 $\mu\text{IU/ml}$) were observed in patients on long-term treatment with febuxostat (5.0%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function (see section 5.1).

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Mercaptopurine/azathioprine

Although interaction studies with febuxostat have not been performed, inhibition of xanthine oxidase (XO) is known to result in an increase in mercaptopurine or azathioprine levels. On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended.

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

Theophylline

Although interaction studies have not been performed with febuxostat, inhibition of XO may cause an increase in the theophylline level (inhibition of the metabolism of theophylline has been reported with other XO inhibitors). Hence caution is advised if these active substances are given concomitantly, and theophylline levels should be monitored in patients starting febuxostat therapy.

Naproxen and other inhibitors of glucuronidation

Febuxostat metabolism depends on 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 250mg BID 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 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/indometacin/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. After initiation of febuxostat therapy, monitoring of anticoagulant activity should be considered in patients receiving warfarin or similar agents.

Desipramine/CYP2D6 substrates.

Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro*. In a study in healthy subjects, 120 mg ADENURIC QD 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.

4.6 Pregnancy and lactation

Pregnancy

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/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition (see section 5.3). The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

Breast feeding

It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As with other xanthine oxidase inhibitors adverse reactions such as somnolence, dizziness and paraesthesia have been reported. 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 Undesirable effects

A total of 2531 subjects received at least one dose of ADENURIC (10 mg – 300 mg) in clinical studies.

Phase 3 randomised controlled studies

In randomised controlled phase 3 clinical studies, >,1000 patients have been treated with the recommended doses of 80 mg or 120 mg (536 subjects enrolled in a 28 week study and 507 subjects enrolled in a 52 weeks study). The treatment-related events (ADRs) were mostly mild or moderate in severity.

The most commonly reported ADRs (investigator assessment) are liver function abnormalities (3.5%), diarrhoea (2.7%), headache (1.8%), nausea (1.7%), rash (1.5 %).

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

Common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ to $< 1/1000$) adverse reactions suspected (investigator assessment) to be drug related occurring in the 80 mg/120 mg treatment groups and reported more than once in the total febuxostat treatment group are listed below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Treatment related adverse reactions in phase 3 randomized controlled studies

Investigations	<u>Uncommon</u> Blood amylase increase, platelet count decrease, blood creatinine increase, haemoglobin decrease, blood urea increase , LDH increase, triglycerides increase
Cardiac disorders	<u>Rare</u> Palpitations
Nervous system disorders	<u>Common</u> Headache <u>Uncommon</u> Dizziness, paraesthesia, somnolence, altered taste
Gastrointestinal disorders	<u>Common</u> Diarrhoea*, nausea* <u>Uncommon:</u> Abdominal pain, gastro-oesophageal reflux disease, vomiting*, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort,
Renal and urinary disorders	<u>Uncommon</u> Nephrolithiasis, haematuria, pollakiuria <u>Rare</u> Renal insufficiency
Skin and subcutaneous tissue disorders	<u>Common</u> Rash** <u>Uncommon</u> Dermatitis, urticaria, pruritus
Musculoskeletal and connective tissue disorders	<u>Uncommon</u> Arthralgia, arthritis, myalgia, muscle cramp, musculoskeletal pain
Metabolism and nutrition disorders	<u>Uncommon</u> Weight increase, increased appetite
Vascular disorders	<u>Uncommon</u> Hypertension, flushing, hot flush,
General disorders and administration site conditions	<u>Uncommon</u> Fatigue, oedema, influenza like symptoms <u>Rare</u> Asthenia, thirst
Hepato-biliary disorders	<u>Common</u> LFT abnormalities
Psychiatric disorders	<u>Uncommon</u> Libido decreased <u>Rare</u> Nervousness, Insomnia

* Diarrhoea, nausea and vomiting are more frequent in patients concomitantly treated with colchicine

** No serious rashes or severe hypersensitivity reactions were noted in the clinical studies.

Long-term open label extension studies

In the long-term open label extension studies, the number of patients treated with febuxostat 80 mg/120 mg up to 1 year was 906, up to 2 years was 322, up to 3 years was 57, and up to 4 years was 53. The treatment-related events reported during the long-term extension studies were similar to those reported in the Phase 3 studies (see Table 1). The most commonly reported treatment-related events (investigator assessment) are: liver function abnormalities, diarrhoea, headache, rash, hypertension.

The following treatment-related events were reported more than once in the total febuxostat treatment group and were reported as uncommon in subjects taking febuxostat 80 mg/120 mg in long-term extension studies (up to 4 years, >1,900 Patient-years of exposure). These treatment-related events were either not reported or reported at a lower frequency for these doses, in the pivotal Phase 3 studies: Diabetes, hyperlipidaemia, insomnia, hypoaesthesia, ECG abnormal, cough, dyspnoea, skin discolouration, skin lesion, bursitis, proteinuria, renal insufficiency, erectile dysfunction, blood potassium increase, blood TSH increase, lymphocyte count decreased, WBC decrease.

4.9 Overdose

No case of overdose has been reported. Patients with an overdose should be managed by symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparations inhibiting uric acid production, ATC code: M04AA03

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 catalyzed 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 potent, non-purine selective inhibitor of XO (NP-SIXO) with an *in vitro* inhibition K_i value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized 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.

Clinical studies results

The efficacy of ADENURIC was demonstrated in two Phase 3 pivotal studies (APEX study and FACT study described below) that were conducted in 1832 patients with hyperuricemia and gout. In each phase 3 pivotal study, ADENURIC demonstrated superior ability to lower

and maintain serum uric acid levels compared to allopurinol. The primary efficacy endpoint in each study was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dl (357 µmol/l). No patients with organ transplant have been included in these studies (see section 4.2).

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 QD (n=267), ADENURIC 120 mg QD (n=269), ADENURIC 240 mg QD (n=134) or allopurinol (300 mg QD [n=258] for patients with a baseline serum creatinine ≤1.5 mg/dl or 100 mg QD [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 both the ADENURIC 80 mg QD and the ADENURIC 120 mg QD treatment arms *versus* the conventionally used doses of allopurinol 300mg (n = 258) /100mg (n = 10) treatment arm in reducing the sUA below 6 mg/dl (357 µmol/l) (see Table 2 and Figure 1).

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 QD (n=256), ADENURIC 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).

The FACT study showed the statistically significant superiority of both ADENURIC 80 mg and ADENURIC 120 mg QD treatment arms *versus* the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6 mg/dl (357 µmol/l).

Table 2 summarises the primary efficacy endpoint results:

Table 2
Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dl (357µmol/l)
Last Three Monthly Visits

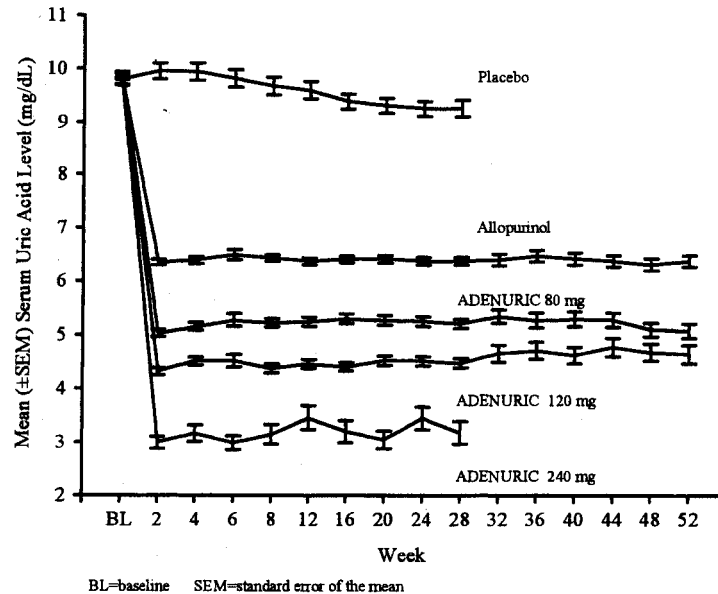
Study	ADENURIC 80 mg QD	ADENURIC 120 mg QD	Allopurinol 300 / 100 mg QD ¹
APEX (28 weeks)	48%* (n=262)	65%*,# (n=269)	22% (n=268)
FACT (52 weeks)	53%* (n=255)	62%* (n=250)	21% (n=251)
Combined Results	51%* (n=517)	63%*,# (n=519)	22% (n=519)

¹ results from subjects receiving either 100 mg QD (n=10: patients with serum creatinine >1.5 and ≤2.0 mg/dl) or 300 mg QD (n=509) were pooled for analyses.
* p < 0.001 vs allopurinol, # p < 0.001 vs 80 mg

The ability of ADENURIC to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to <6.0 mg/dl (357 µmol/l) was noted by the Week 2 visit

and was maintained throughout treatment. The mean serum uric acid levels over time for each treatment group from the Phase 3 pivotal studies are shown in Figure 1.

Figure 1 Mean Serum Uric Acid Levels Combined Phase 3 Studies



Note: 509 patients received allopurinol 300 mg QD; 10 patients with serum creatinine >1.5 and < 2.0 mg/dl were dosed with 100 mg QD. (10 patients out of 268 in APEX study).
240 mg febuxostat was used to evaluate the safety of febuxostat at twice the recommended highest dose.

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

The APEX Study evaluated efficacy in 40 patients with renal impairment (i.e., baseline serum creatinine > 1.5 mg/dl and <=2.0 mg/dl). For renally impaired subjects who were randomized to allopurinol, the dose was capped at 100mg QD. ADENURIC achieved the primary efficacy endpoint in 44% (80 mg QD), 45% (120 mg QD), and 60% (240 mg QD) of patients compared to 0% in the allopurinol 100 mg QD and placebo groups.

There were no clinically significant differences in the percent decrease in serum uric acid concentration in healthy subjects irrespective of their renal function (58 % in the normal renal function group and 55% in the severe renal dysfunction group).

Primary endpoint in the sub group of patients with sUA ≥ 10 mg/dl

Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of ≥ 10 mg/dl. In this subgroup ADENURIC achieved the primary efficacy endpoint in 41% (80 mg QD), 48% (120 mg QD), and 66% (240 mg QD) of patients compared to 9% in the allopurinol 300 mg/100 mg QD and 0 % in the placebo groups.

Clinical Outcomes: proportion of patients requiring treatment for a gout flare and tophi size change

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 <6.0 mg/dl, <5.0 mg/dl, or <4.0 mg/dl compared to the group that achieved an average post-

baseline serum urate level ≥ 6.0 mg/dl during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 48 - 52 intervals).

Two years of data from the Phase 3 Open Label Extension study showed that the maintenance of serum urate levels < 6 mg/dl (< 357 $\mu\text{mol/l}$) resulted in a decrease in the incidence of gout flares with less than 3 % of subjects requiring treatment for a flare (i.e. more than 97 % of patients did not require treatment for a flare) at Month 16-24. This was associated with a reduction of tophus size leading to complete resolution in 54% of subjects at Month 24.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). These rates were similar to the rates reported on allopurinol (3.6%) (see section 4.4). Increased TSH values (> 5.5 $\mu\text{IU/ml}$) were observed in patients on long-term treatment with febuxostat (5.0%) and patients with allopurinol (5.8%) in the long term open label extension studies (see section 4.4).

The total exposure to ADENURIC in phase 3 pivotal studies and long-term extension studies is greater than 2700 patient-years.

5.2 Pharmacokinetic properties

In healthy subjects, maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricemia and gout, treated with ADENURIC 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

Absorption

Febuxostat is rapidly (t_{max} of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, C_{max} is approximately 2.8-3.2 $\mu\text{g/ml}$, and 5.0-5.3 $\mu\text{g/ml}$, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in C_{max} and a 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, ADENURIC may be taken without regard to food.

Distribution

The apparent steady state volume of distribution (V_{ss}/F) of febuxostat ranges from 29 to 75 l after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

Metabolism

Febuxostat is extensively 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%).

Special populations

Renal insufficiency

Following multiple doses of 80 mg of ADENURIC in patients with mild, moderate or severe renal insufficiency, 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.

Hepatic impairment

Following multiple doses of 80 mg of ADENURIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the C_{max} and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

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.

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. No dose adjustment is needed based on gender.

5.3 Preclinical safety data

Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

Carcinogenesis, mutagenesis, impairment of fertility

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

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

Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Magnesium stearate
Hydroxypropylcellulose
Croscarmellose sodium
Silica, colloidal hydrated

Tablet coating

Opadry II, Yellow, 85F42129 containing:
Polyvinyl alcohol
Titanium dioxide (E171)
Macrogols 3350
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

Clear (Aclar/PVC/Aluminium) blister of 14 tablets.

ADENURIC 80 mg is available in pack sizes of 28 and 84 film-coated tablets .

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ipsen Manufacturing Ireland Ltd (IMIL)
Blanchardstown Industrial Park
Snugboro Road
Dublin 15
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>

1. NAME OF THE MEDICINAL PRODUCT

ADENURIC 120 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 120 mg of febuxostat.

Excipients: Each tablet contains 114.75mg of lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale yellow to yellow, film-coated, capsule shaped tablets, engraved with "120" on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The recommended oral dose of ADENURIC is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dl (357 µmol/l) after 2-4 weeks, ADENURIC 120 mg once daily may be considered.

ADENURIC works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dl (357µmol/l).

Gout flare prophylaxis of at least 6 months is recommended (see section 4.4).

Special populations

Renal insufficiency

No dosage adjustment is necessary in patients with mild or moderate renal impairment. The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 ml/min, see section 5.2).

Hepatic impairment

The recommended dosage in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment. The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).

Elderly

No dose adjustment is required in the elderly (see section 5.2).

Children and adolescents

As there has been no experience in children and adolescents, the use of febuxostat in such patients is not recommended.

Organ transplant recipients

As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.8).

4.4 Special warnings and precautions for use

Cardio-vascular disorders

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

Acute gouty attacks (gout flare)

Febuxostat treatment should not be started until an acute attack of gout has completely subsided. As with other urate lowering medicinal products, gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 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.

Xanthine deposition

As with other urate lowering medicinal products, 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 (see section 4.5).

Theophylline

Febuxostat should be used with caution in patients concomitantly treated with theophylline and theophylline levels should be monitored in patients starting febuxostat therapy (see section 4.5).

Liver disorders

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgement (see section 5.1).

Thyroid disorders

Increased TSH values (>5.5 $\mu\text{IU/ml}$) were observed in patients on long-term treatment with febuxostat (5.0%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function (see section 5.1).

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Mercaptopurine/azathioprine

Although interaction studies with febuxostat have not been performed, inhibition of xanthine oxidase (XO) is known to result in an increase in mercaptopurine or azathioprine levels. On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended.

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

Theophylline

Although interaction studies have not been performed with febuxostat, inhibition of XO may cause an increase in the theophylline level (inhibition of the metabolism of theophylline has been reported with other XO inhibitors). Hence caution is advised if these active substances are given concomitantly, and theophylline levels should be monitored in patients starting febuxostat therapy.

Naproxen and other inhibitors of glucuronidation

Febuxostat metabolism depends on 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 250mg BID 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 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/indometacin/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. After initiation of febuxostat therapy, monitoring of anticoagulant activity should be considered in patients receiving warfarin or similar agents.

Desipramine/CYP2D6 substrates.

Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro*. In a study in healthy subjects, 120 mg ADENURIC QD 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.

4.6 Pregnancy and lactation

Pregnancy

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/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition (see section 5.3). The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

Breast feeding

It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As with other xanthine oxidase inhibitors adverse reactions such as somnolence, dizziness and paraesthesia have been reported. 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 Undesirable effects

A total of 2531 subjects received at least one dose of ADENURIC (10 mg – 300 mg) in clinical studies.

Phase 3 randomised controlled studies

In randomised controlled phase 3 clinical studies, >1,000 patients have been treated with the recommended doses of 80 mg or 120 mg (536 subjects enrolled in a 28 week study and 507 subjects enrolled in a 52 weeks study). The treatment-related events (ADRs) were mostly mild or moderate in severity.

The most commonly reported ADRs (investigator assessment) are liver function abnormalities (3.5%), diarrhoea (2.7%), headache (1.8%), nausea (1.7%), rash (1.5 %).

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

Common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ to $< 1/1000$) adverse reactions suspected (investigator assessment) to be drug related occurring in the 80 mg/120 mg treatment groups and reported more than once in the total febuxostat treatment group are listed below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Treatment related adverse reactions in phase 3 randomized controlled studies

Investigations	<u>Uncommon</u> Blood amylase increase, platelet count decrease, blood creatinine increase, haemoglobin decrease, blood urea increase , LDH increase, triglycerides increase
Cardiac disorders	<u>Rare</u> Palpitations
Nervous system disorders	<u>Common</u> Headache <u>Uncommon</u> Dizziness, paraesthesia, somnolence, altered taste
Gastrointestinal disorders	<u>Common</u> Diarrhoea *, nausea * <u>Uncommon:</u> Abdominal pain, gastro-oesophageal reflux disease, vomiting *, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort,
Renal and urinary disorders	<u>Uncommon</u> Nephrolithiasis, haematuria, pollakiuria <u>Rare</u> Renal insufficiency
Skin and subcutaneous tissue disorders	<u>Common</u> Rash ** <u>Uncommon</u> Dermatitis, urticaria, pruritus
Musculoskeletal and connective tissue disorders	<u>Uncommon</u> Arthralgia, arthritis, myalgia, muscle cramp, musculoskeletal pain
Metabolism and nutrition disorders	<u>Uncommon</u> Weight increase, increased appetite
Vascular disorders	<u>Uncommon</u> Hypertension, flushing, hot flush,
General disorders and administration site conditions	<u>Uncommon</u> Fatigue, oedema, influenza like symptoms <u>Rare</u> Asthenia, thirst
Hepato-biliary disorders	<u>Common</u> LFT abnormalities
Psychiatric disorders	<u>Uncommon</u> Libido decreased <u>Rare</u> Nervousness, Insomnia

* Diarrhoea, nausea and vomiting are more frequent in patients concomitantly treated with colchicine

** No serious rashes or severe hypersensitivity reactions were noted in the clinical studies.

Long-term open label extension studies

In the long-term open label extension studies, the number of patients treated with febuxostat 80 mg/120 mg up to 1 year was 906, up to 2 years was 322, up to 3 years was 57, and up to 4 years was 53. The treatment-related events reported during the long-term extension studies were similar to those reported in the Phase 3 studies (see Table 1). The most commonly reported treatment-related events (investigator assessment) are: liver function abnormalities, diarrhoea, headache, rash, hypertension.

The following treatment-related events were reported more than once in the total febuxostat treatment group and were reported as uncommon in subjects taking febuxostat 80 mg/120 mg in long-term extension studies (up to 4 years, >1,900 Patient-years of exposure). These treatment-related events were either not reported or reported at a lower frequency for these doses, in the pivotal Phase 3 studies: Diabetes, hyperlipidaemia, insomnia, hypoaesthesia, ECG abnormal, cough, dyspnoea, skin discolouration, skin lesion, bursitis, proteinuria, renal insufficiency, erectile dysfunction, blood potassium increase, blood TSH increase, lymphocyte count decreased, WBC decrease.

4.9 Overdose

No case of overdose has been reported. Patients with an overdose should be managed by symptomatic and supportive care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparations inhibiting uric acid production, ATC code: M04AA03

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 catalyzed 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 potent, non-purine selective inhibitor of XO (NP-SIXO) with an *in vitro* inhibition K_i value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized 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.

Clinical studies results

The efficacy of ADENURIC was demonstrated in two Phase 3 pivotal studies (APEX study and FACT study described below) that were conducted in 1832 patients with hyperuricemia and gout. In each phase 3 pivotal study, ADENURIC demonstrated superior ability to lower

and maintain serum uric acid levels compared to allopurinol. The primary efficacy endpoint in each study was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dl (357 µmol/l). No patients with organ transplant have been included in these studies (see section 4.2).

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 QD (n=267), ADENURIC 120 mg QD (n=269), ADENURIC 240 mg QD (n=134) or allopurinol (300 mg QD [n=258] for patients with a baseline serum creatinine ≤1.5 mg/dl or 100 mg QD [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 both the ADENURIC 80 mg QD and the ADENURIC 120 mg QD treatment arms *versus* the conventionally used doses of allopurinol 300mg (n = 258) /100mg (n = 10) treatment arm in reducing the sUA below 6 mg/dl (357 µmol/l) (see Table 2 and Figure 1).

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 QD (n=256), ADENURIC 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).

The FACT study showed the statistically significant superiority of both ADENURIC 80 mg and ADENURIC 120 mg QD treatment arms *versus* the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6 mg/dl (357 µmol/l).

Table 2 summarises the primary efficacy endpoint results:

Table 2
Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dl (357µmol/l)
Last Three Monthly Visits

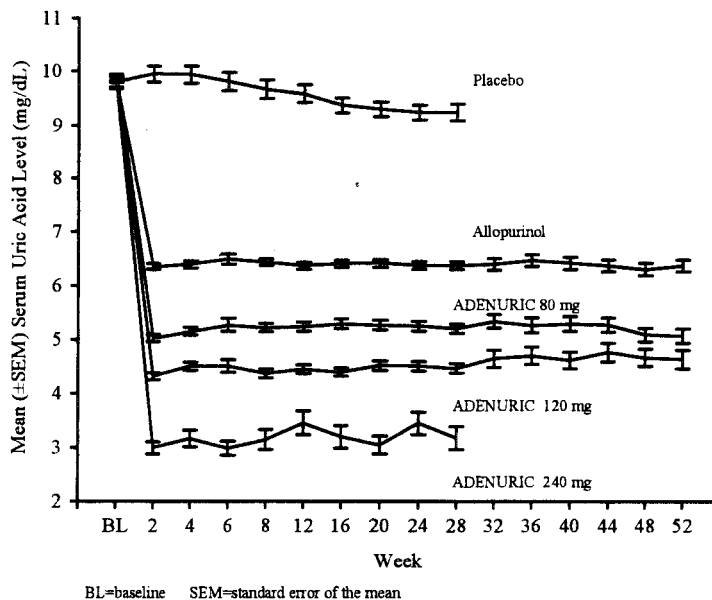
Study	ADENURIC 80 mg QD	ADENURIC 120 mg QD	Allopurinol 300 / 100 mg QD ¹
APEX (28 weeks)	48%* (n=262)	65%*,# (n=269)	22% (n=268)
FACT (52 weeks)	53%* (n=255)	62%* (n=250)	21% (n=251)
Combined Results	51%* (n=517)	63%*,# (n=519)	22% (n=519)

¹ results from subjects receiving either 100 mg QD (n=10: patients with serum creatinine >1.5 and ≤2.0 mg/dl) or 300 mg QD (n=509) were pooled for analyses.
* p < 0.001 vs allopurinol, # p < 0.001 vs 80 mg

The ability of ADENURIC to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to <6.0 mg/dl (357 µmol/l) was noted by the Week 2 visit

and was maintained throughout treatment. The mean serum uric acid levels over time for each treatment group from the Phase 3 pivotal studies are shown in Figure 1.

Figure 1 Mean Serum Uric Acid Levels Combined Phase 3 Studies



Note: 509 patients received allopurinol 300 mg QD; 10 patients with serum creatinine >1.5 and < 2.0 mg/dl were dosed with 100 mg QD. (10 patients out of 268 in APEX study).
240 mg febuxostat was used to evaluate the safety of febuxostat at twice the recommended highest dose.

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

The APEX Study evaluated efficacy in 40 patients with renal impairment (i.e., baseline serum creatinine > 1.5 mg/dl and ≤2.0 mg/dl). For renally impaired subjects who were randomized to allopurinol, the dose was capped at 100mg QD. ADENURIC achieved the primary efficacy endpoint in 44% (80 mgQD), 45% (120 mg QD), and 60% (240 mg QD) of patients compared to 0% in the allopurinol 100 mg QD and placebo groups.

There were no clinically significant differences in the percent decrease in serum uric acid concentration in healthy subjects irrespective of their renal function (58 % in the normal renal function group and 55% in the severe renal dysfunction group).

Primary endpoint in the sub group of patients with sUA ≥ 10 mg/dl

Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of ≥ 10 mg/dl. In this subgroup ADENURIC achieved the primary efficacy endpoint in 41% (80 mg QD), 48% (120 mg QD), and 66% (240 mg QD) of patients compared to 9% in the allopurinol 300 mg/100 mg QD and 0 % in the placebo groups.

Clinical Outcomes: proportion of patients requiring treatment for a gout flare and tophi size change

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 <6.0 mg/dl, <5.0 mg/dl, or <4.0 mg/dl compared to the group that achieved an average post-

baseline serum urate level ≥ 6.0 mg/dl during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 48 - 52 intervals).

Two years of data from the Phase 3 Open Label Extension study showed that the maintenance of serum urate levels < 6 mg/dl (< 357 $\mu\text{mol/l}$) resulted in a decrease in the incidence of gout flares with less than 3 % of subjects requiring treatment for a flare (i.e. more than 97 % of patients did not require treatment for a flare) at Month 16-24. This was associated with a reduction of tophus size leading to complete resolution in 54% of subjects at Month 24.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). These rates were similar to the rates reported on allopurinol (3.6%) (see section 4.4). Increased TSH values (> 5.5 $\mu\text{IU/ml}$) were observed in patients on long-term treatment with febuxostat (5.0%) and patients with allopurinol (5.8%) in the long term open label extension studies (see section 4.4).

The total exposure to ADENURIC in phase 3 pivotal studies and long-term extension studies is greater than 2700 patient-years.

5.2 Pharmacokinetic properties

In healthy subjects, maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricemia and gout, treated with ADENURIC 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

Absorption

Febuxostat is rapidly (t_{max} of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, C_{max} is approximately 2.8-3.2 $\mu\text{g/ml}$, and 5.0-5.3 $\mu\text{g/ml}$, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in C_{max} and a 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, ADENURIC may be taken without regard to food.

Distribution

The apparent steady state volume of distribution (V_{ss}/F) of febuxostat ranges from 29 to 75 l after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.