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 (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 (see section 4.8 and 5.1). At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended (see section 4.2).
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 combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). 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 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 (see section 5.1).

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.

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. 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 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 4,072 subjects received at least one dose of ADENURIC (10 mg – 300 mg) in clinical studies.

Combined phase 3 randomised controlled studies
In randomised controlled phase 3 clinical studies, >2,500 patients have been treated with 40 mg to 120 mg (1513 subjects enrolled in a 26-week study (CONFIRMS), 536 subjects enrolled in a 28-week study (APEX) and 507 subjects enrolled in a 52-weeks study (FACT)). The treatment-related events (ADRs) were mostly mild or moderate in severity.

The most commonly reported ADRs (investigator assessment) are liver function abnormalities (5.0%), diarrhoea (2.7%), nausea (1.3%), headache (1.2%), rash (1.2 %).

Gout flares were also 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. As with other urate lowering medicinal products, gout flare prophylaxis is recommended (see section 4.2 and 4.4).

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 PYs), but not in the CONFIRMS study. The incidence of investigator-reported cardiovascular APTC events in the combined Phase III 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.

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1000) adverse reactions suspected (investigator assessment) to be drug related occurring in patients treated with 40 mg to 120 mg febuxostat 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 combined phase 3 randomized controlled studies

Blood and lymphatic system disorders	Rare Pancytopenia
Metabolism and nutrition disorders	Common** Gout flares Uncommon Decrease appetite Rare Weight increase/decrease, increase appetite, anorexia, hyperlipidemia
Psychiatric disorders	Uncommon Libido decreased, insomnia Rare Nervousness
Nervous system disorders	Common Headache Uncommon Dizziness, paraesthesia, somnolence, altered taste, hypoaesthesia
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, upper respiratory tract infection
Gastrointestinal disorders	Common Diarrhoea*, nausea Uncommon: Abdominal pain, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort Rare Pancreatitis, mouth ulceration
Hepato-biliary disorders	Common Liver function abnormalities*
Skin and subcutaneous tissue disorders	Common Rash Uncommon Dermatitis, urticaria, pruritus Rare Alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon Arthralgia, myalgia, musculoskeletal pain, muscle weakness, muscle spasm

	Rare Arthritis, joint stiffness, musculoskeletal stiffness
Renal and urinary disorders	Uncommon Nephrolithiasis, haematuria, pollakiuria, renal failure Rare Micturition urgency
Reproductive system and breast disorder	Rare Erectile dysfunction
General disorders and administration site conditions	Uncommon Fatigue, oedema, chest pain, chest discomfort Rare Thirst
Investigations	Uncommon Blood amylase increase, platelet count decrease, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased Rare Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase

[*] Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase III studies are more frequent in patients concomitantly treated with colchicine.
** See section 5.1 for incidences of gout flares in the individual Phase 3 randomized controlled studies.

Long-term open label extension studies
In the long-term open label extension studies (1143 patients), the number of patients treated with febuxostat 40 mg/80 mg/120 mg up to 1 year was 909, up to 2 years was 781, up to 3 years was 348, and up to 4 and 5 years was 60. 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, oedema.

The following treatment-related events were reported more than once in the total febuxostat treatment group and were reported as uncommon in patients taking febuxostat 40 mg/80 mg/120 mg in long-term extension studies (up to 5 years, >2,660 Patient-years of exposure). These treatment-related events were either not reported or reported at a lower frequency for these doses, in the combined Phase 3 studies: abdominal distension, cholelithiasis, bronchitis, weight increase, blood creatine increase, diabetes mellitus, hyperlipidaemia, arthritis, muscle tightness, hyposmia, hemiparesis, cough, skin discolouration, skin lesion, bursitis, proteinuria, petechiae, erectile dysfunction, blood potassium increase, blood TSH increase, lymphocyte count decreased, WBC decrease.

Adverse reactions from spontaneous reporting
There have been post-marketing reports of rare serious rashes, generalised skin rashes and severe hypersensitivity reactions. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some of these patients, but not all, reported previous hypersensitivity to allopurinol.

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 Ki 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 three Phase 3 pivotal studies (the two pivotal APEX and FACT studies, and the additional CONFIRMS study described below) that were conducted in 4101 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 the APEX and FACT studies was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dl (357 µmol/l). In the additional phase 3 CONFIRMS study, for which results became available after the marketing authorisation for ADENURIC was first issued, the primary efficacy endpoint was the proportion of patients whose serum urate level was < 6.0 mg/dL at the final visit. 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:

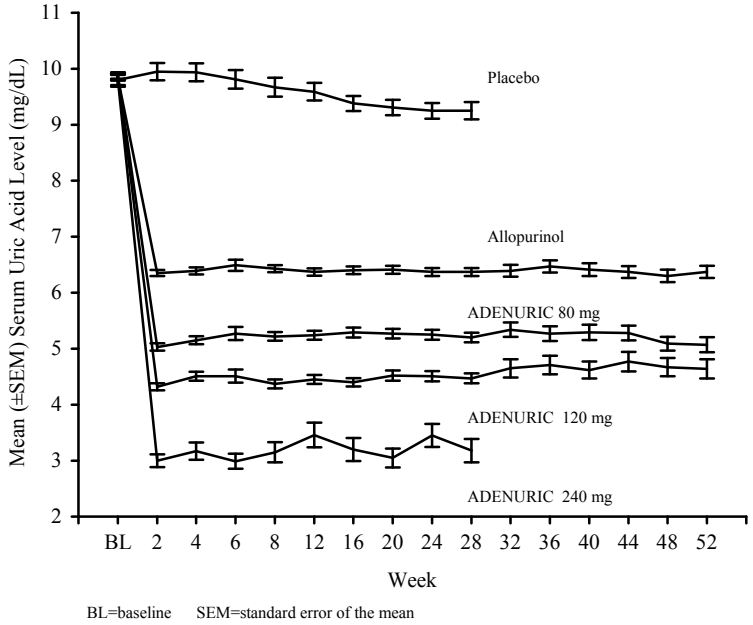
Table 2
Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dl (357µmol/l)
Last Three Monthly Visits

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 two pivotal Phase 3 studies are shown in Figure 1.

Figure 1 Mean Serum Uric Acid Levels in Combined Pivotal 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.

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 randomized: ADENURIC 40 mg QD (n=757), ADENURIC 80 mg QD (n=756), or allopurinol 300/200 mg QD (n=756). At least 65% of the patients had mild-moderate renal impairment (with creatinine clearance of 30-89 mL/min). Prophylaxis against gout flares was obligatory over the 26-week period.
The proportion of patients with serum urate levels of < 6.0 mg/dL (357 µmol/L) at the final visit, was 45% for 40 mg febuxostat, 67% for febuxostat 80 mg and 42% for allopurinol 300/200 mg, respectively.

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).

An analysis in patients with gout and renal impairment was prospectively defined in the CONFIRMS study, and showed that febuxostat was significantly more efficacious in lowering serum urate levels to < 6 mg/dL compared to allopurinol 300 mg/200 mg in patients who had gout with mild to moderate renal impairment (65% of patients studied).

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 (sUA < 6.0 mg/dL at the last 3 visits) 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.

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

Clinical Outcomes: proportion of patients requiring treatment for a gout flare
APEX study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for gout flare compared to febuxostat 80 mg (28%), allopurinol 300 mg (23%) and placebo (20%). Flares increased following the prophylaxis period and gradually decreased over time. Between 46% and 55% of subjects received treatment for gout flares from Week 8 and Week 28. Gout flares during the last 4 weeks of the study (Weeks 24-28) were observed in 15% (febuxostat 80, 120 mg), 14% (allopurinol 300 mg) and 20% (placebo) of subjects.

FACT study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for a gout flare compared to both the febuxostat 80 mg (22%) and allopurinol 300 mg (21%) treatment groups. 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 6-8% (febuxostat 80 mg, 120 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 <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 49 - 52 intervals).

During the 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.

Long-term, open label extension Studies
EXCEL Study (C02-021): The Excel study was a three years Phase III, open label, multicenter, randomised, allopurinol-controlled, safety extension study for patients who had completed the pivotal Phase III studies (APEX or FACT). A total of 1086 patients were enrolled: ADENURIC 80 mg QD (n=649), Adenuric 120 mg QD (n=292) and allopurinol 300/100 mg QD (n=145). About 69 % of patients required no treatment change to achieve a final stable treatment. Patients who had 3 consecutive sUA levels >6.0 mg/dl were withdrawn.
Serum urate levels were maintained over time (i.e. 91% and 93% of patients on initial treatment with febuxostat 80 mg and 120 mg, respectively, had sUA <6 mg/dl at Month 36).

Three years data showed a decrease in the incidence of gout flares with less than 4 % of patients requiring treatment for a flare (i.e. more than 96 % of patients did not require treatment for a flare) at Month 16-24 and at Month 30-36.

46% and 38%, of patients on final stable treatment of febuxostat 80 or 120 mg QD, respectively, had complete resolution of the primary palpable tophus from baseline to the Final Visit.

FOCUS Study (TMX-01-005) was a 5 years Phase II, open-label, multicenter, safety extension study for patients who had completed the febuxostat 4 weeks of double blind dosing in study TMX-00-004. 116 patients were enrolled and received initially febuxostat 80 mg QD. 62 % of patients required no dose adjustment to maintain sUA <6 mg/dL and 38 % of patients required a do se adjustment to achieve a final stable dose.

The proportion of patients with serum urate levels of <6.0 mg/dL (357 μmol/l) at the final visit was greater than 80% (81-100%) at each febuxostat dose.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). These rates were similar to the rates reported on allopurinol (4.2%) (see section 4.4). Increased TSH values (>5.5 μIU/ml) were observed in patients on long-term treatment with febuxostat (5.5%) and patients with allopurinol (5.8%) in the long term open label extension studies (see section 4.4).

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 µg/ml, and 5.0-5.3 µg/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 ^{14}C-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

3 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 14, 28, 42, 56, 84 and 98 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/447/001
EU/1/08/447/002
EU/1/08/447/005
EU/1/08/447/006
EU/1/08/447/007
EU/1/08/447/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/04/2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.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 (see sections 4.8 and 5.1). At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended (see section 4.2).
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 combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). 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 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 (see section 5.1).

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.

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. 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 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 4,072 subjects received at least one dose of ADENURIC (10 mg – 300 mg) in clinical studies.

Combined phase 3 randomised controlled studies
In randomised controlled phase 3 clinical studies, >2,500 patients have been treated with 40 mg to 120 mg (1513 subject enrolled in a 26-week study (CONFIRMS), 536 subjects enrolled in a 28-week study (APEX) and 507 subjects enrolled in a 52-weeks study (FACT)). The treatment-related events (ADRs) were mostly mild or moderate in severity.

The most commonly reported ADRs (investigator assessment) are liver function abnormalities (5.0%), diarrhoea (2.7%), nausea (1.3%), headache (1.2%), rash (1.2%).

Gout flares were also 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. As with other urate lowering medicinal products, gout flare prophylaxis is recommended (see section 4.2 and 4.4).

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 PYs), but not in the CONFIRMS study. The incidence of investigator-reported cardiovascular APTC events in the combined Phase III 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.

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1000) adverse reactions suspected (investigator assessment) to be drug related occurring in patients treated with 40 mg to 120 mg febuxostat 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 combined phase 3 randomized controlled studies

Blood and lymphatic system disorders	Rare Pancytopenia
Metabolism and nutrition disorders	Common** Gout flares Uncommon Decrease appetite Rare Weight increase/decrease, increase appetite, anorexia, hyperlipidemia
Psychiatric disorders	Uncommon Libido decreased, insomnia Rare Nervousness
Nervous system disorders	Common Headache Uncommon Dizziness, paraesthesia, somnolence, altered taste, hypoaesthesia
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, upper respiratory tract infection
Gastrointestinal disorders	Common Diarrhoea*, nausea Uncommon: Abdominal pain, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort Rare Pancreatitis, mouth ulceration
Hepato-biliary disorders	Common Liver function abnormalities*
Skin and subcutaneous tissue disorders	Common Rash Uncommon Dermatitis, urticaria, pruritus Rare Alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon Arthralgia, myalgia, musculoskeletal pain, muscle weakness, muscle spasm

	Rare Arthritis, joint stiffness, musculoskeletal stiffness
Renal and urinary disorders	Uncommon Nephrolithiasis, haematuria, pollakiuria, renal failure Rare Micturition urgency
Reproductive system and breast disorder	Rare Erectile dysfunction
General disorders and administration site conditions	Uncommon Fatigue, oedema, chest pain, chest discomfort Rare Thirst
Investigations	Uncommon Blood amylase increase, platelet count decrease, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased Rare Blood glucose increased, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase

[*] Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase III studies are more frequent in patients concomitantly treated with colchicine.
** See section 5.1 for incidences of gout flares in the individual Phase 3 randomized controlled studies.

Long-term open label extension studies
In the long-term open label extension studies (1143 patients), the number of patients treated with febuxostat 40 mg/80 mg/120 mg up to 1 year was 909, up to 2 years was 781, up to 3 years was 348, and up to 4 and 5 years was 60. 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, oedema.

The following treatment-related events were reported more than once in the total febuxostat treatment group and were reported as uncommon in patients taking febuxostat 40 mg/80 mg/120 mg in long-term extension studies (up to 5 years, >2,660 Patient-years of exposure). These treatment-related events were either not reported or reported at a lower frequency for these doses, in the combined Phase 3 studies: abdominal distension, cholelithiasis, bronchitis, weight increase, blood creatine increase, diabetes mellitus, hyperlipidaemia, arthritis, muscle tightness, hyposmia, hemiparesis, cough, skin discolouration, skin lesion, bursitis, proteinuria, petechiae, erectile dysfunction, blood potassium increase, blood TSH increase, lymphocyte count decreased, WBC decrease.

Adverse reactions from spontaneous reporting
There have been post-marketing reports of rare serious rashes, generalised skin rashes and severe hypersensitivity reactions. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some of these patients, but not all, reported previous hypersensitivity to allopurinol.

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 Ki 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 three Phase 3 pivotal studies (the two pivotal APEX and FACT studies, and the additional CONFIRMS study, described below) that were conducted in 4101 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 the APEX and FACT studies was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dl (357 µmol/l). In the additional phase 3 CONFIRMS study, for which results became available after the marketing authorisation for ADENURIC was first issued, the primary efficacy endpoint was the proportion of patients whose serum urate level was < 6.0 mg/dL at the final visit. 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:

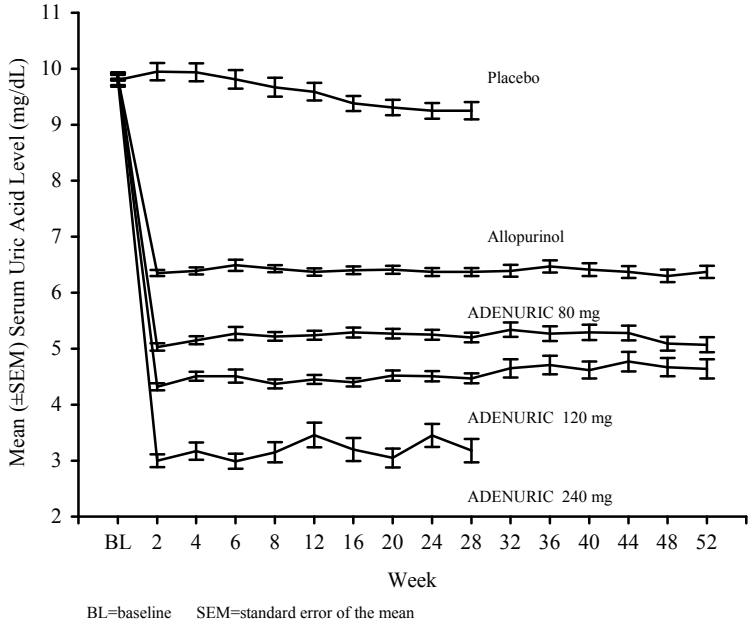
Table 2
Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dl (357µmol/l)
Last Three Monthly Visits

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 two pivotal Phase 3 studies are shown in Figure 1.

Figure 1 Mean Serum Uric Acid Levels in Combined Pivotal 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.

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 randomized: ADENURIC 40 mg QD (n=757), ADENURIC 80 mg QD (n=756), or allopurinol 300/200 mg QD (n=756). At least 65% of the patients had mild-moderate renal impairment (with creatinine clearance of 30-89 mL/min). Prophylaxis against gout flares was obligatory over the 26-week period.
The proportion of patients with serum urate levels of < 6.0 mg/dL (357 µmol/L) at the final visit, was 45% for 40 mg febuxostat, 67% for febuxostat 80 mg and 42% for allopurinol 300/200 mg, respectively.

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).

An analysis in patients with gout and renal impairment was prospectively defined in the CONFIRMS study, and showed that febuxostat was significantly more efficacious in lowering serum urate levels to < 6 mg/dL compared to allopurinol 300 mg/200 mg in patients who had gout with mild to moderate renal impairment (65% of patients studied).

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 (sUA < 6.0 mg/dL at the last 3 visits) 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.

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

Clinical Outcomes: proportion of patients requiring treatment for a gout flare
Apex study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for gout flare compared to febuxostat 80 mg (28%), allopurinol 300 mg (23%) and placebo (20%). Flares increased following the prophylaxis period and gradually decreased over time. Between 46% and 55% of subjects received treatment for gout flares from Week 8 and Week 28. Gout flares during the last 4 weeks of the study (Weeks 24-28) were observed in 15% (febuxostat 80, 120 mg), 14% (allopurinol 300 mg) and 20% (placebo) of subjects.

Fact study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for a gout flare compared to both the febuxostat 80 mg (22%) and allopurinol 300 mg (21%) treatment groups. 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 6-8% (febuxostat 80 mg, 120 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 <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 49 - 52 intervals).

During the 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.

Long-term, open label extension Studies
EXCEL Study (C02-021): The Excel study was a three years Phase III, open label, multicenter, randomised, allopurinol-controlled, safety extension study for patients who had completed the pivotal Phase III studies (APEX or FACT). A total of 1086 patients were enrolled: ADENURIC 80 mg QD (n=649), Adenuric 120 mg QD (n=292) and allopurinol 300/100 mg QD (n=145). About 69 % of patients required no treatment change to achieve a final stable treatment. Patients who had 3 consecutive sUA levels >6.0 mg/dl were withdrawn.
Serum urate levels were maintained over time (i.e. 91% and 93% of patients on initial treatment with febuxostat 80 mg and 120 mg, respectively, had sUA <6 mg/dl at Month 36).

Three years data showed a decrease in the incidence of gout flares with less than 4 % of patients requiring treatment for a flare (i.e. more than 96 % of patients did not require treatment for a flare) at Month 16-24 and at Month 30-36.

46% and 38%, of patients on final stable treatment of febuxostat 80 or 120 mg QD, respectively, had complete resolution of the primary palpable tophus from baseline to the Final Visit.

FOCUS Study (TMX-01-005) was a 5 years Phase II, open-label, multicenter, safety extension study for patients who had completed the febuxostat 4 weeks of double blind dosing in study TMX-00-004. 116 patients were enrolled and received initially febuxostat 80 mg QD. 62 % of patients required no dose adjustment to maintain sUA <6 mg/dL and 38 % of patients required a dose adjustment to achieve a final stable dose.

The proportion of patients with serum urate levels of <6.0 mg/dL (357 μmol/l) at the final visit was greater than 80% (81-100%) at each febuxostat dose.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). These rates were similar to the rates reported on allopurinol (4.2%) (see section 4.4). Increased TSH values (>5.5 μIU/ml) were observed in patients on long-term treatment with febuxostat (5.5%) and patients with allopurinol (5.8%) in the long term open label extension studies (see section 4.4).

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 µg/ml, and 5.0-5.3 µg/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 ^{14}C-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

3 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 120 mg is available in pack sizes of 14, 28, 42, 56, 84 and 98 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/447/003
EU/1/08/447/004
EU/1/08/447/009
EU/1/08/447/010
EU/1/08/447/011
EU/1/08/447/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/04/2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu