Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Febuxostat Pinewood 80 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of febuxostat (as magnesium salts).

Excipient(s) with known effect:
Each tablet contains 76.50 mg lactose monohydrate.
Each tablet contains 0.17 mmol (3.9 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pale yellow to yellow, film-coated, capsule shaped tablets, engraved with "80" on one side, 17.2 ± 0.2 mm in length, 6.2 ± 0.2 mm in width, 5.6 ± 0.2 mm in thickness.

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).

Febuxostat Pinewood is indicated in adults.

4.2 Posology and method of administration

Posology

The recommended oral dose of Febuxostat Pinewood is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dL (357 micromol/L) after 2-4 weeks, Febuxostat Pinewood 120 mg once daily may be considered.

Febuxostat Pinewood 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 micromol/L).

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

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

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).

No dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment
The efficacy and safety of febuxostat have not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

The recommended dose in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment.

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

Method of administration
Oral use.

Febuxostat Pinewood should be taken by mouth and can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
See also section 4.8.

4.4 Special warnings and precautions for use

Cardio-vascular disorders
In patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina), during the development of the product and in one post registrational study (CARES), a higher number of fatal cardiovascular events were observed with febuxostat when compared to allopurinol
However, in a subsequent post registrational study (FAST), febuxostat was not inferior to allopurinol in the incidence of both fatal and non-fatal cardiovascular events.
Treatment of this patient group should be exercised cautiously and they should be monitored regularly.
For further details on cardiovascular safety of febuxostat refer to section 4.8 and section 5.1.

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

Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions (see section 4.8). Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson Syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/ hypersensitivity reactions including Stevens-Johnson Syndrome and acute anaphylactic reaction/ shock, febuxostat must not be re-started in this patient at any time.

Acute gouty attacks (gout flare)
Febuxostat treatment should not be started until an acute attack of gout has completely subsided. 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
In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

Mercaptopurine/azathioprine
Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity.
Where the combination cannot be avoided, a reduction of the dose of mercaptopurine/azathioprine to the 20 % or less of the previously prescribed dose is recommended in order to avoid possible haematological effects (see sections 4.5 and 5.3).

The patients should be closely monitored and the dose of mercaptopurine/azathioprine should be subsequently adjusted based on the evaluation of the therapeutic response and the onset of eventual toxic effects.

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).

Theophylline
Co-administration of febuxostat 80 mg and theophylline 400 mg single dose in healthy subjects showed absence of any pharmacokinetic interaction (see section 4.5). Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels.

No data is available for febuxostat 120 mg.

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 judgment (see section 5.1).

Thyroid disorders
Increased TSH values (> 5.5 microIU/mL) were observed in patients on long-term treatment with febuxostat (5.5 %) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function (see section 5.1).

Lactose
Febuxostat Pinewood tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Mercaptopurine/azathioprine
On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these medicinal products leading to myelotoxicity.
In case of concomitant administration with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to 20 % or less of the previously prescribed dose (see sections 4.4 and 5.3).
The adequacy of the proposed dose adjustment, which was based on a modelling and simulation analysis from preclinical data in rats, was confirmed by the results of a clinical interaction study among medicinal products in healthy volunteers, receiving azathioprine 100 mg alone and a reduced dose of azathioprine (25 mg) in combination with febuxostat (40 or 120 mg).

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

Rosiglitazone/CYP2C8 substrates
Febuxostat was shown to be a weak inhibitor of CYP2C8 *in vitro*. In a study in healthy subjects, coadministration of 120 mg febuxostat QD with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor *in vivo*. Thus, co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.

Theophylline
An interaction study in healthy subjects has been performed with febuxostat to evaluate whether the inhibition of XO may cause an increase in the theophylline circulating levels as reported with other XO inhibitors. The results of the study showed that the co-administration of febuxostat 80 mg QD with theophylline 400 mg single dose has no effect on the pharmacokinetics or safety of theophylline. Therefore no special caution is advised when febuxostat 80 mg and theophylline are given concomitantly.

No data is available for febuxostat 120 mg.

Naproxen and other inhibitors of glucuronidation
Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (UGT) enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250 mg twice daily was associated with an increase in febuxostat exposure (C_{max} 28 %, AUC 41 % and $t_{½}$ 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 febuxostat 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 Fertility, pregnancy and lactation

Pregnancy
Data on a very limited number of exposed pregnancies have not indicated any adverse reactions 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 Pinewood 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 Pinewood should not be used while breast-feeding.

Fertility
In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent adverse reactions on fertility (see section 5.3). The effect of febuxostat on human fertility is unknown.

4.7 Effects on ability to drive and use machines

Somnolence, dizziness, paraesthesia and blurred vision have been reported with the use of febuxostat.

Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that Febuxostat Pinewood does not adversely affect performance.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions in clinical trials (4072 subjects treated at least with a dose from 10 mg to 300 mg), post-authorisation safety studies (FAST study: 3 001 subjects treated at least with a dose from 80 mg to 120 mg) and post-marketing experience are gout flares, liver function abnormalities, diarrhoea, nausea, headache, dizziness, dyspnoea, rash, pruritus, arthralgia, myalgia, pain in extremity, oedema and fatigue. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, and rare events of sudden cardiac death have occurred in the post-marketing experience.

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

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

Table 1: Adverse reactions in combined phase 3, long-term extension studies, post-authorisation safety studies and post-marketing experience

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia, agranulocytosis*, anaemia[#]
Immune system disorders	Rare Anaphylactic reaction[*], drug hypersensitivity[*]
Endocrine disorders	Uncommon Blood thyroid stimulating hormone increased, hypothyroidism[#]
Metabolism and nutrition disorders	Common[***] Gout flares Uncommon Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase Rare Weight decrease, increase appetite, anorexia
Psychiatric disorders	Uncommon Libido decreased, insomnia Rare Nervousness, depressed mood[#], sleep disorder[#]
Nervous system disorders	Common Headache, dizziness Uncommon Paraesthesia, hemiparesis, somnolence, lethargy[#], altered taste, hypoaesthesia, hyposmia Rare Ageusia[#], burning sensation[#]
Eye disorders	Uncommon Blurred vision Rare Retinal artery occlusion[#]
Ear and labyrinth disorders	Uncommon Tinnitus Rare Vertigo[#]
Cardiac disorders	Uncommon Atrial fibrillation, palpitations, ECG abnormal, arrhythmia[#] Rare Sudden cardiac death*
Vascular disorders	Uncommon Hypertension, flushing, hot flush Rare Circulatory collapse[#]

Respiratory system disorders	Common Dyspnoea Uncommon Bronchitis, upper respiratory tract infection, lower respiratory tract infection[#], cough, rhinorrhea[#] Rare Pneumonia[#]
Gastrointestinal disorders	Common Diarrhoea[**], nausea Uncommon Abdominal pain, abdominal pain upper[#], abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort, mouth ulceration, lip swelling[#], pancreatitis Rare Gastrointestinal perforation[#], stomatitis[#]
Hepatobiliary disorders	Common Liver function abnormalities[**] Uncommon Cholelithiasis Rare Hepatitis, jaundice[*], liver injury[*],cholecystitis[#]
Skin and subcutaneous tissue disorders	Common Rash (including various types of rash reported with lower frequencies, see below), pruritus Uncommon Dermatitis, urticaria, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular, hyperhidrosis, alopecia, eczema[#], erythema, night sweats[#], psoriasis[#], rash pruritic[#] Rare Toxic epidermal necrolysis[*], Stevens-Johnson Syndrome[*], angioedema[*], drug reaction with eosinophilia and systemic symptoms[*], generalized rash (serious)[*], exfoliative rash, rash follicular, rash vesicular, rash pustular, rash erythematous, rash morbillifom
Musculoskeletal and connective tissue disorders	Common Arthralgia, myalgia, pain in extremity[#] Uncommon Arthritis, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis, joint swelling[#], back pain[#] musculoskeletal stiffness[#], joint stiffness Rare Rhabdomyolysis[*], rotator cuff syndrome[#], polymyalgia rheumatica[#]
Renal and urinary disorders	Uncommon Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria, micturition urgency, urinary tract infection[#] Rare Tubulointerstitial nephritis[*]
Reproductive system and breast disorders	Uncommon Erectile dysfunction
General disorders and administration site conditions	Common Oedema, fatigue Uncommon Chest pain, chest discomfort, pain[#], malaise[#] Rare Thirst, feeling hot[#]
Investigations	Uncommon Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine

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

[*] Adverse reactions coming from post-marketing experience
[**] Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine.
[***] See section 5.1 for incidences of gout flares in the individual Phase 3 randomized controlled studies.
[#] Adverse reactions coming from post-authorisation safety studies

Description of selected adverse reactions
Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis) (see section 4.4).

Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended (see section 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Patients with an overdose should be managed by symptomatic and supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigout preparation, 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 1 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 efficacy and safety
The efficacy of febuxostat 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 hyperuricaemia and gout. In each phase 3 pivotal study, febuxostat 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 micromol/L). In the additional phase 3 CONFIRMS study, for which results became available after the marketing authorisation for febuxostat 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), febuxostat 80 mg QD (n=267), febuxostat 120 mg QD (n=269), febuxostat 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). 240 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 febuxostat 80 mg QD and the febuxostat 120 mg QD treatment arms *versus* the conventionally used doses of allopurinol 300 mg (n = 258) / 100 mg (n = 10) treatment arm in reducing the sUA below 6 mg/dL (357 micromol/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: febuxostat 80 mg QD (n=256), febuxostat 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).

The FACT study showed the statistically significant superiority of both febuxostat 80 mg and febuxostat 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 micromol/L).

Table 2 summarises the primary efficacy endpoint results:

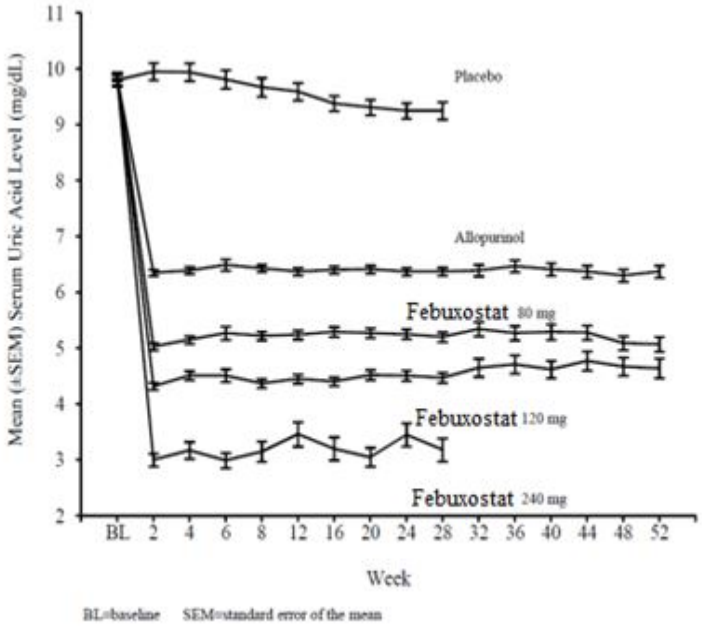
Table 2
Proportion of Patients with Serum Uric Acid Levels < 6.0 mg/dL (357 micromol/L)
Last Three Monthly Visits

Study	Febuxostat 80 mg QD	Febuxostat 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 febuxostat to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to < 6.0 mg/dL (357 micromol/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: febuxostat 40 mg QD (n=757), febuxostat 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 micromol/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 100 mg QD. Febuxostat 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).

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 febuxostat 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 3, open label, multicenter, randomised, allopurinol-controlled, safety extension study for patients who had completed the pivotal
Phase 3 studies (APEX or FACT). A total of 1,086 patients were enrolled: febuxostat 80 mg QD (n=649), febuxostat 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 2, 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 micromol/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 microIU/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).

Post Marketing long term studies
CARES Study was a multicenter, randomized, double-blind, non inferiority trial comparing CV outcomes with febuxostat versus allopurinol in patients with gout and a history of major CV disease including MI, hospitalization for unstable angina, coronary or cerebral revascularization procedure, stroke, hospitalized transient ischemic attack, peripheral vascular disease, or diabetes mellitus with evidence of microvascular or macrovascular disease. To achieve sUA less than 6 mg/dL, the dose of febuxostat was titrated from 40 mg up to 80 mg (regardless of renal function) and the dose of allopurinol was titrated in 100 mg increments from 300 to 600 mg in patients with normal renal function and mild renal impairment and from 200 to 400 mg in patients with moderate renal impairment.
The primary endpoint in CARES was the time to first occurrence of MACE, a composite of non-fatal MI, non-fatal stroke, CV death and unstable angina with urgent coronary revascularization.

The endpoints (primary and secondary) were analysed according to the intention-to-treat (ITT) analysis including all subjects who were randomized and received at least one dose of double-blind study medication.
Overall 56.6 % of patients discontinued trial treatment prematurely and 45 % of patients did not complete all trial visits.
In total, 6,190 patients were followed for a median of 32 months and the median duration of exposure was 728 days for patients in febuxostat group (n=3098) and 719 days in allopurinol group (n=3092).
The primary MACE endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8 % vs. 10.4 % of patients, respectively; hazard ratio [HR] 1.03; two-sided repeated 95 % confidence interval [CI] 0.89-1.21).
In the analysis of the individual components of MACE, the rate of CV deaths was higher with febuxostat than allopurinol (4.3 % vs. 3.2 % of patients; HR 1.34; 95 % CI 1.03-1.73). The rates of the other MACE events were similar in the febuxostat and allopurinol groups, i.e. non-fatal MI (3.6 % vs. 3.8 % of patients; HR 0.93; 95 % CI 0.72-1.21), non-fatal stroke (2.3 % vs. 2.3 % of patients; HR 1.01; 95 % CI 0.73-1.41) and urgent revascularization due to unstable angina (1.6 % vs. 1.8 % of patients; HR 0.86; 95 % CI 0.59-1.26). The rate of all-cause mortality was also higher with febuxostat than allopurinol (7.8 % vs. 6.4 % of patients; HR 1.22; 95 % CI 1.01-1.47), which was mainly driven by the higher rate of CV deaths in that group (see section 4.4).
Rates of adjudicated hospitalization for heart failure, hospital admissions for arrhythmias not associated with ischemia, venous thromboembolic events and hospitalization for transient ischemic attacks were comparable for febuxostat and allopurinol.

FAST study was a prospective, randomised, open-label, blinded-endpoint study comparing the CV safety profile of febuxostat versus allopurinol in patients with chronic hyperuricaemia (in conditions where urate deposition had already occurred) and CV risk factors (i.e. patients 60 years or older and with at least one other CV risk factor). Eligible patients received allopurinol treatment prior to randomization, and dose adjustments were required when needed, according to clinical judgement, EULAR recommendations and the approved posology. At the end of the allopurinol lead-in phase, patients with a sUA level of < 0.36 mmol/L (<6 mg/dL) or receiving the maximum tolerated dose or the maximum licensed dose of allopurinol were randomised in a 1:1 ratio to receive either febuxostat or allopurinol treatment. The primary endpoint of the study FAST was the time to the first occurrence of any event included in the Antiplatelet Trialists' Collaborative (APTC) composite endpoint, which included: i) hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome (ACS); ii) non-fatal stroke; iii) death due to a CV event. The primary analysis was based on the on-treatment (OT) approach.
Overall, 6 128 patients were randomized, 3 063 to febuxostat and 3 065 to allopurinol. In the primary OT analysis, febuxostat was non-inferior to allopurinol in the incidence of the primary endpoint, which occurred in 172 patients (1.72/100 patient years) on febuxostat compared to 241 patients (2.05/100 patient years) on allopurinol, with an adjusted HR 0.85 (95 % CI: 0.70, 1.03), p< 0.001. The OT analysis for the primary endpoint in the subgroup of patients with a history of MI, stroke or ACS showed no significant difference between treatment groups: there were 65 (9.5 %) patients with events in the febuxostat group and 83 (11.8 %) patients with events in the allopurinol group; adjusted HR 1.02 (95 % CI: 0.74-1.42); p=0.202.

Treatment with febuxostat was not associated with an increase in CV death or all-cause death, overall or in the subgroup of patients with a baseline history of MI, stroke or ACS. Overall, there were fewer
deaths in the febuxostat group (62 CV deaths and 108 all-cause deaths), than in the allopurinol group (82 CV deaths and 174 all-cause deaths). There was a greater reduction in uric acid levels on febuxostat treatment compared to allopurinol treatment.

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 ($t_{½}$) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with febuxostat 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 microg/mL, and 5.0-5.3 microg/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, Febuxostat Pinewood 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 %.

Biotransformation
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 %).

Renal impairment
Following multiple doses of 80 mg of febuxostat in patients with mild, moderate or severe renal impairment, 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 microg·h/mL in the normal renal function group to 13.2 microg·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 febuxostat 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 febuxostat in elderly as compared to younger healthy subjects.

Gender
Following multiple oral doses of febuxostat, 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.

Pharmacokinetic modelling and simulation of rat data suggests that, when co-administered with febuxostat, the clinical dose of mercaptopurine/azathioprine should be reduced to 20 % or less of the previously prescribed dose in order to avoid possible haematological effects (see sections 4.4 and 4.5).

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
Cellulose, Microcrystalline
Hydroxypropyl Cellulose
Croscarmellose sodium
Magnesium Oxide
Silica, colloidal anhydrous
Magnesium stearate

Tablet coating
Coating medium (yellow) containing:
Polyvinyl alcohol-part Hydrolysed
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

A cardboard box containing the appropriate number of transparent PVC/PCTFE-Aluminium foil blisters (Aclar) with an instruction leaflet.

Febuxostat Pinewood 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

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/160/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th November 2018
Date of last renewal: 15th August 2023

10 DATE OF REVISION OF THE TEXT

June 2024