FEBUXOSTAT FOR THE TREATMENT OF GOUT

SINGLE TECHNOLOGY APPRAISAL SUBMISSION TO THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final 15 January 2008-revised 14th May 2008

Ipsen, UK

Contents

Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process'—www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class.

Brand name: ADENURIC 80 mg and 120 mg film-coated tablets.

Approved name: Febuxostat.

Therapeutic class: Febuxostat is a 2-arylthiazole derivative that achieves the therapeutic effect of decreasing serum uric acid by selectively inhibiting xanthine oxidase. Febuxostat is a potent, non-purine selective inhibitor of xanthine oxidase with an in vitro inhibition Ki value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidised and reduced forms of xanthine oxidase. 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.

Pharmacotherapeutic group: Urostatic agents

ATC code: M04 AA03.

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

As of January 2007, no.

Ipsen is currently in the process of applying for a European Union (EU) community license, and the product's application currently is process. The date of the application was 17/08/06, and our current best estimate is March/April 2008 for the European Committee for Medicinal Products for Human Use (CHMP) opinion and May/June for the Commission decision. The

CHMP opinion target date is somewhat tentative, and it should be recognised that Ipsen has, at this stage, no indication whether the review will be shorter or longer.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

The target indication is for the treatment of hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

The technology is currently not being used in the National Health Service (NHS). Currently, there are no ongoing clinical trials in Europe.

The anticipated date of availability is June/July 2008, depending on the Commission decision.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

There is currently no regulatory approval in the EU.

In December 15, 2004, TAP Pharmaceutical Products Inc. submitted a New Drug Application with the United States (US) Food and Drug Administration (FDA) for febuxostat 80 mg and 120 mg for the treatment of hyperuricaemia in patients with chronic gout (http://www.tap.com/npr_2004.asp). Approval for febuxostat is expected Q4 2008.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the time scale for completion?

No. However, it should be noted that we have notified the Scottish Medicines Consortium of febuxostat as part of their horizon-scanning process. Febuxostat is listed in the Section 1 of Scottish Medicines Consortium (SMC) report and this report comprises of list of products expected to reach the market 2008/2009.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s)) will be available?

ADENURIC 80 mg will be available in pack sizes of 28 film-coated tablets.

ADENURIC 120 mg will be available in pack sizes of 28 film-coated tablets.

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended dose of ADENURIC is 80 mg once daily without regard to food. If serum uric acid is > 360 µmol/L (6 mg/dL) after 2 to 4 weeks, ADENURIC 120 mg once daily may be considered.

With regards to length of course, it is recommended that treatment with ADENURIC continue every day, even when the patient is not experiencing gout flare or attack for many months, as it is a continuous treatment.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The anticipated drug price for febuxostat 80 mg and 120 mg is £0.870 (€1.25[a]) per day.

1.10 What is the setting for the use of the technology?

Febuxostat is expected to be used mainly in an outpatient setting of middle-aged and elderly, mostly male, patients with symptomatic gout.

Febuxostat lowers and maintains the sUA level more efficiently than allopurinol 300 mg to a serum uric acid level below the target therapeutic level of 360 µmol/L (6 mg/dL), as recommended by EULAR[6]. Maintaining a low sUA prevents and relieves long-term consequences of gout (i.e., gout flares and tophi).

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

[a] Conversion rate 1 £ = €1.436 October 2007

There are no specific tests or investigations required for patient selection as well as for monitoring of patients above usual clinical practice for this condition.

As with other xanthine oxidase inhibitors, gout flares was observed after initiation of ADENURIC therapy and use of prophylaxis for at least 6 months, along with colchicine or a non-steroidal anti-inflammatory drug (NSAID), is recommended.[4,5,6] No particular additional tests or investigations are required.

2 Statement of the decision problem

In this section, the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final Scope Issued by NICE	**Decision Problem Addressed in the Submission**
Population	Adults with hyperuricaemia in whom urate deposition has already occurred (including a history or presence of tophus and gouty arthritis and /or nephrolithiasis)	Adults with hyperuricaemia in whom urate deposition has already occurred (including a history or presence of tophus, gouty arthritis.
Intervention	Febuxostat	Febuxostat
Comparator(s)	The standard comparators to be considered include • Allopurinol • Alternative standard care (including sulphinpyrazone, benzbromarone, probenecid, or a combination of those) for adults unresponsive or intolerant to allopurinol • Allopurinol (dose adjusted according to glomerular filtration rate [GFR]), benzbromarone, or a combination of those for adults with renal impairment	The standard comparators to be considered include • Allopurinol • Allopurinol for adults with renal impairment
Outcomes	The outcome measures to be considered include • Serum uric acid levels • Gout flares • Reduction in tophi size • Tolerance • Health-related quality of life	The outcome measures to be considered include • Serum uric acid levels • Gout flares • Reduction in tophi size • Tolerance • Health-related quality of life

	Final Scope Issued by NICE	Decision Problem Addressed in the Submission
Economic Analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. The time horizon for the economic evaluation should be sufficiently long so as to incorporate all the important costs and benefits related to long-term therapy in this chronic condition. Costs will be considered from an NHS and Personal Social Services perspective.	Cost-effectiveness of treatments expressed in cost per quality – adjusted life-year over 2 years (based on 1-year trial data and a further 1-year extrapolation). Costs considered from NHS and Personal Social Service perspective
Special Considerations and Other Issues	If the evidence allows, the appraisal will consider • Subgroups of patients for whom the technology is particularly appropriate due to greater clinical effectiveness or higher baseline risk (for example, subgroups related to risk factors, comorbidities or clinical features. Patients with sUA levels above 540 µmol/L (9 mg/dL), patients with tophi and patients with mild and moderate renal impairment.) • Patients intolerant of, or contraindicated to, allopurinol • Patients whose gout is unresponsive to allopurinol Guidance will be issued in accordance with the marketing authorisation.	The subgroup analysis showed the response rate of the primary efficacy endpoint increased with age, in female, in Caucasians (versus non-Caucasians), in improved renal function, in lower baseline sUA and presence of tophus.[7] This increase of response rate by subgroup occurred in all treatment groups and does not change statistically significantly superiority of febuxostat 80mg and 120mg to allopurinol 300/100mg. Therefore, no subgroup analyses were conducted as the size of subgroups did not allow for any power to detect any differences of treatments between the subgroups that were clinical relevant relative to differences of treatments provided by the full treatment groups.

Section B

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- **The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.**
- **The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.**
- **The indication(s) and any restriction(s).**
- **The recommended course of treatment.**
- **The main comparator(s).**
- **Whether the key clinical evidence in the submission comes from head-to-head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.**
- **The main clinical results of the randomised trials and any relevant non RCTs.**
- **In relation to the economic evaluation, details of:**
- **The type of economic evaluation and justification for the approach used.**
- **The pivotal assumptions underlying the model/analysis.**
- **The incremental ratios from the evaluation.**

Febuxostat

Febuxostat is a novel, selective xanthine oxidase inhibitor that effectively decreases serum uric acid (sUA) in patients with gout. The target indication for febuxostat is treatment for history of, or presence of, tophus and/or gouty arthritis. The anticipated recommended dose will be febuxostat 80 mg once daily; if an additional urate-lowering effect is required, the dose can be increased to 120 mg once daily. Febuxostat will be dosed continuously to maintain a low sUA level and thus prevent the painful and disabling long-term manifestation of gout arthritis.

In contrast to allopurinol, the currently recommended xanthine oxidase inhibitor on the United Kingdom (UK) market, febuxostat 80 mg does not need any dosage adjustments based on safety, pharmacokinetics, or pharmacodynamic endpoints in patients with mild or moderate renal impairment[8,9] or mild hepatic impairment.[9,10] No dosage adjustments are required for febuxostat with regard to gender or for elderly patients.[9] Neither does febuxostat result in significant drug interactions with other treatments commonly used in conjunction with gout.

The anticipated date of availability of febuxostat on the UK market is June/July 2008, depending on the Commission decision. Febuxostat (brand name ADENURIC) 80 mg and 120 mg film-coated tablets will be provided in pack sizes of 28 tablets. The anticipated unit price of febuxostat will be £0.87 (€1.25[b]) per daily dose (excluding value-added tax [VAT]).

The main comparator to febuxostat is allopurinol, which is the recommended treatment for gout by the British Society for Rheumatology (BSR) and is considered to be the standard urate-lowering therapy in the UK. Clinical opinion and market research data suggest that allopurinol is the most commonly used regimen in the UK. Alternative care with sulphinpyrazone, benzbromarone, probenecid, or a combination of these medications is rarely (3%) used in clinical practice due to safety and efficacy limitations.[11,12]

Clinical context of gout

Gout is most common among men and has a prevalence of 7.3% among men aged 65 to 75 years.[13] The most recent overall prevalence rate of gout in the UK is 1.4%.[11,13] Gout is a chronic, progressive, and destructive condition that erodes and degrades cartilage and muscle tissue; when patients with gout do not receive proper care, the intermittent arthropathy progresses to persistent and progressive joint disease and to physical disability. In the kidney, gout can cause nephrolithiasis (kidney stones) and renal impairment.

The treatment guidelines for gout from the BSR and the British Health Professionals in Rheumatology recommend lowering and maintaining serum uric acid below 300 µmol/L (5 mg/dL) by pharmacological treatment in patients with gouty arthritis and/or tophi, and in patients with uncomplicated gout who experience two or more attacks of gout within 1 year.[14] Unfortunately, gout flares may be triggered during the first months after initiation of urate-lowering therapy before the patient has adjusted to a longer-

[b] Conversion rate 1 £ = €1.436 October 2007

term profile of lower uric acid levels.[4] The BSR treatment guidelines[14] recommend flare-prophylactic treatment with colchicine for up to 6 months following initiation of long-term treatment with urate-lowering therapy—if intolerant of colchicine use, a nonsteroidal anti-inflammatory drug (NSAID) or cyclooxygenase-2 (COX-2) inhibitor for up to 6 weeks. The European League Against Rheumatism (EULAR) guidelines recommend a target serum uric acid level of ≤ 360 µmol/L (6 mg/dL) to eliminate gout flares and to resolve tophi[6], and there remains some discussion on optimal serum uric acid targets. In particular lower targets may be necessary for adequate control of gout in patient already suffering from painful tophi. Units in mg/ml can be converted to SI units (µmol/L) by multiplying the number of mg/dL by 59.5. The conversion of key serum uric acid levels is as follows.

mg/dL	4	5	6	7	8
µmol/L	240	300	360	420	480

Clinical evidence

The datasets from two head-to-head phase III randomized clinical trials (RCTs) (FACT study and APEX study) with febuxostat 80 mg and 120 mg compared to allopurinol were pooled and provided the key clinical efficacy evidence for the economic evaluation. Table ES-1 provides an overview of the design, methods, and pooled results of the two RCTs.

Table ES-1. Febuxostat allopurinol-controlled phase III trials, FACT (C02-010) and APEX (C02-009)

Study	FACT (C02-010)	APEX (C02-009)
Study Dates	11 Jul 2002 to 20 Feb 2004	21 Feb 2003 to 7 Apr 2004
METHODS	A phase III, randomised, multicentre, double-blind, allopurinol-controlled, parallel-group three-arm study with a 52-week, double-blind treatment period in the USA and Canada.	A phase III, randomised, multicentre, double-blind, allopurinol- and placebo-controlled, parallel-group five-arm study with a 28-week double-blind treatment period in the USA.

Study	FACT (C02-010)	APEX (C02-009)
Participants	The study included patients aged 18-85 years with hyperuricaemia (> 480 µmol/L [8.0 mg/dL]) and a history or presence of gout, defined as having 1 or more of the following: • Presence of characteristic urate crystals in the joint fluid and/or • Tophus proven to contain urate crystals and/or • Presence of at least six of the American Rheumatism Association criteria and/or • Renal function, defined as serum creatinine level ≤ 1.5 mg/dL and creatinine clearance ≥ 50 mL per minute (FACT only). Renal function defined as serum creatinine level < 2.0 mg/dL and calculated creatinine clearance ≥ 20 mL per minute (APEX only).	
Interventions	Patients with gout (n = 760) evaluated doses of febuxostat 80 mg (n = 256) or 120 mg (n = 251) and allopurinol 300 mg (n = 253) administered once daily for 52 weeks.	Patients with gout (n = 1072) evaluated doses of febuxostat 80 mg (n = 262), 120 mg (n = 269), or 240 mg (n = 134) and allopurinol 300 (n = 258) or 100 mg (n = 10) administered once daily for 28 weeks compared with placebo (n = 134). Allopurinol dose was based on serum creatinine level.
Supportive Medications	Flare prophylactic treatment with naproxen 250 mg twice daily or colchicine 0.6 mg qd was given from day –14 or day 1 to the day before the week 8 visit.	
Objectives	To compare safety and efficacy of different oral doses of febuxostat versus allopurinol in subjects with gout.	
Outcomes	The primary efficacy endpoint was as follows: • Proportion of patients in each treatment group whose last 3 sUA levels were < 360 µmol/L (6.0 mg/dL) Secondary endpoints were as follows: • Proportion of patients with sUA levels < 360 µmol/L (6.0 mg/dL) • Percentage reduction in sUA levels from baseline • Percentage reduction in primary tophus size as determined by physical measurement in patients with a primary palpable tophus at the screening visit • Reduction in the total number of tophi in the subset of patients with palpable tophi at the screening visit Proportion of patients requiring treatment for a gout flare between weeks 8, 28 (only APEX) and 52 (only FACT) of the double-blind treatment period.	

Study	FACT (C02-010)	APEX (C02-009)
POOLED RESULTS Demography	**Demography**	**FACT (All subjects N=760)**	**APEX (All subjects N=1067)**
	Gender	96% male	94% male
	Mean age	52 years	52 years
	Use of alcohol	66%	66%
	Obese	62%	62%
	Mild-to-moderate renal insufficiency	35%	NA
	History of hypertension	44%	47%
	History of hyperlipidaemia	34%	33%
	Mean years with gout	11.9 years	11 years
	Tophus at baseline	26%	20%
	Overall mean sUA at baseline:	9.8 mg/dL	9.8 mg/dL
	Baseline sUA ≥ 10 mg/dL	41%	39%
	Prior use of a ULT	44%	NA
	Gender	96% male	94% male
	Mean age	52 years	52 years

POOLED RESULTS

Treatment group	Placebo	Febuxostat 80 mg qd	Febuxostat 120 mg qd	Allopurinol 300/100mg qd
ITT (n)	134	517	519	519
Prematurely terminated (n, %)	33 (25%)	181 (35%)	167 (32%)	123 (24%)
sUA < 360 µmol/L (6 mg/dL) at last 3 visits	0%	51%***	63%***	22%
sUA < 360 µmol/L (6 mg/dL) at final visit	1%	73%*	79%*	38%
sUA < 300 µmol/L (5 mg/dL) at final visit	0%	47%*	65%*	13%

* Difference vs. allopurinol $P \leq 0.05$, ***Difference in proportions vs. allopurinol $P < 0.001$.

CI = confidence interval; AE = adverse event; ITT = intend-to-treat; qd = once daily; sUA = serum uric acid; USA = United States of America.
Source: Ipsen (2005).[7]

A subset of patients (n = 735) completing either the FACT or APEX phase III trials were enrolled in an open-label extension study, EXCEL, to evaluate the long-term efficacy of febuxostat 80 mg (n = 299), febuxostat 120 mg (n = 291), and allopurinol 100 to 300 mg (n = 145) in patients with gout who were treated for more than 24 months. Four patients received allopurinol 100 mg due to elevated serum creatinine (> 1.5 mg/dL).[15,16]

Cost-Utility Model

A decision-tree model in Microsoft Excel was developed to estimate costs and outcomes for patients with gout after initiation of urate-lowering therapy with febuxostat 80 mg or 120 mg daily, or allopurinol 300 mg daily. The model was designed to run over a time horizon of up to 2 years and was populated and analysed from a UK National Health Service (NHS) payer perspective.

A mixed cohort of men and women with gout and with a baseline sUA level of 480 µmol/L (8 mg/dL), or higher, entered the model after initiation of urate-lowering therapy. The clinical trial protocol required flare prophylactic treatment with naproxen or colchicine during the first 8 weeks. The model was split into two time periods because of the initial flare-triggering period:

- An initial period of 3 months, during which patients may, or may not, suffer from a treatment-initiated flare.
- A treatment maintenance period from months 4 to 24, during which patients were grouped into four subgroups according the clinical effect achieved i.e., sUA level:
  - ≤ 360 µmol/L (6 mg/dL)
  - > 360 µmol/L (6 mg/dL) and ≤ 480 µmol/L (8 mg/dL)
  - > 480 µmol/L (8 mg/dL) and ≤ 600 µmol/L (10 mg/dL)
  - > 600 µmol/L (10 mg/dL)

The premise of the model was that in achieving an improved level of sUA, patients entered into a disease severity state that could be strongly correlated with health-related quality of life, which in turn could be directly assessed using a standard and UK-validated method of quality-adjusted survival. The model was therefore designed to generate an economic evaluation based on a cost-utility analysis (CUA) driven by treatment- and flare-related costs and the overall cost and quality of life (QoL) associated with disease severity states measured using sUA. Decrements to quality of life were also applied to acccount for the short durations of acute gout flares. Utility weights were derived from an observational study in three European countires (the UK, Germany, and France) conducted by IMS between May 2005 and May 2007.[12] The study obtained QoL data from EQ-5D questionnaires completed by patients with gout who were visiting a physician (n = 417). Combining the clinical trial data from North America with cross-sectional data based on the gout population in Europe provides results that have high internal validity and are generalizable to the UK population.

Model results are summarized in Table ES-2 and Figure ES-1 and Figure ES-2. Sensitivity analysis showed the results to be most sensitive to the effect of flare prophylactic treatment and unit cost of febuxostat.

Table ES-2. Cost and effectiveness results: UK setting, health care payer's perspective

Treatment	Total cost	Incremental cost	QALY	QALYG	ICER /QALYG
12 months horizon					
Allopurinol	£1,314		0.709		
Febuxostat (80 mg + 120 mg pooled)	£1,592	£278	0.726	0.017	£16,574
24 months horizon					
Allopurinol	£2,605		1.395		
Febuxostat (80 mg + 120 mg pooled)	£3,146	£540	1.430	0.035	£15,565

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; QALYG = quality-adjusted life-year gained.

Figure ES-1. Scatterplot: UK setting

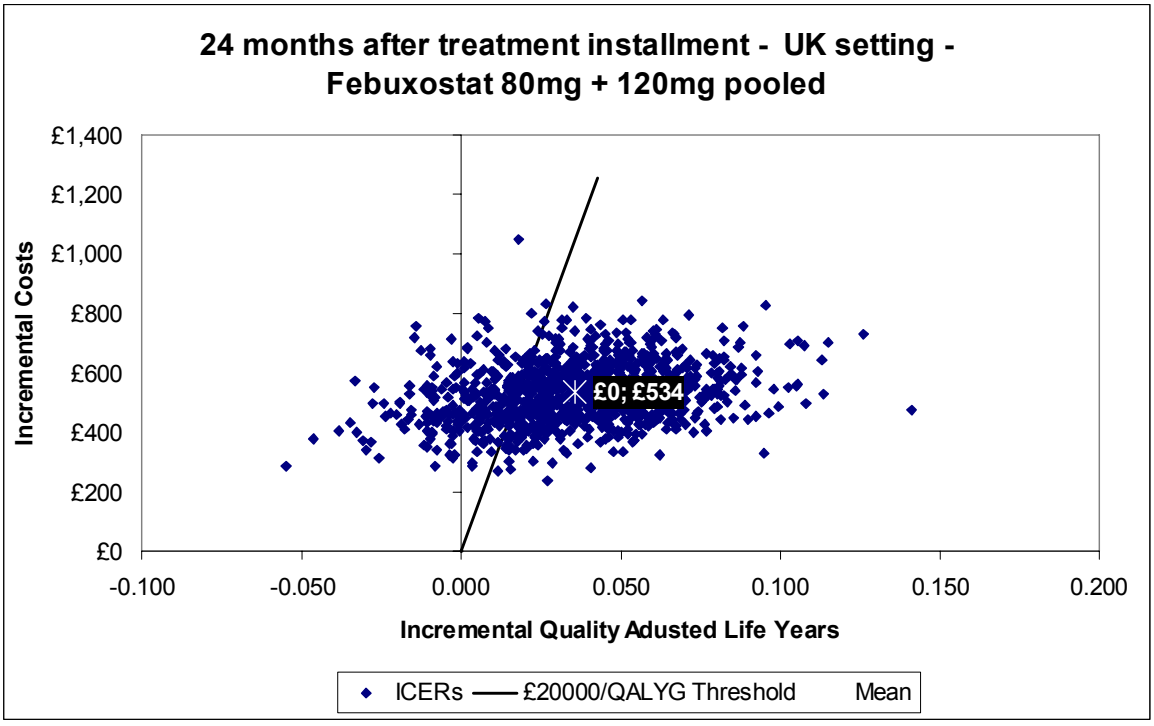
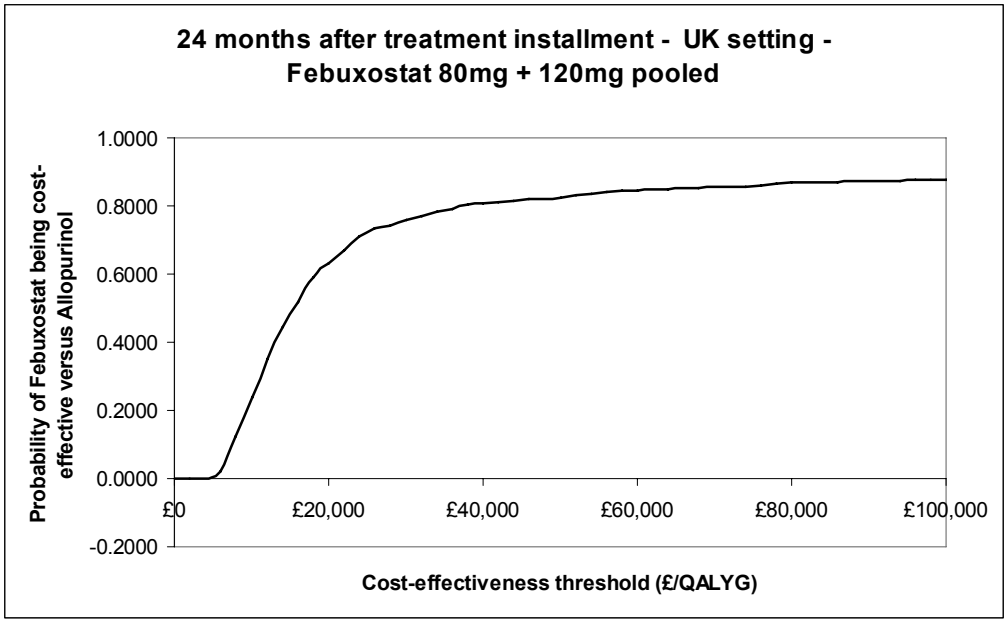


Figure ES-2. Cost-effectiveness acceptability curve: UK setting



Budget impact for the NHS in England and Wales

The cost part of the cost-effectiveness model was used to calculate the budget impact of introducing febuxostat to the UK market. No discounting was applied for the budget impact calculations.

The market is based on the expected population with gout currently taking allopurinol and is assumed to remain the same over the modelled 5-year period, i.e., the allopurinol market share will decrease with the corresponding percentage increase of febuxostat market share. The analysis was conducted from the perspective of the NHS for the entire England and Wales population. The 5-year budget impact of introducing febuxostat to the the England and Wales market is represented in Table ES-3.

Table ES-3. Within-year incremental population-based budget impact results per year for febuxostat on the England and Wales market.

Year	Total cost	Drug cost	Flare cost	Follow-up cost	Market share
Year 1	£2,595,911	£2,746,895	-£150,984	£0	2.3%
Year 2	£17,082,683	£18,272,825	-£1,190,142	£0	15.3%
Year 3	£25,233,244	£26,991,232	-£1,757,988	£0	22.6%
Year 4	£31,039,123	£33,201,604	-£2,162,481	£0	27.8%
Year 5	£31,039,123	£33,201,604	-£2,162,481	£0	27.8%

Assumes a total population of 406,189 treated gout patients. The febuxostat costs are combined for 80 mg and 120 mg doses. Conversion rate 1 £ = €1.436 as of October 2007.

Overall flares and follow-up costs represent 98% of the total estimated budget for gout. The drug element of the estimated budget represents approximately 2%. Over the 5-year budget horizon, the £106,990,083 additional budget represents an approximate increase of 4% compared to the current estimated 5-year budget based on using only allopurinol (£2,707,365,805). The BI model assumes no difference in the follow-up cost of complication to gout (£2,028,914,055) which stands for 75% of the major total budget costs (Table ES-4).

Table ES-4. Cumulative overall 5-year budget compared between only allopurinol and the introduction of febuxostat.

	Total Cost	Drug cost	Flare cost	Follow-up cost	Market share
Allopurinol	£2,707,365,805	£48,217,173	£630,234,577	£2,028,914,055	0%
Febuxostat	£2,814,355,888	£162,631,332	£622,810,502	£2,028,914,055	27.8%
Incremental	£106,990,083	£114,414,159	-£7,424,075	£0	

Note: Assumes that the total gout population (N = 406,189) uses either allopurinol or febuxostat. Febuxostat costs are combined for 80 mg and 120 mg doses.

Conclusion

Compared with allopurinol, febuxostat is significantly more effective in achieving the BSR-recommended sUA of < 300 µmol/L (5 mg/dL). Febuxostat offers physicians an effective, safe and convenient product to prescribe in patients with gout regardless of old age, comorbidities, and concomitant medications.

A simple cost-utility model including only the utility associated with sUA and not including the prevention and resolution of tophi shows that febuxostat is cost-effective compared to allopurinol over a 2-year treatment period with an incremental cost-effectiveness ratio (ICER) of £15,565 per quality-adjusted life-year (QALY). This level of cost per QALY is likely to decrease if febuxostat is evaluated over a longer time period of up to 5 years and where the effect of maintaining low uric acid levels on preventing gout arthritis can be quantified.

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

4.1.1 Epidemiology of gout

Gout is a chronic, progressive, and destructive condition that erodes and degrades cartilage and muscle tissue. Gout is a common condition: the most recent overall prevalence rate of gout in the United Kingdom is projected to be 1.4%.[11,13] The estimates are based on two independent retrospective analyses of data in the General Practice Research Database (GPRD) from 1990 to 1999[13] and in the IMS Disease Analyzer from 2000 to 2005.[11] Both studies showed that the prevalence of gout is higher in men and increases with age. The mean age at diagnosis is 61.6 years, and approximately 80% of the people suffering from gout are male,[11] with a prevalence of 7.3% noted among men aged 65 to 75 years.[13]

According to the analysis of the GPRD data, the incidence of new cases of gout was relatively stable over the studied 10-year period, ranging between 11.9 and 18.0 cases per 10,000 patient-years.[13] Older men (65-84 years) had the highest incidence of 53.4 new gout cases per 10,000 patient-years. Only few younger women (< 45 years) were diagnosed with gout (0.8 cases per 10,000 patient-years).[13]

4.1.2 Etiology and progression of gout

Gout is a heterogeneous disease resulting from the deposition of the end product of purine metabolism, monosodium urate (urate) in supersaturated body fluids.[17,18] Urate is deposited in and around joints and other tissues, forming crystals, called tophi, after many years.

The disease severity of gout can be best described as patients progressing through four recognisable stages, which are described in Table 4-1.[19]

Table 4-1. Description of asymptomatic and symptomatic gout stages

Stage	Description of Disease State
1. Asymptomatic Hyperuricaemia	May exist for many years before a gout attack is experienced.
2. Acute Gout Attack	An intense inflammatory response to the deposition of uric acid crystals, usually resulting in severe pain, inflammation, warmth, and erythema at the affected joint; restricted movement; and fever. Common sites of flares are toes, feet, ankles, knees, and fingers.[18] Initially, attacks are months or years apart and usually subside after 3 to 10 days, but often become more frequent with time and longer in duration.[17,18]
3. Intercritical Gout	Asymptomatic period between attacks, in which joints appear to return to normal.[17]
4. Chronic Tophaceous Gout	Monosodium urate crystals accumulate in tissues and are visible in between attacks as nodular masses, called tophi, which are made of monosodium urate crystals and inflammatory cells.[17] Flares become polyarticular, additive, and ascending, with a longer duration and increased severity.[18] Tophi commonly develop at the elbow and the joints of the hands and feet.[19] As tophi develop, they become destructive and can erode tendons and take the place of or destroy (but not replace) cartilage and bone.[17]

Severe gout with recurrent flares and tophi causes significant suffering; joint degeneration leads to pain and fatigue, and may lead to progressive loss of mobility and function, disability, and emotional distress. The risk of a gout flare is greater in patients with elevated, uncontrolled sUA levels of greater than 360 µmol/L (6 mg/dl) than in patients with lower sUA levels. Deposition in and around joints and tissues leads to the formation of crystal deposits in bone and tissue, called tophi. [17] Tophi can cause significant pain and joint destruction.

When patients with gout do not receive proper care, the intermittent arthropathy progresses to persistent and progressive joint disease and to physical disability. In the kidney, gout can cause nephrolithiasis (kidney stones), interstitial kidney disease, and monosodium urate crystal intrarenal obstructive uropathy. Renal impairment is common among gout patients. The prevalence of gout patients with renal impairment ranges between 9.5% and 19% in cross-sectional studies in the UK and Europe and up to 35% in a clinical trial population in the US.[1,11,12]

4.1.3 Treatment of gout

Effective treatment exists to treat gout and to prevent the severe physical symptoms seen in the course of the disease. Drugs that lower serum uric acid levels are prescribed to patients with gout to prevent recurrent gout flares and to prevent the deposition of monosodium urate crystals.[20] Body fluids are

saturated with urate when concentrations are greater than 400 µmol/L (6.8 mg/dL); by lowering the serum uric acid (sUA) level with such drugs, deposition does not occur and dissolution of crystal deposits can occur.[14,21,22] Several trials of urate-lowering therapy have shown that an effective reduction of sUA reduces and ultimately prevents the occurrence of gout flares[7,22,23,24] and that tophi can be reduced and may even disappear.[25,26]

Conventional recommended treatments for acute gout flare include NSAIDs, steroids, and colchicine, with the aim to reduce the pain associated with the flare.

The treatment for chronic gout cases with recurrent flares and tophi focuses on the cause of gout; hyperuricaemia and include lifestyle changes and a urate-lowering therapy consisting of allopurinol, benzbromarone, sulphinpyrazone, and/or probenecid (see the British and EULAR guidelines in Section 4.6).

Both the European League Against Rheumatism (EULAR) and British Society for Rheumatology (BSR) have indicated a target level in their recent recommendations.

- The EULAR guidelines recommend a target serum uric acid level of ≤ 360 µmol/L (6 mg/dL) to eliminate gout flares and to resolve tophi. [6]
- The treatment guidelines for gout from BSR and the British Health Professionals in Rheumatology recommend lowering and maintaining serum uric acid below 300 µmol/L (5 mg/dL) by pharmacological treatment in patients with gouty arthritis and/or tophi, and in patients with uncomplicated gout if a second attack or further attacks of gout occur within 1 year.[14]

Unfortunately, gout flares may be triggered during the first months after initiation of urate-lowering therapy before the patient has adjusted to a longer-term profile of lower uric acid levels.[4] The BSR treatment guidelines[14] recommend flare-prophylactic treatment with colchicine for up to 6 months following initiation of long-term treatment with urate-lowering therapy.[140] In patients who cannot tolerate colchicine, flare prophylactic treatment of an NSAID or COX-2 inhibitor may be used for up to 6 weeks. The EULAR guidelines recommend flare prophylactic treatment with colchicine and/or an NSAID during the first months of urate-lowering therapy.[6]

Allopurinol is the urate-lowering therapy most commonly used (89% of gout treatments) in the UK according to an IMS Disease Analyzer database

study.[11] Most cases treated with allopurinol (98%) use doses of 300 mg or less per day.[11] Attrition rates for patients on allopurinol treatment are relatively high. After 1 year of allopurinol treatment, 39% of UK patients and 69% of German patients had stopped treatment.[11] An observational study showed lower attrition rates, with 23% of the patients having stopped treatment during the mean observation period of 739 days.[12] Most of these patients stopped treatment because of adverse effects, e.g., rash and urticaria (7.1%) or gastrointestinal effects (4%). Allopurinol also has limited efficacy in lowering sUA. In one double-blind randomized study, only 13 % of patients treated with 300 mg allopurinol daily reached the BSR guideline target sUA level of less than 300 µmol/L (5 mg/dL) after 52 weeks of treatment.[1,14] Allopurinol may be carefully titrated in increments of 50 to 100 mg, up to 900 mg per day, to achieve the targeted sUA level. However, in practice only few patients tolerate the higher dosage. [27]

The other urate-lowering therapies recommended by BSR in the UK, sulphinpyrazone and benzbromarone, are used in less than 1% of the gout patients receiving drug treatment, and probenecid is not used at all in the UK.[11] These alternative treatments are limited by potential severe side effects (Table 4-2).

Table 4-2. Advantages and disadvantages of current therapies for gout

Treatment	Advantages	Disadvantages
Allopurinol	• Single daily dose has shown efficacy for all causes of hyperuricaemia • In dose ranges adapted to renal function, has shown some efficacy in patients with renal impairment	• Potentially fatal allopurinol hypersensitivity syndrome • Often ineffective at reducing sUA to target < 360 µmol/L (6 mg/dL) and < 300 µmol/L (5 mg/dL) at the most commonly used dose; efficacy can be limited in patients with renal impairment or the drug could be poorly tolerated • Slow resolution of tophi • Drug interactions with warfarin and azathioprine • Limitations in patients with renal impairment
Probenecid	• Effective in patients with normal renal function and underexcretion of uric acid	• Multiple daily dosing, ineffective in renal impairment (creatinine clearance < 50 mL per minute) or if renal calculi are present • Potential for urate nephropathy and kidney stones • Known drug interactions with aspirin, heparin, and frusemide

Treatment	Advantages	Disadvantages
Benzbromarone	• Effective in patients with renal impairment (creatinine clearance > 25 mL per minute) • Enables more patients to achieve the serum uric acid target of < 360 µmol/L (6 mg/dL)	• Potentially fatal hepatic toxicity • Withdrawn from the market in many countries
Oral Colchicine	• Rapidly treats acute gout • Not used for chronic gout	• Cautious use required in patients with hepatic or renal impairment • Gastrointestinal symptoms with diarrhoea and vomiting are common • Risk of neuromyopathy

Source: adapted from Kim et al., (2003)[19] and Stamp et al., (2007)[27]

4.1.4 Quality of life related to gout

Gout has a significant impact on the physical well-being of patients.[28] Patients with uncontrolled serum uric acid levels experience more frequent flares and tophus build-up, causing greater pain and complications, than patients with serum uric acid levels controlled by drugs. Increasing symptoms and complications of gout in patients with elevated serum uric acid levels also can impair physical functioning, ability to work, productivity, and overall well-being.[12]

One recent study investigated the effect of gout on quality of life in patients in the UK, using the World Health Organization Quality of Life BREF (WHOQOL-BREF) instrument.[28] The WHOQOL-BREF consists of a questionnaire that asks patients to rate their quality of life and their satisfaction with their health. A further 24 questions relate to four individual domains: physical, psychological, social, and environment. A total of 137 gout patients were compared with 2,848 control subjects who had never experienced gout.[28] The study reported that gout significantly reduced the patients' overall rating of their quality of life ($P < 0.01$), their overall satisfaction with their health ($P < 0.001$), and their physical health ($P < 0.001$) when compared with subjects without gout in the UK.

An unpublished multicountry study conducted by IMS assessed the health-related quality of life of gout patients.

The duration of a flare is about 3 to 10 days.[18]

Table 4-3. Baseline utility by sUA level

sUA level	Mean utility	SE
sUA ≤ 360 µmol/L (6 mg/dL)		
sUA > 360 µmol/L (6 mg/dL) and ≤ 480 µmol/L (8 mg/dL)		
sUA > 480 µmol/L (8 mg/dL) and ≤ 600 µmol/L (10 mg/dL)		
sUA > 600 µmol/L (10 mg/dL)		

sUA = serum uric acid.

Table 4-4. Impact of gout flare on health-related quality of life

Health-Related Quality of Life Measurement	Baseline (Not Experiencing Flare)	When Experiencing Flare
EQ-5D Range: 1 (perfect health) to –0.59 (worse than death)		

4.1.5 Productivity in persons with gout

During flare-ups, gout can severely impact quality of life, which can affect all aspects of life, including normal activities of daily living, employment, family, and social life. One recent study of 300,000 employees in the United States reported that gout severely impacted a patient's ability to work and resulted in an average of 6.34 days of sick leave and 6.21 days of short-term disability from work, compared with 3.56 days of sick leave and 3.18 of short-term disability in workers without gout ($P < 0.0001$ and $P = 0.0003$, respectively).[29]

4.1.6 Economic burden of gout

Gout patients suffer from a painful disease that can be prevented with effective urate-lowering therapy. In patients who have been diagnosed with gout, poorly managed and uncontrolled gout place a significant burden on health services as continuous medical care is required to manage gout flare-ups and as the gout patient develops joint disability. Gout patients, especially those with uncontrolled disease, need greater health care resources, resulting in a greater economic burden on the health care system. Gout-related health care costs include cost of prescription drugs as well as medical attention such as physician visits, inpatient visits, outpatient visits, emergency room visits, and costs incurred through laboratory tests.[30,31,32,33,34] In a study of 40,508 United States veterans, those with gout (n = 1,090) were more likely to be admitted to the hospital (26% vs. 13% per year) and had a higher number of primary care (4.7 ± 4.1 vs. 2.5 ± 3.4 per year; $P < 0.001$), medical specialist care (2.0 ± 3.8 vs. 1.2 ± 3.9 per year; $P < 0.001$), and surgical care visits (2.2 ± 3.3 vs. 1.6 ± 3.0; $P < 0.001$) than those without gout.[32]

4.2 What was the rationale for the development of the new technology?

Existing therapies for treatment of gout has limited efficacy in lowering uric acid levels at tolerable doses and also have safety concerns and/or limitations in patients with renal impairment (Table 4-2 in Section 4.1.2).[19,27]

There have been no new therapeutic agents to treat gout and hyperuricaemia since 1964 when allopurinol, a xanthine oxidase inhibitor, was approved.[21] Therefore, there is a medical need for a drug that would be more efficacious, and at least as safe, as the standard therapy.

- Febuxostat is a novel, nonpurine, selective inhibitor of xanthine oxidase and is more potent than allopurinol at inhibiting both the oxidized and reduced forms of the enzyme.[35,36]

- Febuxostat can prevent future gout flares and help to reverse complications of gout (e.g., tophus formation).[9] At week 52 of treatment, febuxostat reduced sUA to the BSR target level of below 300 µmol/L (5 mg/dL) in 47% of patients treated with 80 mg daily and in 66% of patients treated with 120 mg daily, compared with only 13% of patients with allopurinol (300 mg).[1]

- In contrast to allopurinol, febuxostat is safe and effective for use in patients with mild and moderate renal impairment without dose

adjustment. Long-term extension studies have also shown febuxostat to be safe and effective in patients intolerant to allopurinol[15] (Further information of clinical efficacy and safety is provided in Section 5).

4.3 What is the principal mechanism of action of the technology?

Febuxostat is a novel, potent, nonpurine selective inhibitor of xanthine oxidase.

In humans, uric acid is produced as the end product of purine metabolism via a cascade reaction when hypoxanthine is metabolised to xanthine and eventually to uric acid. Xanthine oxidase acts as a catalyst in both steps of the metabolism.[5]

Febuxostat achieves its therapeutic effect of decreasing serum uric acid levels by selectively inhibiting xanthine oxidase. Febuxostat inhibits both the oxidised and reduced forms of the enzyme. At therapeutic doses, febuxostat is a more selective xanthine oxidase inhibitor than allopurinol and is therefore more potent than allopurinol in reducing serum uric acid levels.[35,36]

Febuxostat at therapeutic concentrations does not inhibit other enzymes involved in purine or pyrimidine metabolism. In addition, febuxostat is a non–purine-based molecule and does not form any oxypurinol metabolites. The inhibition of other enzymes involved in purine and pyrimidine metabolism and the formation of oxypurinol metabolites have been attributed to the development of the potentially fatal allopurinol hypersensitivity reaction, bone marrow depression, and other adverse effects seen with allopurinol.[9,35,36]

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

The suggested place for febuxostat is for the treatment of hyperuricaemia in conditions where urate crystal deposition has already occurred (including a history or the presence of tophi and/or gouty arthritis).

- Febuxostat can prevent future gout flares and can help to reverse the primary complication of gout (tophus formation).[9]
- Febuxostat lowers and maintains sUAs level better than allopurinol 300 mg (below the target therapeutic level of 300 µmol/L [5 mg/dL]), which prevents and relieves the long-term symptoms of gout (i.e., gout flares, tophi).

The proposed indication and dose in the EU dossier submitted to the European Medicines Agency (Sections 4.1 and 4.2 of the SPC[5]) is as follows: "Treatment of hyperuricaemia in conditions where urate/uric acid deposition has already occurred (including a history, or presence of, tophus and gouty arthritis). If serum uric acid is > 360 µmol/L (6 mg/dL) after 2-4 weeks, ADENURIC 120 mg once daily may be considered … "

In addition, febuxostat will provide an effective and safe alternative to existing urate-lowering treatments where:

- The current treatment fails to provide the desired response
- The patient does not tolerate allopurinol, for certain populations that need special consideration when determining their treatment (e.g., patients with renal impairment),
- Patients with tophi require a more pronouced decrease in their sUA level than achieved by the current treatment, and
- Patients require concomitant medications that may lead to adverse drug interactions with other urate-lowering treatments.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Gout is undertreated and sUA is uncontrolled among many patients in the UK. Current British guidelines recommend treatment of an acute gout flare with NSAIDs and colchicines and chronic urate-lowering therapy with allopurinol (for details see Section 4.6). Several recent studies of treatment patterns for gout in the UK consistently show suboptimal treatment of gout patients.[1,11,12,37] Numerous factors contribute to undertreament of gout, e.g., lack of disease awareness among physicians and patients, lack of knowledge that gout flares and tophi is preventable, sub-optimal dosing and poor compliance because of poor efficacy and adverse effects of current treatments. A brief description of the studies and results follow.

- One study of gout treatment in practices in the UK identified 164 patients with gout through a postal survey of 13,684 primary care patients.[37] Most of the patients (70%, or 114 out of 164) had suffered from more than one gout attack. Only 32% of these patients (44 out of 114) were currently treated with allopurinol. Additionally, 18 patients (16%) had discontinued allopurinol treatment because of side effects or no flares. Most of the

patients (81%) took an allopurinol dose of ≤ 300 mg; no patients reported having been treated with uricosuric agents. Two of 10 patients with tophi were currently treated with allopurinol, furthermore 4 patients with tophi have discontinued treatment. Serum uric acid levels were significatly lower in patients with treatment; 77% (34/44) of the allopurinol users achieved sUA < 360 µmol/l (6 mg/dL) compared to 25% (75/101) of the patients not treated with allopurinol (*P* = 0.005).

- Another UK study, based on the IMS Disease Analyzer (2000-2005) reported a higher rate of medication use (63%) in gout patients.[11] Among the patients using medications, NSAIDs was the most commonly used medication (89%) for treatment of gout. Gout preparations was used in 63% of the patients; mainly allopurinol (89%), colchicine (16%) and less than 1% received uricosuric agents such as probenecid and sulfinpyrazone (the same patient could have more than one treatment).

Several subpopulations of gout patients exist, which have a significant unmet medical need that is not currently resolved by existing treatments. These subpopulations include patients who are intolerant to allopurinol, those with higher sUA levels, those with tophi, and patients with renal impairment.

As previously described in Section 4.1.3 there are a number of very clear limitations with allopurinol, the most commonly prescribed drug treatment for gout in the UK.

4.6 Provide details of any relevant guidelines or protocols.

Gout is a chronic condition requiring effective, safe, and long-term therapy. The BSR has recently published treatment guidelines for the management of acute gout and for the prevention of recurrent and chronic gout in the UK.[14] The EULAR also have published European guidelines. The two sets of guidelines are similar, with a few variations.

The guidelines are divided up into management of acute gout, lifestyle modification and non-pharmacological approaches, and management of recurrent, intercritical, and chronic gout.

4.6.1 The British treatment guidelines

The British treatment algorithm for management of gout in the UK is presented in Figure 4-1 and Table 4-5.

Figure 4-1. Treatment algorithm for gout management in the UK, as proposed by the British Society of Rheumatology

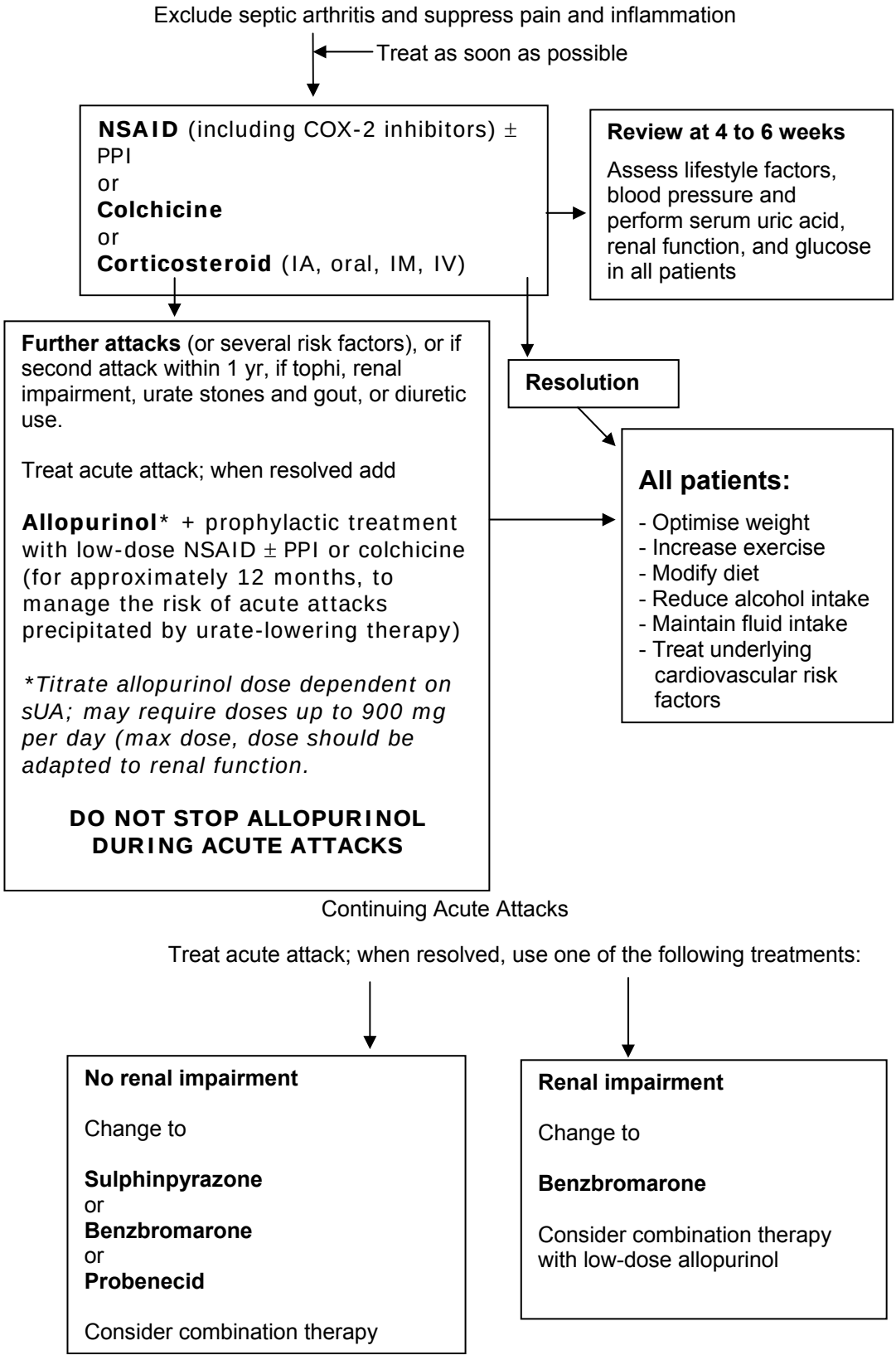


Table 4-5. BSR guidelines for the management of recurrent, intercritical, and chronic gout

	Recommendation
1	Serum uric acid should be lowered and maintained below 300 µmol/L (5 mg/dL) by pharmacological treatment in patients with gouty arthritis and/or tophi and in uncomplicated gout if one or more additional gout attacks occur within 1 year.
2	Specific treatment should be considered and begun as soon as the acute gout attack has resolved in patients with visible gouty tophi, patients with renal insufficiency (raised plasma creatinine, creatinine clearance, or glomerular filtration rate less than 80 mL per minute), patients with uric acid stones and gout, and patients who need to continue to take diuretics. Treatment with uric acid-lowering drug therapy should not begin until 1 to 2 weeks after inflammation has resolved in all patients with acute or subacute gout.
3	Allopurinol is the first-line treatment in uncomplicated gout patients with more than one attack per year and in gout patients with comorbidity. The starting dose for allopurinol is 50 to 100 mg daily, which is increased by 50-mg to 100-mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (serum uric acid < 300 µmol/L) is reached (the maximum dose is 900 mg). Doses of allopurinol should be lowered according to renal function in all patients with a reduction in estimated glomerular filtration rate, including normal, elderly subjects.
4	Uricosuric agents (sulphinpyrazone with normal renal function and benzbromarone with mild or moderate renal insufficiency) should be used only as second-line drugs in the chronic treatment of gout, in those patients producing and underexcreting a normal or reduced amount of urate, and in those patients resistant to or intolerant of allopurinol.
5	Colchicine should be given for up to 6 months following initiation of long-term treatment with allopurinol or uricosuric drugs. In patients who cannot tolerate colchicine, an NSAID or COX-2 inhibitor can be substituted, provided there are no contraindications, but the treatment duration for the NSAID or COX-2 inhibitor should be limited to 6 weeks.

Source: Jordan et al. (2007).[14]

4.6.2 EULAR guidelines

In 2006, the EULAR task force was formed to develop evidence-based recommendations for the management of gout. This multidisciplinary group, representing 13 European countries, consisted of 19 rheumatologists and one evidence-based medicine expert.[6]

The EULAR guidelines (see Table 4-6) differ from the British treatment guidelines in following ways:

- The goal of gout treatment is to reduce and maintain serum uric acid levels at or lower than 360 µmol/L (6 mg/dL), eliminate gout flares, and resolve tophi.[6]
- Conventional recommended treatments for gout also include probenecid in addition to NSAIDs, steroids, colchicine, allopurinol, benzbromarone, and sulphinpyrazone.

- Specific patient populations may require more aggressive treatment, with combination treatment in those patients with high baseline serum uric acid levels (greater than 540 µmol/L [9 mg/dL]), in elderly patients, and in patients with tophi.[6]
- EULAR recommend the xanthine oxidase inhibitor allopurinol as an appropriate urate-lowering therapy; in cases of allopurinol toxicity, another xanthine oxidase inhibitor or a uricosuric agent are considered alternative options. Probenecid and sulphinpyrazone are suggested as suitable uricosuric agents in patients with normal renal function, and benzbromarone can be used in patients with mild to moderate renal impairment.

Table 4-6. EULAR guidelines for the management of gout

	Recommendation
1	Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to (a) specific risk factors (levels of serum uric acid, previous attacks, radiographic signs); (b) clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout); and (c) general risk factors (age, gender, obesity, alcohol consumption, urate-elevating drugs, drug interactions, and comorbidity).
2	Patient education and appropriate lifestyle advice regarding weight loss, if obese; diet; and reduced alcohol (especially beer) are core aspects of management.
3	Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity, and smoking should be addressed as an important part of the gout management program.
4	Oral colchicine and/or NSAIDs are first-line agents for systemic treatment of acute attacks. In the absence of contraindications, an NSAID is a convenient and well-accepted option.
5	High doses of colchicine lead to side effects; low doses (for example, 0.5 mg three times daily) may be sufficient for some patients with acute gout.
6	Intra-articular aspiration or injection of long-acting steroids is an effective and safe treatment for an acute attack.
7	Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout.
8	The therapeutic goal of urate-lowering therapy is to promote crystal dissolution and prevent crystal formation. This is achieved by maintaining the serum uric acid below the saturation point for monosodium urate (≤ 360 µmol/L).
9	Allopurinol is an appropriate long-term urate-lowering therapy. It should be started at a low dose (e.g., 100 mg daily) and increased by 100 mg every 2 to 4 weeks, if required. The dose must be adjusted in patients with renal impairment. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitisation (the latter is an option only in patients with a mild rash).
10	Uricosuric agents, such as probenecid and sulphinpyrazone, can be used as an alternative to allopurinol in patients with normal renal function but are relatively contraindicated in patients with urolithiasis. Benzbromarone can be used in patients with mild to moderate renal insufficiency on a named-patient basis but carries a small risk of hepatotoxicity.

	Recommendation
11	Prophylaxis against acute attacks during the first months of urate-lowering therapy can be achieved by the use of colchicine (0.5 mg to 1 mg daily) and/or an NSAID (with gastroprotection, if indicated).
12	When gout is associated with diuretic therapy, stop the diuretic if possible. For hypertension, consider the use of losartan, and for hyperlipidaemia consider using fenofibrate (both drugs have modest uricosuric effects).

Source: Zhang et al. (2006).[6]

5 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUOROM statement checklist (www.consort-statement.org/QUOROM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. Where no head-to-head RCTs are available, consideration will be given to indirect comparisons, subject to careful and fully described analysis and interpretation.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data.

5.1 *Identification of studies*

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or

sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Rigorous electronic and manual literature searches were conducted to identify published and unpublished randomised controlled trials of febuxostat used as urate-lowering therapy for gout. The most recent literature search was undertaken on 3rd December 2007. A protocol was prepared for the literature search, detailing inclusion and exclusion criteria and search terms, search dates and data span searched. Articles were identified in electronic database searches of Medline, EMBASE and the Cochrane Library using a predetermined search strategy (Table 5-1 to Table 5-3). Broad search terms ensured that no analyses were inadvertently excluded.

The literature search spanned 1950 to 2007 (inclusive). The complete search strategies included all the search terms—Text words (free text), Subject Index Headings (MeSH)—and the relationship between the search terms (e.g., Boolean).

The complete search strategies are presented in Table 5-1 to Table 5-3.

Table 5-1. Medline (PubMed) search strategy

Search String	Description	Number of Records
1	"Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "randomised controlled trial"[Text Word] OR "randomised controlled trials"[Text Word] OR "randomized controlled trial"[Text Word] OR "randomized controlled trials"[Text Word] OR "Random Allocation"[MeSH] OR "random allocation"[Text Word] OR "Double-Blind Method"[MeSH] OR "double blind method"[Text Word] OR "Single-Blind Method"[MeSH] OR "single blind method"[Text Word] OR "Clinical Trial "[Publication Type] OR "Clinical Trials as Topic"[MeSH] OR "placebo"[Title/Abstract] OR "placebos"[Title/Abstract] OR "Placebos"[MeSH] OR random*[Title/Abstract] OR "research design"[Title/Abstract] OR "Research Design"[MeSH]	946806
2	"clinical"[Text Word] AND ("trial"[Text Word] OR "trials"[Text Word])	624423
3	Search (singl*[Text Word] OR doubl*[Text Word] OR trebl*[Text Word] OR tripl*[Text Word]) AND (blind*[Text Word] OR mask*[Text Word])	135006
4	#1 OR #2 OR #3	1017658

Search String	Description	Number of Records
5	“febuxostat “[Substance Name] OR “febuxostat”[All Fields]	55
6	“Gout”[MeSH] OR “Gout Suppressants”[MeSH] OR “Gout Suppressants “[Pharmacological Action] OR “gout”[All Fields]	56105
7	#4 AND #5 AND #6	19
8	“Animals”[MeSH] NOT “Humans”[MeSH]	3202450
9	#7 NOT #8	19

MeSH = Medical Subject Headings.

Table 5-2. EMBASE search strategy

Search String	Description	Number of Records
S1	RANDOMIZED()CONTROLLED()TRIAL? OR RANDOMISED()CONTROLLED()TRIAL? OR CONTROLLED()CLINICAL()TRIAL? OR CONTROLLED STUDY! OR CLINICAL()TRIAL? OR RANDOM()ALLOCATION OR DOUBLE()BLIND()METHOD OR DOUBLE()BLIND()PROCEDURE OR SINGLE()BLIND()METHOD OR SINGLE()BLIND()PROCEDURE OR CLINICAL(3N)TRIAL? OR PLACEBO? OR RANDOM?	3036864
S2	CLINICAL TRIAL!	510709
S3	(SINGL? OR DOUBL? OR TREBL? OR TRIPL?)(3N)(BLIND? OR MASK?)	118026
S4	S1 OR S2 OR S3	3043106
S5	FEBUXOSTAT	95
S6	GOUT	6709
S7	S4 AND S5 AND S6	56
S*	S7/HUMAN	55

Table 5-3. Cochrane Library search strategy (including DARE, National Health Service’s Economic Evaluation Database and the Health Technology Assessment Database)

Search String	Description	Number of Records
1	“febuxostat”	7
2	MeSH descriptor “gout”: explode all trees	98
3	(gout)	234
4	(Search #2 OR #3)	240
5	(Searches #1 AND #4)	6
	Cochran reviews	0
	Other reviews	0

Search String	Description	Number of Records
	Clinical trials	4 (3 unique records)
	Methods studied	0
	Technology assessments	2

MeSH = Medical Subject Headings.

5.2 *Study selection*

5.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The electronic search of the literature identified only one published peer-reviewed randomised phase II trial and one published peer-reviewed randomised phase III trial of febuxostat for the treatment of gout.

In addition, eight published phase I trials with febuxostat, one article about instrument development, and 51 review articles were identified and excluded. The results of the search are attached as an appendix. The electronic literature searches were supplemented with information from internal company data sources to identify any unpublished studies listed in Table 5-4 (in Section 5.2.3). All of these trials were selected and the data abstracted by an experienced reviewer using standardised data abstraction forms to reduce bias.

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

The identified records were checked when they matched the following inclusion and exclusion criteria.

Inclusion criteria:

Randomised phase II and phase III studies including the clinical effect of febuxostat on gout, compared to plabeco or an active control.

Exclusion criteria:

Non-randomised clinical studies, e.g., phase I studies on healthy volunteers

Preclinical studies

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUOROM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUOROM statement should equal the total number of studies listed in section 5.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Three pivotal randomised controlled trials are available on file at Ipsen and TAP Pharmaceuticals (Table 5-4).

- Two phase III trials (C02-009 and C02-010) compared febuxostat head-to-head with allopurinol and placebo.[2,3] An extension study of the phase III trials followed up the results of treatment of febuxostat and allopurinol over the long term (C02-021).[16]

- One controlled, randomised phase II trial (TMX-00-004) compared febuxostat with placebo.[38] An extension study of the phase II trial followed up the results of the febuxostat treatment up to 5 years (TMX-00-005).[39]

Table 5-4. RCTs conducted on febuxostat in the USA and Canada

Study Number/ Short Name	Study Title	Country	Study Dates
C02-009 APEX	Phase III, randomized, multicenter, allopurinol and placebo-controlled study assessing the safety and efficacy of oral febuxostat in subjects with gout	USA	21 Feb 2003 Completed: 7 Apr 2004
C02-010 FACT	Phase III, randomized, multicenter, allopurinol-controlled study assessing the safety and efficacy of oral febuxostat versus allopurinol in subjects with gout	USA, CANADA	11 Jul 2002 Completed: 20 Feb 2004
TMX-00-004	Phase II, dose-response, safety and efficacy study of oral febuxostat (TMX-67) in subjects with gout	USA	31 Jan 2001 Completed: 9 Jul 2001
C02-021 EXCEL	Phase III, open-label, randomized, allopurinol-controlled study to assess the long-term safety of oral febuxostat in subjects with gout	USA, CANADA	28 Jul 2003 Ongoing
TMX-01-005	Phase II, open-label study to assess the long-term safety of oral TMX-67 in subjects with gout	USA	21 Mar 2001 Ongoing

RCT = randomised controlled trial; USA = United States of America.

The results of the phase II and III trials have been or are in the process of being publically available in following citations (Table 5-5).

Table 5-5. List of publications of RCTs with febuxostat and allopurinol

References
Becker MA, Macdonald PA, Lloyd E, Lademacher C, Joseph-Ridge N. Urate-lowering pharmacotherapy with febuxostat or allopurinol in Black-American subjects with gout. Poster presented at the European League Against Rheumatism. Ann Rheum Dis 2007;66(Suppl II):231
Becker MA, Macdonald PA, Lloyd E, Lademacher C, Joseph-Ridge N. Urate-Lowering Pharmacotherapy with Febuxostat (FEB) or Allopurinol (ALLO) in African-American Subjects with Gout. ACR Presentation 1622 (2007)
Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, Streit J, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricaemia and gout. N Engl J Med 2005;353:2450-61. **[FACT Study]**
Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Palo WA, Eustace D, Vernillet L, Joseph-Ridge N. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. Arthritis Rheum 2005 Mar;52(3):916-23. **[Phase II placebo conparison Study TMX-00-004]**
Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Palo WA, Eustace D, Streit J, Joseph-Ridge N. Reduction in Gout Flares in Subjects with Chronic Gout Treated with Febuxostat or Allopurinol for 52-Weeks: FACT Trial. ACR Presentation (2005) **[FACT Study]**

References
Becker MA, Schumacher HR, MacDonald PA , Lloyd EJ, Lademacher C, Joseph-Ridge N. Urate-Lowering Therapy (Febuxostat [FEB] or Allopurinol [ALLO]) in Subjects with Gout: Interim Results from the Febuxostat Comparative Extension Long-Term Study (EXCEL). ACR Presentation 757 (2007) **[EXCEL Study]**
Becker MA, Schumacher HR, MacDonald PA, Lloyd EJ, Lademacher C, Joseph-Ridge N. Urate-lowering therapy in subjects with gout: interim results from the febuxostat/allopurinol comparative extension long-term study (EXCEL). Poster presented at the European League Against Rheumatism; Ann Rheum Dis 2007;66(Suppl II):230. **[EXCEL Study]**
Becker MA, Schumacher HR, Wortmann RL, Lloyd E, Streit J, Joseph-Ridge N. The long-term clinical benefits of febuxostat vs allopurinol in subjects with gout: interim analysis of the excel trial, an ongoing phase 3, open-label extension study. Poster presented at the European League Against Rheumatism. Ann Rheum Dis 2006;65(Suppl II):431 **[EXCEL Study: interim data]**
Schumacher HR, Wortmann R, Becker M, MacDonald P, Palo W, Streit J, Lademacher C, Joseph-Ridge N. Long-term safety and efficacy of febuxostat, a novel non-purine selective inhibitor of xanthine oxidase, in subjects with hyperuricemia and gout. Poster presented at the European League Against Rheumatism. Ann Rheum Dis 2005;64(Suppl III):498
Schumacher HR, Becker MA, Macdonald PA, Lloyd EJ, Lademacher C, Joseph-Ridge N. Febuxostat vs allopurinol in the treatment of gout in subjects 65 years of age or older. Poster presented at the European League Against Rheumatism. Ann Rheum Dis 2007;66(Suppl II):234.
Schumacher HR, Becker MA, Wortmann RL, Lloyd E, MacDonald PA, Joseph-Ridge N. The FOCUS trial 48-month interim analysis: long-term clinical outcomes of treatment with febuxostat in subjects with gout in an ongoing phase 2, open-label extension study. Ann Rheum Dis 2006;65(Suppl II):93 **[Phase II FOCUS extension TMX-01-005]**
Schumacher HR, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, Lademacher, Joseph-Ridge N. Febuxostat vs allopurinol and placebo in subjects with hyperuricaemia and gout: the 28-week APEX study. Poster presented at the Annual Scientific Meeting of the American College of Rheumatology; San Diego, CA. 16-17 Nov 2005. **[APEX Study]**
Whelton A, Macdonald P, Lloyd E, Lademacher C. The long-term stability of renal function in hyperuricemic subjects with gout treated with febuxostat. Abstract submitted to ASN Renal Week 2007 [in press].
Wortmann RL, Becker MA, Schumacher HR, MacDonald PA, Hunt BJ, Joseph-Ridge N. Effect of Febuxostat or Allopurinol on the Clinical Manifestations of Gout: Reduction in Gout Flares and Tophus Size Over Time in the EXCEL Trial. ACR Presentation 1592 (2006) **[EXCEL Study: interim data]**
Wortmann RL, Schumacher HR, Becker MA, MacDonald PA, Palo WA, Eustace D, Joseph-Ridge N. Reduction in Tophus Size in Subjects with Chronic Gout Treated with Febuxostat or Allopurinol for 52 Weeks - FACT Trial. ACR Presentation (2005) **[FACT Study]**

RCT = randomised controlled trial.

5.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

No non-randomised data has been used in the NICE STA submission document. The economic evaluation (Section 6) is based on randomised data comparing directly with allopurinol (from the APEX, FACT and EXCEL studies).

5.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

An ongoing additional phase III trial compares febuxostat to allopurinol. The study (known as Study 153) is a randomized, double blinded, parallel study designed to directly compare febuxostat with allopurinol in patients diagnosed with gout. The active treatment arms includes febuxostat 40 mg once daily, febuxostat 80 mg once daily, and allopurinol at a 200 mg or 300 mg dose (depending on renal function). The active treatment period in the study is 6 months. Estimated enrollment is 2250 patients.

The primary outcome is the proportion of subjects whose serum urate levels are <360 µmol/L (6.0 mg/dL) at final visit. The secondary outcomes include the proportion of subjects whose serum urate levels are <360 µmol/L (6.0 mg/dL), <300 µmol/L (5.0 mg/dL) and <240 µmol/L (4.0 mg/dL), at each visit.

The clinical trial identifier is NCT00430248 and the full study number is F-GT06-153. The sponsor is TAP Pharmaceutical Products.

5.3 *Summary of methodology of relevant RCTs*

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

5.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding and randomisation) and interventions.

Febuxostat efficacy and safety has been evaluated in three main trials.

- One dose-finding phase II trial comparing three doses of febuxostat (40[c], 80 and 120 mg) to placebo over 4 weeks[49], followed by a 5-year extension trial (FOCUS). [15]

[c] Efficacy data for the 40 mg dose will not be provided in the STA as the dose was found in the dose-finding study to be below recommended dose of 80 mg qd.

- One phase III trial (FACT) [1] comparing two doses of febuxostat (80 and 120 mg) to allopurinol for 52 weeks, followed by a 2-year extension trial (EXCEL). [15]
- One phase III trial (APEX) [49] comparing three doses of febuxostat (80, 120, and 240[d] mg) to allopurinol and placebo for 28 weeks, followed by a 2-year extension trial (EXCEL). [15]

Allopurinol was used in the febuxostat trials as an active comparator because it is the most widely used chronic medication to lower uric acid levels in gout patients.[12,40,41] The dose of 300 mg was chosen because the most commonly prescribed dose of allopurinol is 200 to 300 mg per day.[11,12] While allopurinol may be used at higher doses, doses of more than 300 mg per day are used infrequently (≤ 3% of patients) in practice because the risk of developing allopurinol hypersensitivity increases with higher doses.[11,12] A reduced dose of 100 mg was used for 10 patients with renal impairment (serum creatinine > 1.5 but ≤ 2.0 mg/dL) in the APEX trial, based on the allopurinol dosing recommendations on the label.

The following results sections focus on the SPC recommended doses of 80 mg once daily and 120 mg once daily of febuxostat.

In all trials, the efficacy analyses were conducted on the intention-to-treat (ITT) population where all randomised patients received at least one dose of the study drug and a baseline sUA ≥ 480 µmol/L (8mg/dL). No per-protocol analyses were conducted.

Table 5-6 to Table 5-8 present the details of the trial design for the phase II trial and the phase III trials.

Table 5-6. Study design: phase II, Study TMX-00-004

Title	Phase II, dose-response, safety and efficacy study of oral febuxostat (TMX-67) in subjects with gout
INTRODUCTION Background	Gout is a chronic urate crystal deposition disorder, which if left untreated may result in progressive disease characterised by joint and bone destruction from tophaceous deposits and renal impairment due to gouty nephropathy. Hyperuricaemia is the underlying cause leading to urate crystal deposition of gout. Febuxostat is a novel xanthine oxidase inhibitor developed for the treatment of hyperuricaemia in gout.

[d] Efficacy data for the 240mg dose will not be provided in the STA as the dose was only included in the trial “to evaluate safety at twice the highest dose proposed for this indication" at the FDA request.

Title	Phase II, dose-response, safety and efficacy study of oral febuxostat (TMX-67) in subjects with gout
METHODS Participants	A randomised, double-blind, placebo-controlled, parallel design, multicentre, dose-response phase II clinical trial with a 2-week wash-out period and a 4-week, double-blind treatment period (Study TMX-00-004). The study included male and female subjects between 18 and 85 years of age with hyperuricaemia ≥ 480 µmol/L (8.0 mg/dL) in the USA who were eligible for the trial and who met the ACR preliminary criteria for classification of the acute arthritis of primary gout.
Interventions	Patients with gout (n = 153) evaluated doses of febuxostat 40 mg (n = 37), 80 mg (n = 40) and 120 mg (n = 38) administered once daily for 4 weeks, compared with placebo (n = 38).
Supportive Medications	Flare prophylactic treatment with colchicine 0.6 mg qd was given from day –14 to the day before the day 14 visit.
Objectives	Dose-response trial
Outcomes	The primary efficacy endpoint was as follows: • Proportion of patients in each treatment group with sUA levels < 360 µmol/L (6.0 mg/dL)on day 28. Secondary endpoints were as follows: • Proportion of patients with sUA levels that had decreased to < 360 µmol/L (6.0 mg/dL) on day 7, 14 and 21; • Percent reduction in sUA levels from baseline at each visit; • Percent reduction in daily urinary uric acid excretion from baseline to day 28.
Sample Size	To have at least 90% power to detect a difference between febuxostat and placebo with a 2-sided significance level of 0.05, an 80% responder rate for any of the febuxostat-dose groups and a 30% responder rate for the placebo group was assumed. Accounting for a 20% dropout rate, 30 subjects per treatment group (120 in total) were required.
Randomisation: Sequence Generation	Subjects were randomised and assigned subject numbers based on a computer-generated randomisation schedule by the statistics department at TAP.
Randomisation: Allocation Concealment	An interactive voice response system managed by ClinPhone Inc. was used for subject randomisation, assigning subject numbers and drug management services at the investigational site.
Randomisation: Implementation	The statistics department at TAP generated the allocation sequence. 24 investigators in the USA enrolled and randomised subjects.
Blinding (masking)	All the study drug tablets (febuxostat 20-mg tablets and placebo) were identical in appearance and each dose consisted of 6 tablets in order to preserve the blinding. Both participants and investigators were blinded to the assigned treatment.
Statistical Methods	The primary and secondary efficacy analyses were conducted on the ITT population, defined as all randomised subjects with a sUA level of ≥ 480 µmol/L (8.0 mg/dL) on day –2. “Success rates” of primary and secondary endpoint were summarised and compared between each of the febuxostat-treatment groups and the placebo group using Fisher’s exact test. A one-way analysis of variance model with the treatment group as a factor was used to compare percent reduction of sUA. Pair-wise comparisons of febuxostat-treatment groups used t-tests. Adjustment for pair-wise comparisons used Hochberg’s procedure.

Title	Phase II, dose-response, safety and efficacy study of oral febuxostat (TMX-67) in subjects with gout				
RESULTS Participant Flow		Placebo	Febuxostat 40 mg qd	Febuxostat 80 mg qd	Febuxostat 120 mg qd
	Randomised	38	37	40	38
	ITT (baseline sUA ≥ 8.0 mg/dL on day –2)	35	34	37	34
	Subjects who completed the study	36	36	37	35
	Primary reason for premature termination	1 AE 1 flare	1 AE	2 AEs 1 non-compliance	2 AEs
	No protocol deviations were planned. Altogether, 15 subjects included in the analysis deviated from the protocol, mostly due to admission criteria of impaired renal function or mistiming of procedures/visits.				
Study Dates	31 Jan 2001 Completed 9 Jul 2001				

ACR = American College of Rheumatology; AE = adverse event; ITT = intend-to-treat; qd = once daily; sUA = serum uric acid; USA = United States of America.

Sources: Becker et al., 2005b [42]; Ipsen TMX-00-004, 2001

Table 5-7. Febuxostat allopurinol-controlled trial (FACT) phase III trial, C02-010

Title Abstract	Phase III, randomized, multicenter, allopurinol controlled study assessing the safety and efficacy of oral febuxostat versus allopurinol in subjects with gout
INTRODUCTION Background	Febuxostat is a novel xanthine oxidase inhibitor developed for the treatment of hyperuricaemia in gout.
METHODS Participants	A phase III, randomised, multicentre, double-blind, allopurinol-controlled, parallel-group 3-arm study with a 52-week, double-blind treatment period in the USA and Canada. The study included patients aged 18-85 years with hyperuricaemia ≥ 480 µmol/L (8.0 mg/dL) and a history or presence of gout, defined as having 1 or more of the following: • Presence of characteristic urate crystals in the joint fluid and/or • Tophus proven to contain urate crystals and/or • Presence of at least 6 of the American Rheumatism Association criteria and/or • Renal function, defined as serum creatinine level ≤ 1.5 mg/dL and calculated (using Cockroft-Gault formula) creatinine clearance ≥ 50 mL per minute.
Interventions	Patients with gout (n = 760) evaluated doses of febuxostat 80 mg (n = 256), 120 mg (n = 251) and allopurinol 300 mg (n = 253) administered once daily for 52 weeks.
Supportive Medications	Flare prophylactic treatment with naproxen 250 mg twice daily or colchicine 0.6 mg qd was given from day –14 or day 1 to the day before the week 8 visit.
Objectives	To compare safety and efficacy of different oral doses of febuxostat versus allopurinol in subjects with gout
Outcomes	The primary efficacy endpoint was as follows: • Proportion of patients in each treatment group whose last three sUA levels were < 360 µmol/L (6.0 mg/dL). Secondary endpoints were as follows: • Proportion of patients with sUA levels < 360 µmol/L (6.0 mg/dL); • Percent reduction in sUA levels from baseline; • Percent reduction in primary tophus size as determined by physical measurement in patients with a primary palpable tophus at the screening visit; • Reduction in the total number of tophi in the subset of patients with palpable tophi at the screening visit; • Proportion of patients requiring treatment for a gout flare between weeks 8 and 52 of the double-blind treatment period.

Title Abstract	**Phase III, randomized, multicenter, allopurinol controlled study assessing the safety and efficacy of oral febuxostat versus allopurinol in subjects with gout**
Sample Size	A total of 750 subjects (250 in each group) were needed to provide the following: • (1) To have at least 80% power to meet the non-inferiority criteria between at least 1 febuxostat-treatment group and the allopurinol group for the primary efficacy variable. Sample size calculations assumed a true response rate of 60% for the allopurinol-treatment group and at least 64% for the febuxostat-treatment groups. • (2) At least 90% power to detect a 15% difference between a febuxostat-treatment group and allopurinol-treatment group for the primary efficacy variable. No interim analyses were conducted.
Randomisation: Sequence Generation	Subjects were randomised and assigned subject numbers based on a computer-generated randomisation schedule by the statistics department at TAP.
Randomisation: Allocation Concealment	An interactive voice response system was used for subject randomisation and assigning subject numbers at the investigational site.
Randomisation: Implementation	The statistics department at TAP generated the allocation sequence. 117 investigators at 106 sites in the USA and 6 sites in Canada enrolled and randomised subjects.
Blinding (Masking)	Febuxostat, placebo and allopurinol tablets were overencapsulated with an iron-grey opaque gelatin capsule to assure blinding. Both participants and investigators were blinded to assigned treatment.
Statistical Methods	The primary efficacy analyses were conducted on the ITT population, defined as all randomised subjects who received at least 1 dose and who had an sUA level of ≥ 8.0 mg/dL at day –2. A sequential, closed, two-step procedure compared the primary efficacy variables. • Step 1: Test for non-inferiority for each febuxostat-treatment group compared with allopurinol. Binomial 97.5 % CIs were calculated for the differences in response rates for each febuxostat dose (80 mg and 120 mg) compared with allopurinol. Non-inferiority was defined as the absolute lower value of the lower bound of the 97.5% CI that did not exceed 10%. • Step 2: If shown non-inferior in Step 1, the analysis continued to test for superiority to allopurinol using Fisher's exact test. Superiority was defined as a higher response rate for allopurinol compared with febuxostat and *P* value equal or less than the significance level based on Hochberg's procedure.

Title Abstract	Phase III, randomized, multicenter, allopurinol controlled study assessing the safety and efficacy of oral febuxostat versus allopurinol in subjects with gout			
RESULTS Participant Flow		Febuxostat 80 mg qd	Febuxostat 120 mg qd	Allopurinol 300 mg qd
	Randomised	256	251	253
	Subjects who completed the study	168 (66%)	153 (61%)	187 (74%)
	Primary reason for premature termination:	n = 88	n = 98	n = 66
	Lost to follow-up	25 (28%)	18 (18%)	21 (32%)
	AE	16 (18%)	23 (23%)	8 (12%)
	Gout flare	10 (11%)	28 (29%)	9 (14%)
	Personal reason	19 (22%)	13 (13%)	13 (20%)
	Other	11 (13%)	14(14%)	14(21%)
	Protocol violation	7 (8%)	2 (2%)	1 (2%)
	No protocol deviations were planned. Altogether, 50 subjects included in the analysis deviated from the protocol, mostly due to admission criteria of impaired renal function or mistiming of procedures/visits.			
Study Dates	11 Jul 2002 to 20 Feb 2004			

CI = confidence interval; AE = adverse event; ITT = intend-to-treat; qd = once daily; sUA = serum uric acid; USA = United States of America.

Sources: Becker et al., 2005a[1]; Ipsen, C02-010, 2004[3].

Table 5-8. Allopurinol- and placebo-controlled efficacy study of febuxostat (APEX) phase III trial, C02-009

Title Abstract	A phase III, randomised, multicentre allopurinol- and placebo-controlled trial assessing safety and efficacy of oral febuxostat in subjects with gout.
INTRODUCTION Background	Febuxostat is a novel xanthine oxidase inhibitor developed to reduce sUA.
METHODS Participants	A phase III, randomised, multicentre, double-blind, allopurinol- and placebo-controlled, parallel-group 5-arm study with a 28-week double-blind treatment period in the USA. The study included patients aged 18-85 years with hyperuricaemia 480 µmol/L (8.0 mg/dL) and a history or presence of gout, defined as having 1 or more of the following: • Presence of characteristic urate crystals in the joint fluid and/or • Tophus proven to contain urate crystals and/or • Presence of at least 6 of the American Rheumatism Association criteria and/or • Renal function defined as serum creatinine level < 2.0 mg/dL and calculated (using Cockroft-Gault formulas) creatinine clearance > 20 mL per minute.
Interventions	Patients with gout (n = 1072) evaluated doses of febuxostat 80 mg (n = 262), 120 mg (n = 269), 240 mg (n = 134) and allopurinol 300/100 mg (n = 268) administered once daily for 28 weeks compared with placebo (n = 134). The dose of allopurinol was based on serum creatinine levels.
Supportive Medications	Flare prophylactic treatment with naproxen 250 mg twice daily or colchicine 0.6 mg qd was given from day –14 or at day 1 to the day before the week 8 visit.
Objectives	To evaluate safety and efficacy of different oral doses of febuxostat versus placebo and allopurinol in subjects with gout
Outcomes	The primary efficacy endpoint was as follows: • Proportion of patients in each treatment group whose last three sUA levels were < 360 µmol/L (6.0 mg/dL) Secondary endpoints were as follows: • Proportion of patients with sUA levels < 360 µmol/L (6.0 mg/dL) at the final visit; • Percent reduction in sUA levels; • In patients with palpable tophi at screening visit: – Percent reduction in primary tophus size, – The reduction in the total number of tophi, • Proportion of patients requiring treatment for gout flare between week 8 and week 28.
Sample Size	A total of 1,000 subjects (250 in each febuxostat 40-mg, 80-mg and allopurinol 300/100 group; 125 in the placebo group and the febuxostat 240-mg group) were needed to provide the following: • (1) At least 95% power to detect a 45% difference between each febuxostat-treatment group and the placebo group for the primary efficacy variable. • (2) To have at least 80% power to meet the non-inferiority criteria between at least 1 febuxostat-treatment group and the allopurinol-

Title Abstract	**A phase III, randomised, multicentre allopurinol- and placebo-controlled trial assessing safety and efficacy of oral febuxostat in subjects with gout.**
	treatment group for the primary efficacy variable. • (3) At least 90% power to detect a 15% difference between a febuxostat-treatment group and the allopurinol-treatment group for the primary efficacy variable. No interim analyses were conducted.
Randomisation: Sequence Generation	Unequal randomisation 1:2:2:1:2 (placebo:febuxostat 80 mg:febuxostat 120 mg:febuxostat 240 mg:allopurinol 300/100). Subjects were randomised and assigned subject numbers based on a computer-generated randomisation schedule by the statistics department at TAP.
Randomisation: Allocation Concealment	An interactive voice response system was used for subject randomisation and for assigning subject numbers at the investigational site.
Randomisation: Implementation	The statistics department at TAP generated the allocation sequence. 167 investigators at 167 sites in the USA enrolled and randomised subjects.
Blinding (Masking)	Febuxostat and febuxostat placebo were provided as matching tablets in two sizes. Allopurinol 300/100 mg and allopurinol placebo were provided as gelatin capsules. To ensure blinding, subjects took small tablets, large tablets and capsules every day. Both participants and investigators were blinded to assigned treatment.
Statistical Methods	The primary efficacy analyses were conducted on the ITT population, defined as all randomised subjects who received at least 1 dose and who had a sUA level of ≥ 8.0 mg/dL at day –2. A sequential closed, three-step procedure compared the primary efficacy variables • Step 1: Comparing each febuxostat treatment with placebo for test for superiority with CMH Test stratified by baseline renal function. Superiority was defined as a *P* value less than or equal to the critical significance level using Hochberg's method. If superior to placebo, proceed to Step 2. • Step 2: Comparing each febuxostat 80-mg qd and 120-mg qd treatment with allopurinol 300/100 mg, test for non-inferiority. Binomial 97.5 % CIs were calculated for the differences in response rates for each febuxostat dose (80 mg and 120 mg) compared with allopurinol. Non-inferiority was defined as the absolute lower value of the lower bound of the 97.5% CI that did not exceed 10%. • Step 3: Comparing each non-inferior febuxostat-treatment group with allopurinol 300/100 mg, test for superiority with CMH Test stratified by baseline renal function. Non-inferiority tests used overall 0.05 alpha-level and binomial 97.5% confidence interval. Superiority tests used Hochberg's method. • Summary statistics and pair-wise-comparison of treatment groups with Fisher's exact test for proportion of patients with sUA levels < 6.0 mg/dL and proportion of patients requiring treatment for gout flare; • Analysis of variance for percent reduction in sUA levels; • Wilcoxon rank sum test for percent reduction in primary tophus size and reduction in the total number of tophi.

Title Abstract	A phase III, randomised, multicentre allopurinol- and placebo-controlled trial assessing safety and efficacy of oral febuxostat in subjects with gout.					
RESULTS Participant Flow		Pla-cebo	Febu-xostat 80 mg qd	Febu-xostat 120 mg qd	Febu-xostat 240 mg qd	Allo-purinol 300/100 mg qd
	(N) enrolled	134	267	269	134	268
	(N) ITT	134	262	269	134	268
	Completed study	101 (75%)	174 (65%)	200 (74 %)	86 (64%)	211 (79%)
	Prematurely discontinued	33	93	69	48	57
	Primary reason[a]:					
	Lost to follow-up	30%	20%	25%	19%	30%
	AE	15%	19%	23%	23%	32%
	Gout flare	27%	17%	23%	19%	16%
	Personal reason	9%	16%	12%	13%	9%
	Other	0%	14%	9%	17%	2%
	Protocol violation	9%	6%	4%	6%	11%
	Therapeutic failure	9%	6%	4%	6%	2%
	[a] Denominator is the number of subjects who prematurely discontinued in each group.					
	No protocol deviations were planned. Altogether, 28% (300/1072) of the subjects prematurely discontinued, mostly due to lost to follow up, AE, gout flares or personal reasons..					
Study Dates	21 Feb 2003 to 7 Apr 2004					

CI = confidence interval; CMH = Cochran-Mantel-Haenszel Test; AE = adverse event; ITT = intend-to-treat; qd = once daily; sUA = serum uric acid; USA = United States of America.

Source: Schumacher et al., 2005c (abstract) [49]; Ipsen, C02-009, 2004[2]

Open-label extension studies of phase II and III trials

A long-term trial (FOCUS) with febuxostat enrolled 116 patients who had completed a phase II, 4-week, placebo-controlled double-blind study. [42] Patients could be titrated from febuxostat 80 mg to 40 mg or from 80 mg to 120 mg in the first 28 weeks. Results are available for 67 patients who completed at least 48 months of treatment.[39, 56]

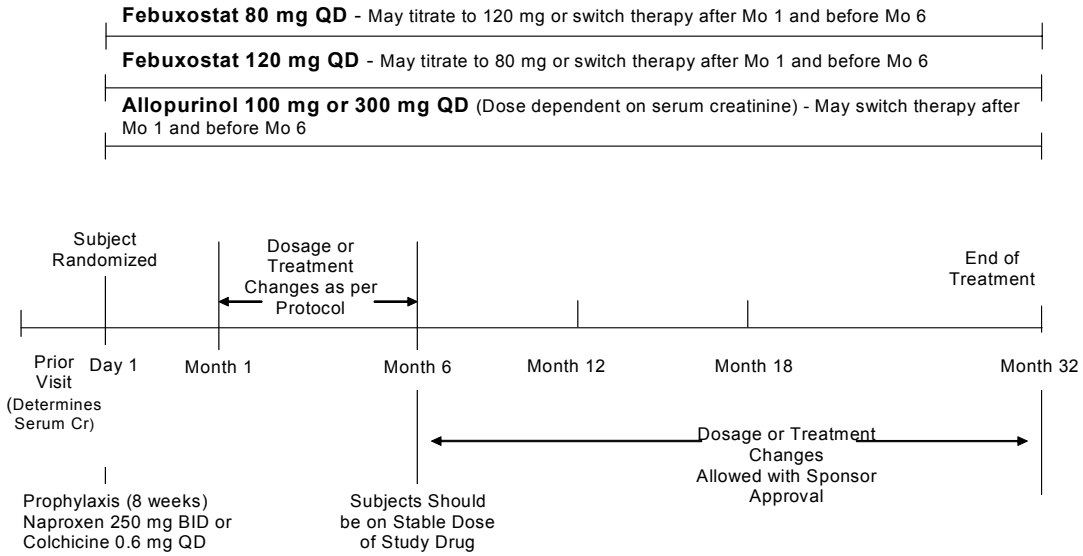
The patients in the FACT or APEX phase III trials were enrolled in an open-label extension study (EXCEL), and were initially only assigned to febuxostat 80 mg. The study was amended on recommendation by the Food and Drug Administration to be randomized and actively controlled to evaluate the long-

term efficacy. A subset of patients (n = 735) were randomised in the amended open-label extension study, EXCEL, to evaluate the long-term (24 months) efficacy of:

- febuxostat 80 mg (n = 299),
- febuxostat 120 mg (n = 291). and
- allopurinol 100 to 300 mg (n = 145).

Four patients received allopurinol 100 mg due to serum creatinine > 1.5 mg/dL)[15,16] (Figure 5-1). The Final visit in the FACT and APEX trials was regarded as the First visit in the EXCEL trial, thus patients were treated for at least 24 months after the last visit in the FACT or APEX trial.

Figure 5-1. EXCEL trial: FACT and APEX long-term extension, open-label revised study design (Protocol amendment 2)



Source: Ipsen C02-021, 2005[16]

5.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Inclusion criteria at screening (day –14) were as follows:

- Subjects were male or female, aged 18 to 85 years (inclusive).
- Females were either post-menopausal for at least 2 years, surgically sterile or using a medically accepted means of contraception.
- Females were required to have a negative serum pregnancy test at screening.
- Subjects had a history or presence of gout, as defined by the preliminary criteria of the American Rheumatism Association for the classification of the acute arthritis of primary gout:
  - The presence of characteristic urate crystals in the joint fluid and/or
  - A tophus proven to contain urate crystals by chemical or polarised light microscopic means and/or
  - The presence of at least 6 of the following clinical, laboratory and x-ray phenomena:
    - More than one attack of acute arthritis
    - Maximum inflammation developed within 1 day
    - Monoarticular arthritis
    - Redness observed over joints
    - First metatarsophalangeal joint painful or swollen
    - Unilateral first metatarsophalangeal joint attack
    - Unilateral tarsal joint attack
    - Tophus (proven or suspected)
    - Hyperuricaemia
    - Asymmetric swelling within a joint on x-ray
    - Subcortical cysts without erosions upon x-ray
    - Joint fluid culture negative for organisms during attack
- Subjects had normal renal function defined as the following (in the FACT study and the phase II study):
  - A serum creatinine level less than or equal to 1.5 mg/dL or less than or equal to 133 µmol/L on the day –14;
  - An estimated creatinine clearance of 50 mL per minute or greater or 0.83 mL per second or greater could have been calculated according to the following Cockcroft-Gault formula:

    Estimated creatinine clearance in mL/min for males:

    $$\frac{(140 - \text{age in years}) \times (\text{weight in kilograms})}{72 \times (\text{serum creatinine in mg/dL})}$$

    For females, multiply the above calculation by 0.85.
- Subjects had normal renal function defined as the following (in the APEX study):
  - A serum creatinine level less than or equal to 2.0 mg/dL;

– An estimated creatinine clearance of 20 mL per minute or greater or 0.83 mL per second or greater.

Inclusion criteria at day –2 were as follows:

- Subjects had hyperuricaemia defined as a serum urate levels (sUA) of 8.0 mg/dL or more. Levels of sUA were based on the laboratory result received from the central laboratory.
- Subjects continued to meet all inclusion and exclusion criteria.

Exclusion criteria at screening (day –14) were as follows:

- Female subjects who were breast-feeding or pregnant;
- Subjects with a history of xanthinuria;
- Subjects who were on concomitant therapy with any systemic or topical medications, prescribed or non-prescribed, containing aspirin or other salicylates, at the screening visit. Stable, low doses of aspirin were allowed;
- Subjects on thiazide diuretic therapy;
- Subjects receiving prednisone doses of greater than 10 mg per day. Stable doses (≤ 10 mg per day), as well as inhaled and intranasal steroids were allowed;
- Female subjects who had a change in hormone replacement therapy or oral contraceptive therapy within 3 months of screening;
- Subjects whose alcohol intake was 14 or more drinks per week. Alcohol abuse within 5 years or current excessive alcohol use was prohibited;
- Subjects on any concomitant urate-lowering therapy;
- Subjects with active liver disease or hepatic dysfunction (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] more than 1.5 times the upper limit of normal);
- Subjects with any other significant medical condition as defined by the investigator that would have interfered with the treatment, safety, or compliance with the protocol (e.g., a clinically significant electrocardiogram result);
- Subjects with a sUA level of less than 8.0 mg/dL who were not taking uric acid-lowering therapy;
- Subjects who had previously participated in a clinical study with febuxostat;
- Subjects intolerant to allopurinol (in FACT and APEX trials only);

- Subjects were not to receive naproxen if they had a history of hypersensitivity to naproxen or any other non-steroidal anti-inflammatory drug, active gastric ulcer disease, or a history of recent gastrointestinal intolerance with bleeding, due to naproxen or any other non-steroidal anti-inflammatory drug;
- Subjects were not to receive colchicine if they had a history of hypersensitivity to colchicine;
- Subjects with a history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the screening visit or subjects who had taken any systemic cancer chemotherapy within 5 years prior to the screening visit;
- Subjects who had active rheumatoid arthritis and were required to take medication for the treatment of their rheumatoid arthritis (subjects receiving prednisone ≤ 10 mg qd were allowed);
- Subjects with secondary hypericaemia;
- Subjects with a Body Mass Index greater than 50 kg/m^2 (phase II only).

Demographic Characteristics of Patients in Phase III Trials

The demographic and baseline values of the patients included in the FACT and APEX studies are described in Table 5-9. No clinically relevant differences were observed across treatment groups in any demographic or baseline characteristic. Most patients were white males aged around 52 years and with a 12-year history of gout; almost every fourth patient had tophus present. [1,43,56] Cardiovascular risk factors were predominantly obesity, hypertension, and hyperlipidaemia; 66% admitted to excessive alcohol use.[1, 56]

Patients enrolled in the phase III clinical trials were representative of patients with gout; gout typically is seen in association with obesity, hypertension, and excessive alcohol intake. [44]

Table 5-9. Demographic and baseline characteristics of patients in the phase III febuxostat trials (FACT and APEX)

Demography	FACT (All subjects N=760)	APEX (All subjects N=1067)
Gender	96% male	94% male
Mean age	52 years	52 years
Use of alcohol	66%	66%
Obese	62%	62%

Demography	FACT (All subjects N=760)	APEX (All subjects N=1067)
Mild-to-moderate renal insufficiency	35%	NA
History of hypertension	44%	47%
History of hyperlipidaemia	34%	33%
Mean years with gout	11.9 years	11 years
Tophus at baseline	26%	20%
Overall mean sUA at baseline:	9.8 mg/dL	9.8 mg/dL
Baseline sUA ≥ 10 mg/dL	41%	39%
Prior use of a ULT	44%	NA

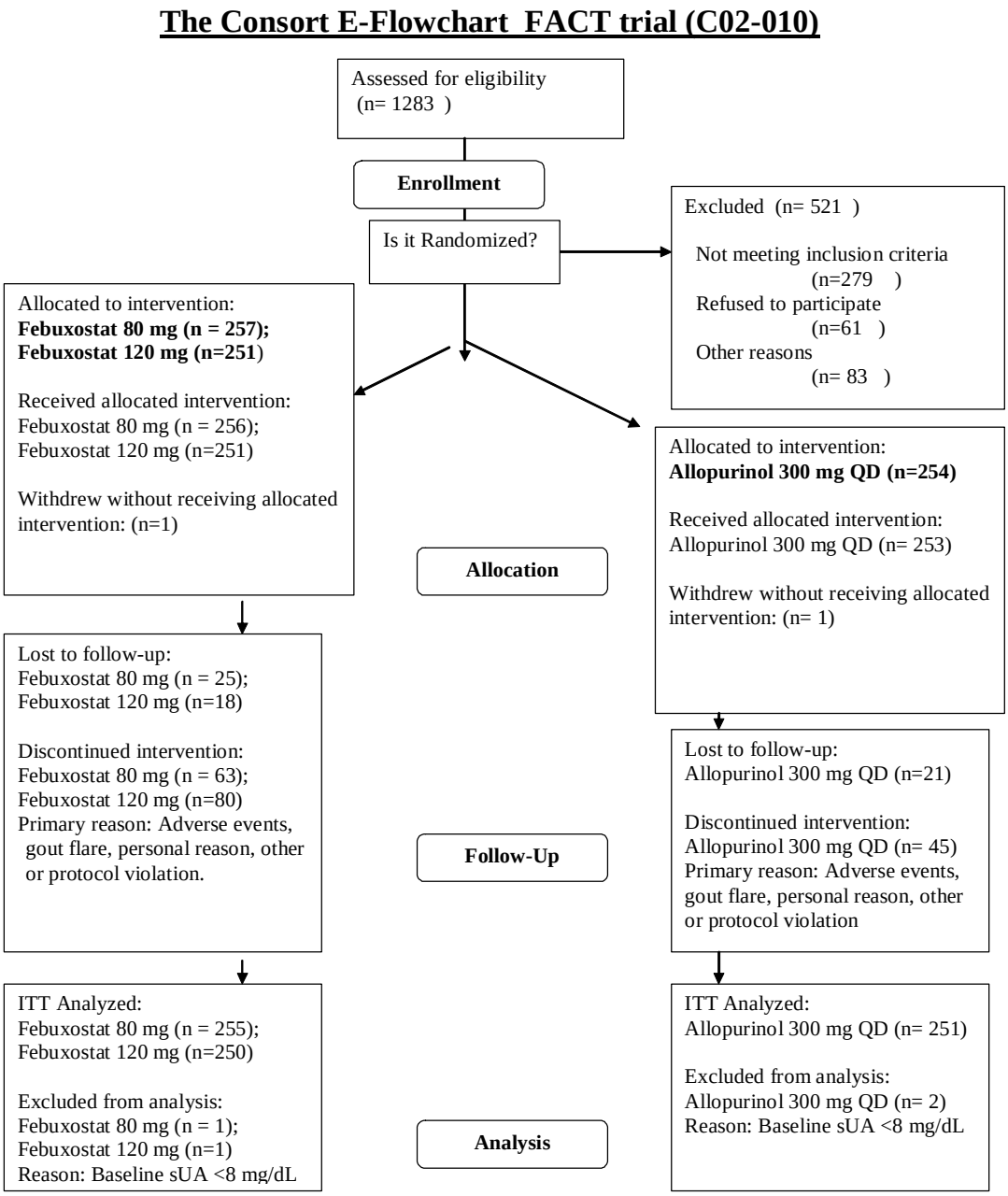
sUA = serum uric acid; ULT = urate-lowering therapy; NA= Not available.
Source: Becker et al., 2005a[1]; Schumacher et al. 2006 (abstract) [56].

5.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow-up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

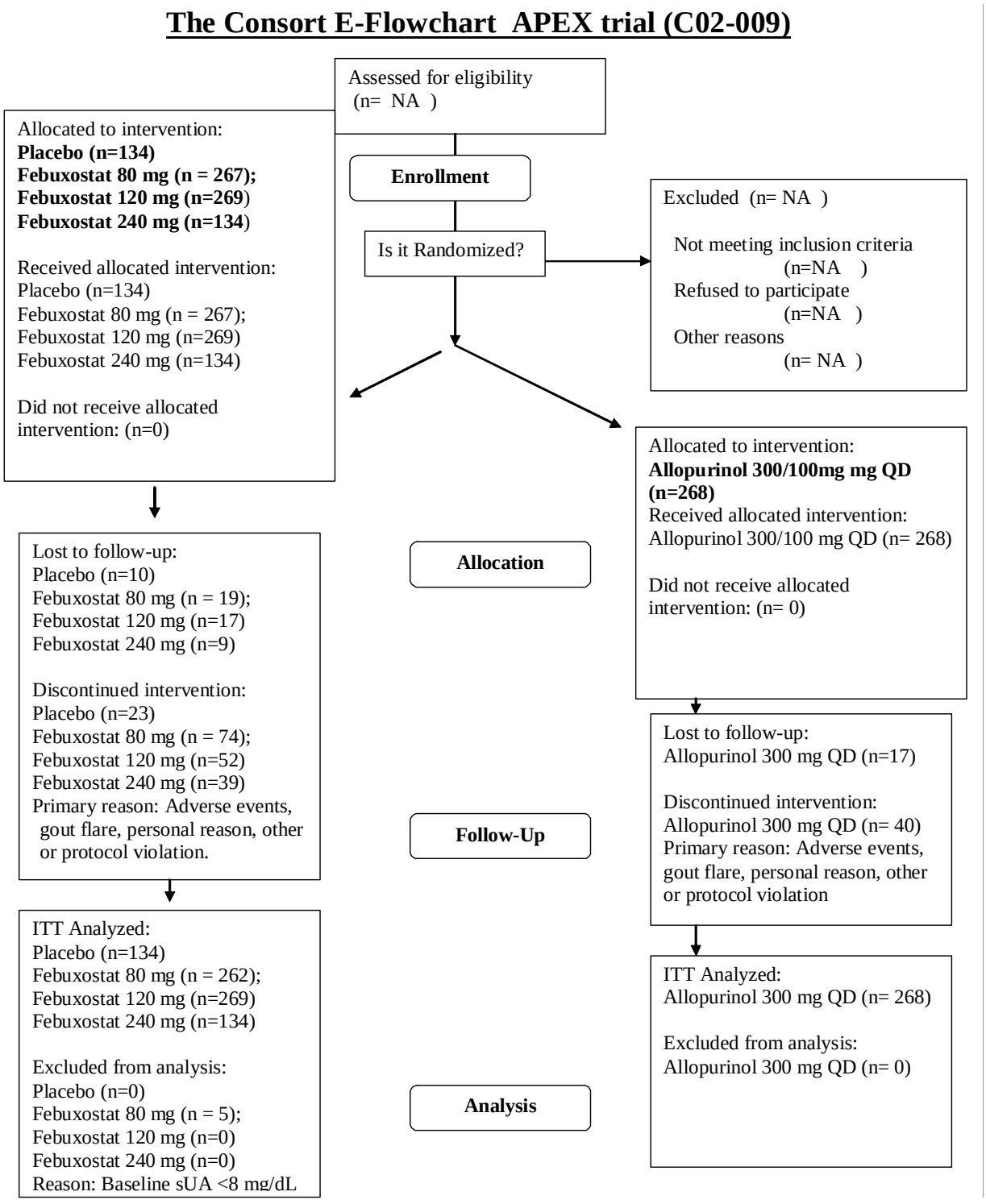
Details of the patients entered in the FACT trial and the APEX trial are provided in following flowcharts. Figure 5-2 and Figure 5-3.

Figure 5-2. Flowchart of subject disposition of FACT trial (C02-010)



Source: Becker et al., 2005a[1]

Figure 5-3. Flowchart of subject disposition of APEX trial (C02-009)



NA=not available

Source: Ipsen C02-009, 2004[2]

5.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

Outcome measures in each trial are summarised in Table 5-10.

Table 5-10. Primary and secondary efficacy variables

Primary efficacy endpoint
The proportion of subjects whose last 3 sUA levels were < 360 µmol/L (6.0 mg/dL)
Secondary efficacy endpoints
The proportion of subjects whose sUA levels were < 360 µmol/L (6.0 mg/dL)
The percent reduction in sUA levels
The percent reduction in primary tophus size, as determined by physical measurement in the subset of subjects with a primary palpable tophus at the screening visit
The reduction in the total number of tophi in the subset of subjects with palpable tophi at the screening visit
The proportion of subjects requiring treatment for a gout flare between weeks 8 and 52 of the 52-week, double-blind treatment period

sUA = serum uric acid.

Throughout the study, the efficacy of the study drug was assessed through sUA levels, physical assessment of tophus and gout flares at screening day –14 and day –2 and after drug treatment is initiated at weeks 2, 4[e], 8, 12, 16, 20, 24, 28[f], 32, 36, 40, 44, 48 and 52. Levels of sUA were measured by the central laboratory using the enzymatic method, which is commonly used in routine chemistry panels.

The safety of the study drug was assessed throughout the study by monitoring adverse events, laboratory tests, physical examinations, concomitant medication use, vital signs and 12-lead electrocardiogram results. All clinical

[e]Phase II study only for 4 weeks.
[f]APEX only for 28 weeks.

and laboratory procedures used in this study are standard and generally accepted.

The primary efficacy measure—the proportion of subjects whose last three sUA levels were less than 360 µmol/L (6.0 mg/dL)—was selected to demonstrate the ability of febuxostat to reduce and maintain sUA levels below 360 µmol/L (6.0 mg/dL), the target level recommended by the European League Against Rheumatism (EULAR).[6] A post hoc analysis also analysed the ability of febuxostat to reduce and maintain sUA levels below 300 µmol/L (5.0 mg/dL) - the target level recommended more recently by the British Society of Rheumatism (BSR).[14]

The investigator or designated assessor identified any primary tophus and was trained to measure it in a consistent way at each visit. At the screening visit, the subject was assessed for the presence and number of palpable tophi. If tophi were present, a primary palpable tophus was selected, marked with a ballpoint pen and measured at each visit (starting at 4 weeks) for any changes in tophus size. Whenever possible, the same assessor evaluated the patient throughout the study. For subjects who had more than 1 tophus, the assessor also counted the total number of tophi. If a subject developed a new tophus during the study, the assessor included this tophus in the count for the total number of tophi. A study (C02-019 without study treatment) validating the method found the average percentage difference between assessors was 32% and between visits (same assessor) was 29%.[45]

Subjects who experienced a flare during the 2-week wash-out/run-in period or during the 52-week, double-blind treatment period were allowed to continue in the study and were instructed to notify the investigator when they began to feel the onset of a flare. If a subject was experiencing a gout flare at the time of the day 1 visit, double-blind therapy was not to be initiated until the flare resolved. The subject was to be treated for the flare, and the study site was to repeat the day –2 visit procedures after the gout flare subsided. All gout flares were to be recorded by the investigator on a gout flare collection form.

5.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol

analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post hoc.

In the FACT trial, the primary hypothesis was that febuxostat at a daily dosage of 80 mg or 120 mg was not inferior (with a non-inferiority margin of 10%) in response rate (sUA ≤ 360 µmol/L [6 mg/dL] at three last visits) when compared with allopurinol at a response rate of 60% over 52 weeks in gout patients with baseline sUA ≥ 480 µmol/L (8 mg/dL). Sample size calculations are provided in Table 5-7 (C02-010).

In the APEX trial, the primary hypothesis was that febuxostat at a daily dosage of 40 mg, 80 mg, or 120 mg will result in a 45% greater response rate (sUA ≤ 360 µmol/L [6 mg/dL] at three last visits) when compared with placebo over 28 weeks in gout patients with baseline sUA ≥ 480 µmol/L (8 mg/dL). Sample size calculations are provided in Table 5-8 (C02-009).

All primary and secondary efficacy analyses were performed on the ITT population, except for the secondary efficacy analyses for the percent reduction in primary tophus size and the reduction in the total number of tophi. The ITT population was defined as all randomised subjects who received at least one dose of study drug and who had sUA levels 480 µmol/L (8.0 mg/dL) or greater at day –2 as determined by the central laboratory. The analysis for the percent reduction in primary tophus size was performed on the subset of ITT subjects with a primary palpable tophus at baseline. The analysis for the reduction in the total number of tophi was performed on the subset of ITT subjects with palpable tophi at baseline.

Two post hoc subgroup analyses were conducted in the both phase III trials; one subgroup analysis on the primary endpoint evaluating the urate-lowering effect of febuxostat and allopurinol in severe gout with high baseline defined in subgroups of sUA levels < 540 µmol/L (9 mg/dL); 540 to < 600 µmol/L (9 to < 10 mg/dL), and; ≥ 600 µmol/L (10 mg/dL); another post hoc analysis evaluated the urate-lowering effect of febuxostat and allopurinol to the recently issued guidelines from the British Society of Rheumatology target sUA level of 300 µmol/L (5 mg/dL).[14]

Handling of dropouts or missing data

In order to be considered a responder in the primary efficacy analysis, each of a subject's last three sUA levels must have been less than 360 µmol/L (6.0 mg/dL) each. If a subject prematurely discontinued from the study before at

least three sUA levels were obtained, the subject was considered a non-responder. A sensitivity analysis was conducted for the primary efficacy variable by using the available (1 or 2) sUA levels to determine response for subjects who prematurely discontinued before at least three sUA levels were obtained. This analysis examined the effect of assigning these subjects as non-responders in the primary analysis. Subjects without post-baseline sUA levels were not included in this analysis.

The baseline sUA level was defined as the average of the sUA measurements obtained on days –2 and 1. If a subject had a missing measurement for day 1, the baseline was defined as the measurement taken on day –2. For all primary and secondary efficacy analyses, missing data were not imputed. Details of ITT study populations and study terminations for each study are provided in the tables in section 5.3.1.

5.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive (see table).

See Table 5-11 for the list of criteria and the response.

Table 5-11. Critical appraisal of relevant RCTs

Critical appraisal	FACT APEX Phase II
How was allocation concealed?	By interactive voice response system
What randomisation technique was used?	Computer generated
Was a justification of the sample size provided?	Yes
Was follow-up adequate?	Yes
Were the individuals undertaking the outcomes assessment aware of allocation?	No
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	Parallel-group
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	No. The trials were conducted in the USA (FACT in Canada as well). The clinical practice for gout treatment, e.g., using allopurinol and the target sUA level, was similar as that in the UK. However, in the UK, 2007 BSR guidelines recommend a more stringent target sUA level of 300 µmol/L (5 mg/dL).

Critical appraisal	FACT APEX Phase II
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, and setting.	The RCT participants are representative overall of UK patients with gout and sUA ≥ 480 µmol/L (8 mg/dL) regarding clinical setting in primary care, demographics, comorbidities and disease severity, except that the RCT participants had a higher rate of obesity and renal impairment than UK patients in general.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Allopurinol 300 mg (100 mg for renally impaired) was used as an active comparator. The dose used is the recommended dose for moderate gout in the SPC and the dose of ≤ 300 mg per day is used in the majority (97.9%) of the GP patients in the UK treated with allopurinol.[11]
Were the study groups comparable?	Yes
Were the statistical analyses used appropriate?	Yes
Was an intention-to-treat analysis undertaken?	Yes
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	No. There were no clinically relevant differences in baseline characteristics between the febuxostat-treatment group and the allopurinol-treatment group.

RCT = randomised controlled trial; SPC = Summary of Product Characteristics; UK = United Kingdom; US = United States of America.

5.4 *Results of the relevant comparative RCTs*

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- **The unit of measurement.**
- **The size of the effect—for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**

- **The number of patients included in the analysis.**
- **The median follow-up time of analysis**
- **State whether intention-to-treat was used for the analysis and how data were imputed, if necessary.**
- **Discuss and justify definitions of any clinically important differences.**
- **Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**

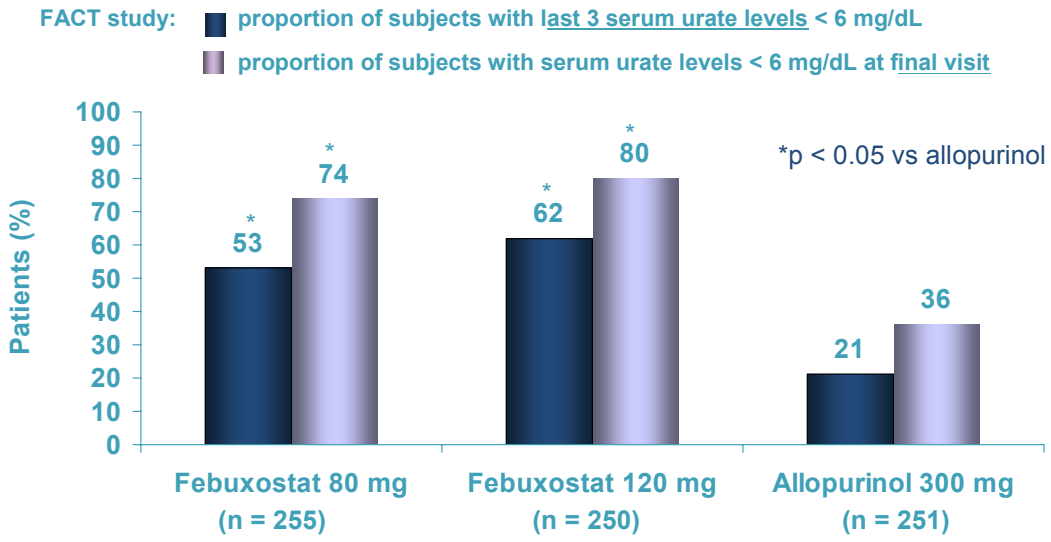
5.4.1 Results of the primary efficacy endpoint: proportion of patients in each treatment group whose last 3 sUA levels were less than 360 µmol/L (6.0 mg/dL)

Two large RCTs have shown febuxostat 80 mg qd and 120 mg qd to be more effective than allopurinol 300/100 mg at reducing sUA concentrations to a target level of less than 360 µmol/L (6 mg/dL) during the last three visits, regardless of baseline sUA levels.[1,2, 3, 49] Concentrations of sUA were reduced as early as 2 weeks and persisted throughout both studies, i.e., 28 and 52 weeks, respectively.

FACT trial: febuxostat 80 mg and 120 mg significantly reduced sUA levels compared with allopurinol 300 mg

A randomised, allopurinol-controlled, phase III clinical trial (n = 760) evaluated doses of 80 mg and 120 mg of febuxostat for 52 weeks in patients with gout. Figure 5-4 and Table 5-12 display the results of the trial.

Figure 5-4. FACT study: proportion of patients with sUA level less than 360 µmol/L (6 mg/dL) at 52 weeks



ITT population: subjects with serum urate level ≥ 8.0 mg/dL on day –2.

ITT = intention to treat; sUA = serum uric acid; 6 mg/dL= 360 µmol/L; 8 mg/dL = 480 µmol/L.
Source: Becker et al., 2005[1]

Table 5-12. FACT study: difference in proportion of patients with last three sUA levels less than 360 µmol/L (6 mg/dL)

	Difference in proportions	97.5% CI (Normal approximation for binomial distribution)	*P* value (Fishers's Exact Test)
Febuxostat 80 mg vs. allopurinol	32%	(23.1%, 41.3%)	< 0.001
Febuxostat 120 mg vs. allopurinol	41%	(31.5%, 49.5%)	< 0.001

CI = confidence interval; sUA = serum uric acid.
Source: Becker et al., 2005[1]; IPSEN, C02-010, 2004.[3]

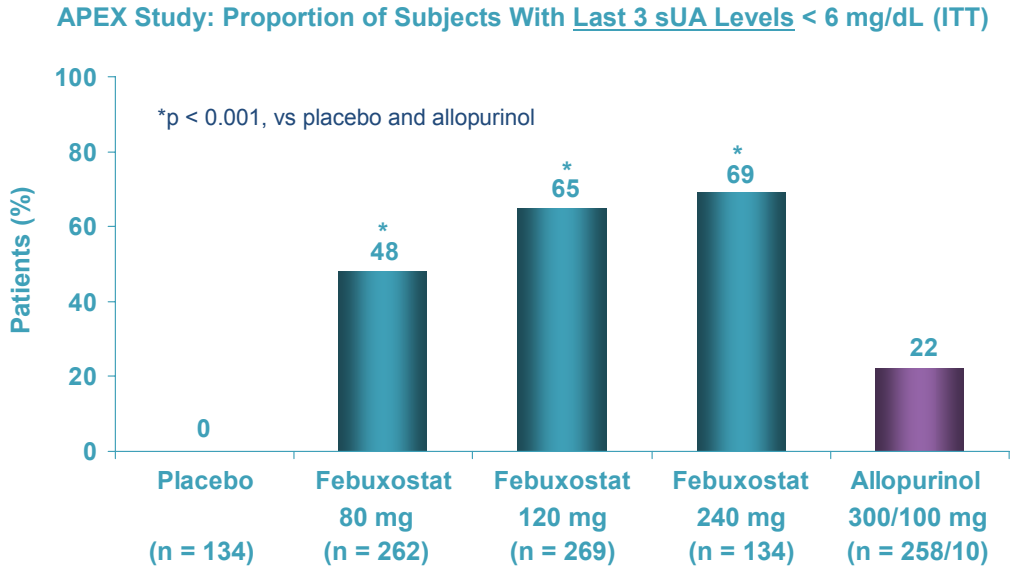
Febuxostat 80 mg and 120 mg significantly reduced sUA levels (< 360 µmol/L [6 mg/dL]) in 53% and 62% of patients, respectively, compared with 21% of patients receiving allopurinol 300 mg, when measured in the last 3 months of a 52-week trial.[1]

APEX trial: febuxostat 80 mg, 120 mg and 240 mg significantly reduced sUA levels compared with allopurinol 300/100 mg and placebo

A randomised, allopurinol- and placebo-controlled, phase III clinical trial (n = 1,072) evaluated doses of 80 mg, 120 mg and 240 mg of febuxostat for

28 weeks in patients with gout. Figure 5-5 and Table 5-13 display the results of the trial. [2,49]

Figure 5-5. APEX study: proportion of patients with last three sUA levels less than 360 µmol/L (6 mg/dL) at 28 weeks (ITT)



Within combined allopurinol 300/100 group, allopurinol 100 mg efficacy: 0%; allopurinol 300 mg efficacy: 23%.

ITT = intention to treat; sUA = serum uric acid.
Sources: Schumacher et al., 2005c [abstract] [49]; Ipsen, C02-009, 2004.[2]

Table 5-13. APEX study: difference in proportion of patients with last three sUA levels less than 360 µmol/L (6 mg/dL) at 28 weeks

	Difference in proportions	97.5% CI (Normal approximation for binomial distribution)	*P* value (CMH test stratified by baseline renal function)
Febuxostat 80 mg vs. allopurinol 300/100mg	26%	(16.7%, 34.7%)	< 0.001
Febuxostat 120 mg vs. allopurinol 300/100mg	43%	(34.0%, 51.3%)	< 0.001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel (test); sUA = serum uric acid.
Source: Ipsen C02-009, 2004.[2]

Febuxostat 80 mg, 120 mg and 240 mg significantly reduced sUA levels (< 360 µmol/L [6 mg/dL]) in 48%, 65% and 69% of patients, respectively, compared with 22% of patients receiving allopurinol 300/100 mg and 0% of placebo patients and based on the last three sUA levels.

5.4.2 Secondary endpoint: proportion of patients with sUA levels less than 360 µmol/L (6.0 mg/dL) at the final visit

FACT trial: febuxostat 80 mg and 120 mg significantly reduced sUA levels compared with allopurinol 300 mg

At the final visit, the proportion of patients with sUA concentrations less than 360 µmol/L (6 mg/dL) was 74% for febuxostat 80 mg, 80% for febuxostat 120 mg and 36% for allopurinol ($P \leq 0.001$ for each febuxostat group vs. allopurinol) (Figure 5-4).[1,3]

APEX trial: febuxostat 80 mg, 120 mg and 240 mg significantly reduced sUA levels compared with allopurinol 300/100 mg and placebo

At the final visit, the proportion of patients with sUA concentrations less than 360 µmol/L (6 mg/dL) was 72% for febuxostat 80 mg, 79% for febuxostat 120 mg, 92% for febuxostat 240 mg, 39% for allopurinol and 1% for placebo ($P < 0.05$ for each febuxostat group vs. allopurinol).[2]

At Week 28, the proportion of patients with sUA concentrations less than 360 µmol/L (6 mg/dL) was 76% for febuxostat 80 mg, 87% for febuxostat 120 mg, 94% for febuxostat 240 mg, 41% for allopurinol and 1% for placebo ($P < 0.05$ for each febuxostat group vs. allopurinol). [49]

5.4.3 Secondary endpoint: percentage reduction in sUA levels

FACT trial: each of the febuxostat groups significantly lowered the mean percentage change from baseline in sUA levels compared with allopurinol 300 mg

At the final visit, the mean percentage change from baseline in sUA levels was statistically significantly different between each of the febuxostat groups and the allopurinol 300-mg qd treatment group (Table 5-14). The percentage reduction in sUA level was observed in all treatment groups at the week 2 visit and was maintained throughout the treatment.[3]

Table 5-14. FACT study: mean percentage change from baseline in sUA at final visit (ITT)

	Febuxostat 80 mg qd		Febuxostat 120 mg qd		Allopurinol 300 mg qd	
Actual value (mg/dL) baseline	n = 255	9.80 (SD 1.24)	n = 250	9.84 (SD 1.26)	n = 251	9.90 (SD 1.23)

	Febuxostat 80 mg qd	Febuxostat 120 mg qd	Allopurinol 300 mg qd
Percentage change from baseline			
Final visit	–44.73% (SD 19.10)	–51.52% (SD 19.91)	–32.99% (SD 15.33)
P value vs. allopurinol, using ANOVA	P <0.001	P < 0.001	n/a

ANOVA = analysis of variance; ITT = intention to treat; n/a = not applicable; qd = once daily; SD = standard deviation; sUA = serum uric acid. Final visit: Assess the effect of febuxostat and allopurinol prior to drug or dose switch, or discontinuation.
Source: Becker et al., 2005a [1]; Ipsen, C02-010, 2004.[3]

APEX trial: each of the febuxostat groups significantly lowered the mean percentage change from baseline in sUA levels compared with allopurinol 300/100 mg and placebo

At the final visit, the mean percentage change from baseline in sUA levels was statistically significantly different between each of the febuxostat groups and the allopurinol 300/100-mg qd treatment and the placebo-treatment groups (Table 5-15). The percentage reduction in sUA level was observed in all treatment groups at the week 2 visit and was maintained throughout the treatment.[2]

Table 5-15. APEX study: mean percentage change from baseline in sUA at final visit (ITT)

	Placebo	Febuxostat 80 mg qd	Febuxostat 120 mg qd	Allopurinol 300/100 mg qd
Actual value (mg/dL) Baseline	n = 134 9.80 (SD 1.67)	n = 262 9.96 (SD 1.33)	n = 269 9.88 (SD 1.22)	n = 268 9.78 (SD 1.22)
Percentage change from baseline				
Final visit	–2.99% (SD 13.28)	–45.23% (SD 18.16)	–51.89% (SD 17.99)	–33.70% (SD 14.74)
P-value vs. placebo or allopurinol	n/a	P ≤ 0.05	P ≤ 0.05	n/a

ANOVA = analysis of variance; ITT = intention to treat; n/a = not applicable; qd = once daily; SD = standard deviation; sUA = serum uric acid. *P* value using 2-way ANOVA with treatment and renal function as factors.
Source: Ipsen, C02-009, 2004.[2]

5.4.4 Secondary endpoint: percentage reduction in primary tophus size and the reduction in the total number of tophi in patients with palpable tophi at screening visit

Two phase III trials and two extension studies have shown that the effective reduction of sUA levels with febuxostat over the long term results in reduction of size and even resolution of tophi.

The FACT trial: tophi reduction in all treatment groups at 52 weeks

In the 52-week phase III FACT trial, the median reduction in the tophus area was assessed in 156 patients with tophi at baseline. A reduction in the tophus areas was observed over time for all three treatment groups; this reduction was not statistically different when compared with allopurinol. The median reduction in the tophus area was 83% in patients receiving 80-mg febuxostat, 66% in those receiving 120-mg febuxostat and 50% for allopurinol.[1]

No difference in reduction of total number of tophi was seen between the febuxostat 80-mg and the febuxostat 120-mg qd patients, when compared with the allopurinol 300-mg patients at final visit.[2]

A post hoc analysis of the results of the trial tested for differences in the reduction of tophus area between patients with a mean postbaseline sUA concentration of < 360 µmol/L (6 mg/dL) and those with a concentration of ≥ 360 µmol/L (6 mg/dL). The median reduction from baseline in tophus area at week 52 was 75% among patients who reached an average postbaseline sUA concentration of < 360 µmol/L (6 mg/dL), as compared with 50% among those who did not reach the target sUA level (P = 0.06).[1]

The APEX trial: a significant reduction of number of tophi with febuxostat 120 mg compared to allopurinol 300/100 at 28 weeks

In the 28-week phase III APEX trial, the results from all five treatment groups were similar among the 217 patients with a primary palpable tophus at baseline. A decrease in median tophus size was noted over time in each treatment group, with no statistically significant treatment difference in percentage decrease from baseline in tophus size at the week 28 or final visits.

Due to the variability in measurements occurring at the elbow (possibly due to olecranon bursal fluid), change in tophus size was evaluated excluding elbow tophi. In the analysis excluding elbow locations (n = 124), the percent change from baseline in primary tophus size was significantly different between the

febuxostat 120-mg (–54.4%; n = 34) and the allopurinol 300/100-mg treatment groups (–10.5% n = 42) (*P* ≤ 0.05 using the Wilcoxon rank-sum test) at the final visit.[2]

Only febuxostat 120 mg qd showed significant difference in reduction of total number of tophi (mean –1.2 n = 38) compared with placebo (mean –0.3 n = 22) at week 28 (*P* ≤ 0.05 using the Wilcoxon rank-sum test).[2]

A post hoc analysis of the results of the trial tested for differences in the reduction of tophus area between patients with a mean postbaseline sUA concentration of < 360 µmol/L (6 mg/dL) and those with a concentration of > 360 µmol/L (6 mg/dL). Among patients who achieved an average sUA level < 360 µmol/L (6 mg/dL), a numerically greater reduction in tophus size was noted at the final visit (median percent change of -47% [25th and 75th percentile: -96.8, -7.6] n = 104), when compared with patients who achieved an average sUA level ≥ 360 µmol/L (6 mg/dL) (median percent change -22.6% [25th and 75th percentile: -62.5, 0.0]n = 95).[2]

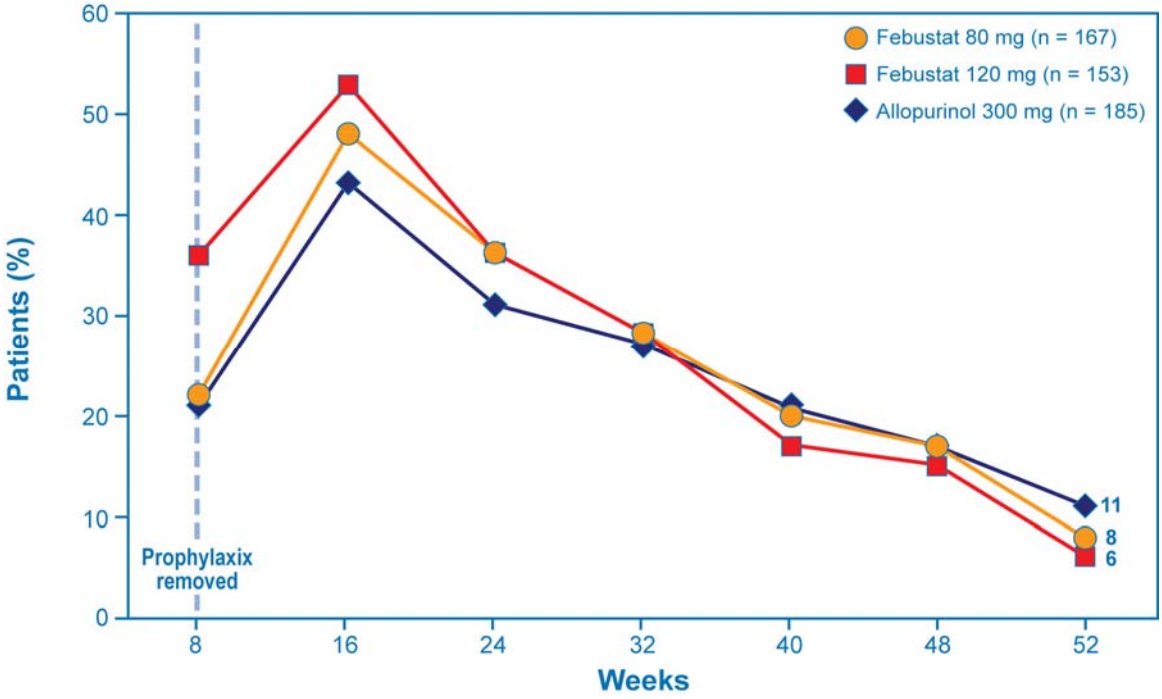
5.4.5 Secondary endpoints: proportion of patients requiring treatment for gout flare

Febuxostat provides sustained improvement in disease activity. When administered for up to 2 years, febuxostat maintained reduced sUA levels (below 360 µmol/L [6.0 mg/dL]) and reduced the average frequency of gout flares to less than one per year. Additionally, fewer patients required treatment of gout flares over time.[1,2,16,46,56] In the short term, initiation of urate-lowering therapy leads to an increased frequency of gout flares, probably due to a rapid fall of serum uric acid, which mobilises urate crystals from crystal aggregates.[4]

The FACT trial: a reduction of flare by the end of 52 weeks in all treatment groups.

The phase III FACT febuxostat study recorded the incidence of gout flares over 52 weeks. Figure 5-6 illustrates a characteristic spike of flares at 16 weeks for all treatment groups, indicating the lower the sUA level the higher the initial rate of flares over the first 6 months and a reduction of flares over time. The incidence of gout flares in the last 4 weeks of therapy was lower in the febuxostat groups: 8% for febuxostat 80 mg, 6% for febuxostat 120 mg and 11% for allopurinol, as shown in Figure 5-6.[1]

Figure 5-6. FACT study: percentage of patients requiring treatment for a gout flare over 52 weeks



Sources: Becker et al., 2005a[1]; Ipsen, C02-010, 2004[3]

A post hoc analysis of the results of the trial was performed to test for differences in the reduction of gout flares among patients with a mean postbaseline sUA concentration of less than 360 µmol/L (6 mg/dL) and those with a concentration of 360 µmol/L (6 mg/dL) or greater. The proportion of patients requiring treatment for a gout flare was significantly lower among patients who reached a mean postbaseline sUA concentration of less than 360 µmol/L (6 mg/dL) (6%) than among those who did not (14%) in the last 4 weeks of the 52-week trial (weeks 49 through 52).[1]

The APEX trial: a reduction of flare by the end of 28 weeks in all treatment groups except for placebo

The phase III APEX febuxostat study also reported reductions in the incidence of gout flares over time. There were numerically fewer patients with flares requiring treatment during the last 4 weeks of the study (the interval of week 24 to week 28) in the febuxostat 80-mg (15%), 120-mg (15%), 240-mg (8% [$P \leq 0.05$ compared with placebo]) and allopurinol 300/100-mg groups (14%), compared with the placebo group (20%)..[2]

A numerically greater proportion of patients who achieved an average postbaseline sUA level of 360 µmol/L (6 mg/dL) or more required treatment for a gout flare during the time interval of week 24 to week 28 (18%)

compared with patients who achieved an average postbaseline sUA level of less than 360 µmol/L (6 mg/dL) (13%).[2]

5.4.6 Analysis results based on BSR recommended target sUA less than 300 µmol/L (5 mg/dL)

The recently issued guidelines from the British Society of Rheumatology use a target sUA level of 300 µmol/L (5 mg/dL).[14]

- Febuxostat consistently demonstrated better efficacy in decreasing sUA levels below 300 µmol/L (5 mg/dL) and below 240 µmol/L (4 mg/dL), in comparison with allopurinol 300 mg, and provided an advantage for treating severe tophaceous gout.

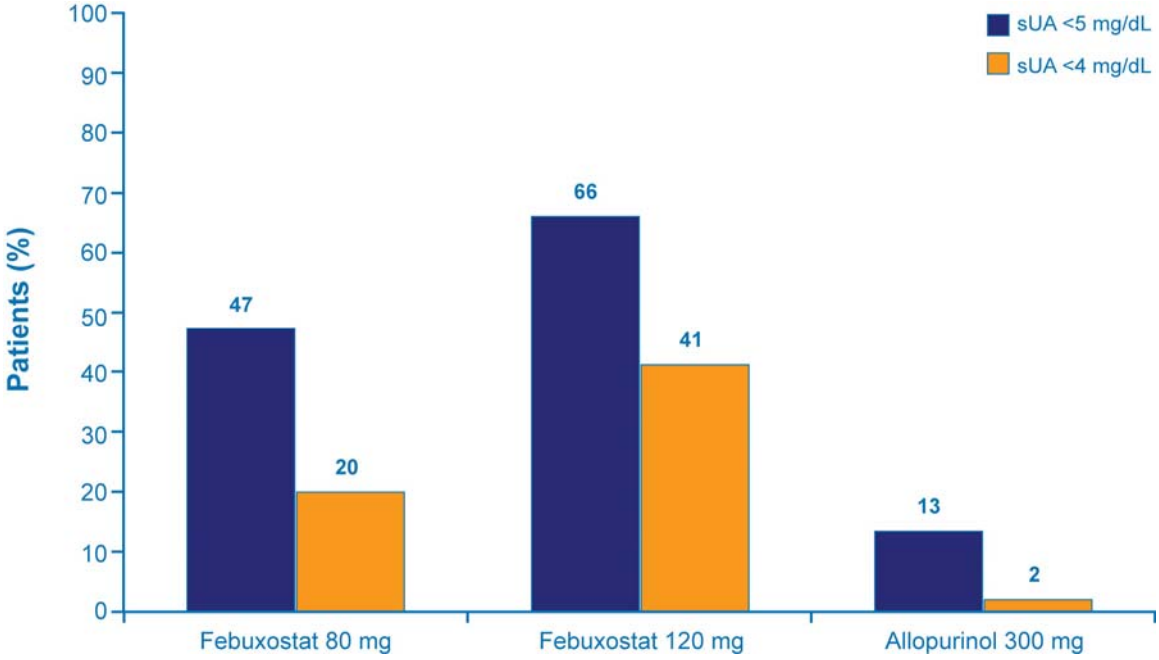
Phase II clinical trial: febuxostat is effective in reducing sUA to below BSR target sUA level

In a placebo-controlled, phase II clinical trial (n = 140), febuxostat administered for 4 weeks reduced sUA levels to less than 300 µmol/L (5 mg/dL) in 49% of patients treated with febuxostat 80 mg and in 88% of patients treated with febuxostat 120 mg. Over the same interval, febuxostat reduced sUA to less than 240 µmol/L (4 mg/dL) in 19% of patients treated with febuxostat 80 mg and in 56% of patients treated with 120 mg.[42]

FACT trial: febuxostat is more effective than allopurinol in reducing sUA to below BSR target sUA level

In the phase III FACT febuxostat trial, a significantly greater proportion of patients receiving febuxostat had sUA concentrations of less than 300 µmol/L (5 mg/dL) or less than 240 µmol/L (4 mg/dL), when compared with patients treated with allopurinol at the final visit (Figure 5-7).

Figure 5-7. Percentage of patients with reduced sUA level to BSR target level of less than 300 µmol/L (5 mg/dL) on febuxostat and allopurinol



sUA = serum uric acid.

Source: Becker et al., 2005a.[1]

APEX trial: febuxostat is more effective than allopurinol in reducing sUA to below BSR target sUA

In phase III APEX trial, the proportion of patients whose sUA levels were less than 300 µmol/L (5 mg/dL) or less than 240 µmol/L (4 mg/dL) were significantly greater in each of the febuxostat groups, compared with the proportion of patients in the placebo and allopurinol 300/100-mg groups, at week 28 and the final visit.[2]

- The percentages of patients having sUA concentrations less than 300 µmol/L (5 mg/dL) at the final visit were 46% for febuxostat 80 mg, 65% for febuxostat 120 mg, 13% for allopurinol and 0% for placebo ($P < 0.001$ for each febuxostat groups, when compared with the allopurinol or placebo group using the Cochran-Mantel-Haenszel test stratified by baseline renal function).

- The percentages of patients having sUA concentrations less than 240 µmol/L (4 mg/dL) at the final visit were 18% for febuxostat 80 mg, 38% for febuxostat 120 mg, 75% for febuxostat 240 mg, 2% for allopurinol and 0% for placebo ($P < 0.001$ for each febuxostat group, when

compared with the allopurinol or placebo group using the Cochran-Mantel-Haenszel test stratified by baseline renal function).[2]

5.4.7 Subgroup analysis results of primary endpoint based on baseline sUA levels

The urate-lowering effect of febuxostat is maintained in severe gout with high baseline sUA levels (up to 600 µmol/L [10 mg/dL]), while the efficacy of allopurinol is reduced with each milligram per decilitre increase of baseline sUA level. Clinical trials have shown 80 mg and 120 mg febuxostat to be superior to 300 mg allopurinol in a population with gout with baseline sUA levels greater than 480 µmol/L (8 mg/dL).[1,2,42] The efficacy results are consistent in subgroup analyses of patients with severe gout whose sUA levels are greater than 540 µmol/L (9 mg/dL). [1]

The FACT trial: febuxostat is more effective in reducing sUA at high baseline sUA compared with allopurinol

In the phase III FACT trial, about 40% of the patients entering the trial had baseline sUA levels that were 600 µmol/L (10 mg/dL) or greater. The proportion of patients with sUA levels less than 360 µmol/L (6 mg/dL) based on the sUA concentrations measured in the last 3 months of the 52-week study are presented in Table 5-16 by baseline sUA levels[1] The data presented in Figure 5-8 are the proportions of patients with sUA levels at the final visit categorised by baseline sUA levels.[3] Febuxostat was significantly more effective, when compared with allopurinol, in reducing sUA concentrations in patients with baseline sUA concentrations less than 540 µmol/L (9 mg/dL), in patients with concentrations between 540 and 600 µmol/L (9 and 10 mg/dL), and even in patients whose baseline sUA levels were greater than 600 µmol/L (10 mg/dL).

Table 5-16. FACT study: percentage of patients with sUA levels less than 6 mg/dL in the last 3 months

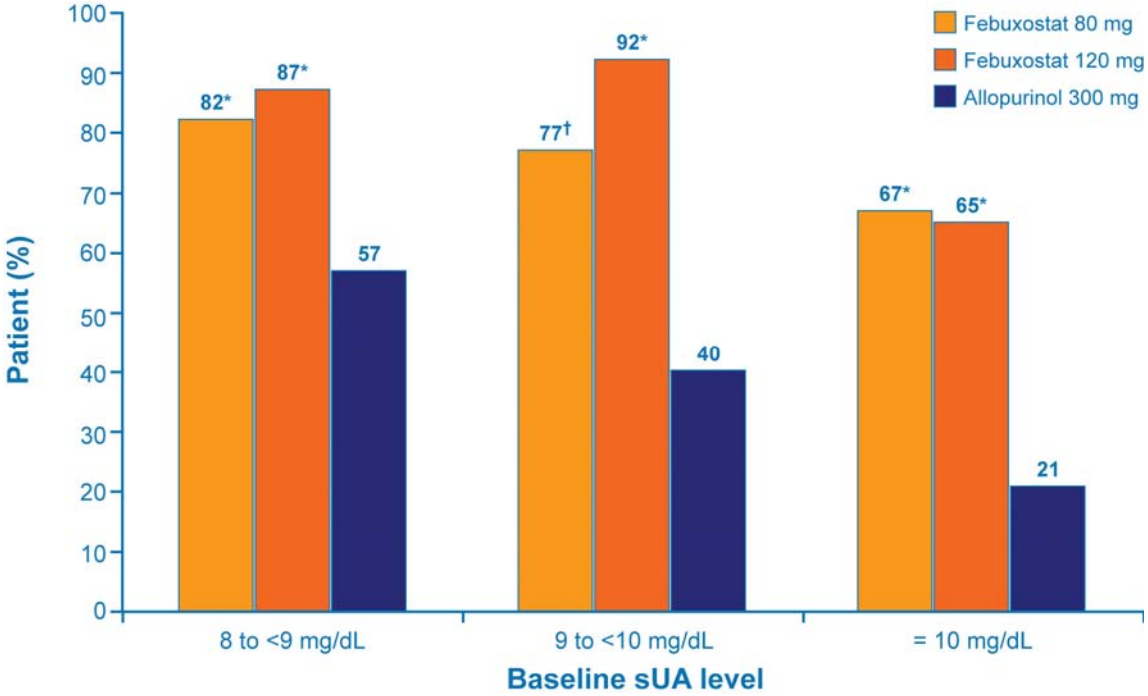
Baseline sUA	Febuxostat 80 mg[a]	Febuxostat 120 mg[a]	Allopurinol 300/100 mg
< 9 mg/dL (540 µmol/L)	(43/75) 57%	(50/69) 72%	(25/63) 40%
9 to < 10 mg/dL	(44/75) 59%	(60/81) 74%	(19/80) 24%
≥ 10 mg/dL (600 µmol/L)	(49/105) 47%	(44/100) 44%	(9/108) 8%

CMH = Cochran-Mantel-Haenszel Test; sUA = serum uric acid.

[a] Statistically significant versus allopurinol ($P \leq 0.05$) using CMH test adjusting for the baseline sUA level.

Source: Ipsen, C02-010, 2004;[3] Becker et al. (2005).[1]

Figure 5-8. FACT study: proportion of patients with sUA less than 6 mg/dL at final visit, by baseline sUA



sUA = serum uric acid. Final visit: Assess the effect of febuxostat and allopurinol prior to drug or dose switch or discontinuation.
Sources: Ipsen, C02-010, 2004.[3]

APEX trial: febuxostat is more effective in reducing sUA at high baseline sUA compared with allopurinol

In the phase III APEX trial, about 30% of the patients entering the trial had baseline sUA levels that were 600 µmol/L (10 mg/dL) or greater. The proportion of patients with sUA levels less than 360 µmol/L (6 mg/dL), based on the sUA concentrations measured in the last 3 months of the 28-week study, is presented in Table 5-17, by baseline sUA levels.[2]

Table 5-17. APEX study: percentage of patients with sUA level less than 360 µmol/L (6 mg/dL) at the final visit, by baseline sUA (ITT)

Baseline sUA	Placebo	Febuxostat 80 mg[a,b]	Febuxostat 120 mg[a,b]	Allopurinol 300/100 mg
< 9 mg/dL (540 µmol/L)	(1/32) 3%	(56/61) 92%	(66/74) 89%	(44/79) 56%
9 to < 10 mg/dL	(0/50) 0%	(65/89) 73%	(66/78) 85%	(39/95) 41%
> 10 mg/dL (600 µmol/L)	(0/45) 0%	(62/103) 60%	(77/113) 68%	(19/89) 21%

CMH = Cochran-Mantel-Haenszel Test; ITT = intention to treat; sUA = serum uric acid.
[a] Statistically significant versus placebo.
[b] Statistically significant versus allopurinol.
Source: Ipsen, C02-009, 2004.[2]

Febuxostat was significantly more effective compared with allopurinol in reducing sUA concentrations, regardless of baseline sUA level.

5.4.8 Compliance rate

The mean compliance rate ranged from 95.0% to 97.8% across the treatment groups in the two phase III trials (Table 5-18).

Table 5-18. Compliance rates in the FACT and APEX studies (ITT population)

	Placebo		Febuxostat 80 mg qd		Febuxostat 120 mg qd		Allopurinol 300/100 mg qd	
FACT study			n = 255		n = 250		n = 251	
Mean (SD)	n/a	n/a	95.1%	(16.5)	95.0%	(6.83)	95.5%	(6.24)
Range			46%-100%		56%-100%		63%-100%	
APEX study	n = 134		n = 262		n = 269		n = 268	
Mean (SD)	97.3%	(4.28)	95.7%	(8.56)	96.7%	(5.36)	96.0%	(6.61)
Range	76%-100%		17%-100%		80%-100%		52%-100%	

ITT = intention to treat; n/a = not applicable; qd = once daily; SD = standard deviation.
Source: Ipsen, C02-009, 2004; Ipsen, C02-010, 2004; Becker et al. 2005a [1,2,3]

5.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 5.2.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis where appropriate.**
- **Tabulate and/or graphically display the individual and combined results.**

5.5.1 Comparison and analyses of results across studies

No meta-analysis was considered necessary as patient-level data from pooled head-to-head RCTs was available which provided high level evidence of efficacy and safety.

Pooled analyses of the two phase III trials (FACT and APEX)

Pooled analyses of the primary and secondary endpoints from the two phase III trials (FACT and APEX) over 28 weeks and 52 weeks were conducted. The pooled analyses included 1,698 subjects who were randomised into the studies and who received at least one dose of the study drug. The disposition of subjects included in the pooled analysis is provided in Table 5-19. The phase II study (TMX-01-004) included only data for 4 weeks of treatment and was therefore not included in the pooled population.

Table 5-19. Disposition of subjects in the pooled analyses of the FACT and APEX studies

	Placebo	Febuxostat 80 mg qd	Febuxostat 120 mg qd	Allopurinol 300/100 mg qd
Randomised and received at least 1 dose (N)	134	523	520	521
ITT population: randomised and received at least 1 dose, with sUA ≥ 8.0 mg/dL at baseline (N)	134	517	519	519
Prematurely terminated	33 (25%)	181 (35%)	167 (32%)	123 (24%)
Primary reason for termination				
Adverse event	5 (4%)	34 (7%)	39 (8%)	26 (5%)
Protocol violation	3 (2%)	13 (2%)	5 (1%)	7 (1%)
Personal reason	9 (7%)	35 7(%)	29 (6%)	22 (4%)
Lost to follow-up	10 (7%)	44 (8%)	35 (7%)	38 (7%)
Therapeutic failure	3 (2%)	6 (1%)	3 (1%)	1 (< 1%)
Gout flare	0 (0%)	23 (4%)	34 (7%)	10 (2%)
Other	3 (2%)	26 (5%)	22 (4%)	19 (4%)

qd = once daily; sUA = serum uric acid.
Source: Ipsen, Integrated summary of efficacy, 2005.[7]

Table 5-20. Demographic and baseline characteristic of subjects in the pooled analyses of the FACT and APEX studies (ITT population)

	Febuxostat 80 mg qd N = 517	Febuxostat 120 mg qd N = 519	Allopurinol 300/100 mg qd N = 519
Male	94%	96%	95%

	Febuxostat 80 mg qd N = 517	Febuxostat 120 mg qd N = 519	Allopurinol 300/100 mg qd N = 519
Caucasian	75%	79%	77%
Mean age (years)	51.2 (SD 12.0) (Range 22-84)	51.6 (SD 11.84) (Range 23-81)	51.7 (SD 12.4) (Range 24-84)
Weight (kg) Mean	103 (SD 20) (Range 60-180)	103 (SD 21) (Range 62-212)	102 (SD 20) (Range 62-203)
Renal function Normal (serum creatinine ≤ 1.5 mg/dL)	98%	97%	98%

ITT = intention to treat; qd = once daily;
Source: Ipsen, Integrated summary of efficacy, 2005.[7]

In conjunction to the results of the pooled analysis of the combined studies, the results from the open-label phase II (TMX-01-005) and phase III (EXCEL) extension trials are presented in Section 5.5.

Open-label phase II (TMX-01-005) extension trial

The long-term phase II trial with febuxostat 40 mg, 80 mg and 120 mg enrolled 116 patients. [39,56] All subjects initially received received febuxostat 80 mg in this study and were between week 4 to 24 allowed to be titrated to lower (40 mg) or higher doses (120 mg) of febuxostat, if needed. Most patients (74%-81%) had sustained reductions in sUA (< 6 mg/dL [360 µmol/L]) throughout the trial from week 28 to week 104. About one-third (36%) of patients enrolled with a baseline sUA levels of 10 mg/dL (600 µmol/L) or greater.

Open-label phase III (EXCEL) extension trial

A subset of patients (n = 735) completing either the FACT trial or the APEX trial were enrolled in an open-label extension study, EXCEL, for more than 24 months.[15] Patients were randomized to febuxostat 80 mg, febuxostat 120 mg or allopurinol 300/100 mg and changes in doses or medication was allowed during the first 6 months after randomization. After 6 months, patients were regarded as therapeutic failures and were to be discontinued if their sUA levels remained at 6 mg/dL (360 µmol/L) or greater. Thus, only patients who achieved sUA levels of less than 6 mg/dL continued to participate in the study long term. In order to assess the effect of febuxostat and allopurinol on sUA levels prior to drug or dose switch, an analysis of the final visit data prior to drug or dose switch was performed.

5.5.2 Results of the primary efficacy endpoint: proportion of patients achieving less than 0.36 mmol/L (6 mg/dL) at the last three visits

Pooled analyses of the two phase III trials (FACT and APEX)

The results of the combined phase III trials showed that febuxostat significantly reduced sUA levels (< 360 µmol/L [6 mg/dL]) in patients receiving febuxostat 80 mg qd and 120 mg qd, when compared with allopurinol and placebo (P < 0.001 for each febuxostat group compared with allopurinol) (Table 5-21).[45] Concentrations of sUA were reduced as early as 2 weeks from initiation of febuxostat treatment.

Table 5-21. Proportion of patients with sUA levels less than 360 µmol/L (6 mg/dL) at the last three visits—ITT patients (phase III pivotal studies)

Last 3 sUA < 6.0 mg/dL	Placebo n/N (%)	Febuxostat 80 mg qd n/N (%)	Febuxostat 120 mg qd n/N (%)	Allopurinol 300/100 mg qd n/N (%)
Yes	0/134 (0%)	262/517[a] (51%)	329/519 (63%)	113/519 (22%)

Difference in Proportions (%)			
	Point estimate	97.5% CI [b]	*P* value [c]
Febuxostat 80 mg vs allopurinol 300/100mg	29	(22.5, 35.3)	< 0.001[d]
Febuxostat 120 mg vs allopurinol 300/100mg	42	(35.4, 47.9)	< 0.001[d]

ITT = intention to treat; qd = once daily; sUA = serum uric acid.
[a] Statistically significant versus febuxostat 120mg qd ($P \leq 0.05$).
[b] 97.5% CI for the difference in proportions based on the normal approximation for the binomial distribution.
[c] P values from a CMH test stratified by study.
[d] Statistically significant versus allopurinol 300/100 mg qd using Hochberg's procedure for multiple comparisons.
Source: Ipsen, Integrated summary of efficacy, 2005.[45]

5.5.3 Results of the secondary efficacy endpoint: proportion of patients who achieved less than 360 µmol/L (6 mg/dL) at the final visit

Pooled analyses of the two phase III trials (FACT and APEX)

An analysis of the combined phase III trials (APEX and FACT) showed that febuxostat was significantly better than placebo and allopurinol in decreasing sUA levels to less than 360 µmol/L (6 mg/dL), 300 µmol/L (5 mg/dL) and 240 µmol/L (4 mg/dL), respectively (Table 5-22).

The percentages of patients having the BSR target sUA levels of less than 300 µmol/L (5 mg/dL) at the final visit were 0% for the placebo group, 47% for the febuxostat 80 mg group, 65% for the febuxostat 120 mg group, 84% for the febuxostat 240 mg group and 13% for the allopurinol group ($P \leq 0.05$).

The reduction in sUA levels for all different levels was observed in all active treatment groups at the week 2 visit, and this reduction was maintained throughout treatment.[47]

Table 5-22. Proportion of patients with sUA levels less than 360 µmol/L (6 mg/dL), 300 µmol/L (5 mg/dL), and 240 µmol/L (4 mg/dL) at the final visit—ITT patients (phase III pivotal studies)

sUA level at final visit	Placebo n/N (%)	Febuxostat 80 mg qd n/N (%)	Febuxostat 120 mg qd n/N (%)	Allopurinol 300/100 mg qd n/N (%)
< 6.0 mg/dL	1/127 (1%)	368/502 (73%)[ab]	402/507 (79%)[a]	190/505 (38%)
< 5.0 mg/dL	0/127 (0%)	234/502 (47%)[ab]	331/507 (65%)[a]	65/505 (13%)
< 4.0 mg/dL	0/127 (0%)	96/502 (19%)[ab]	200/507 (39%)[a]	10/505 (2%)

ITT = intention to treat; qd = once daily; sUA = serum uric acid. Final visit: Assess the effect of febuxostat and allopurinol prior to drug or dose switch or discontinuation.

[a] Statistically significant difference versus allopurinol 300/100 mg QD ($P \leq 0.05$) using a CMH test stratified by study.

[b] Statistically significant difference versus febuxostat 120 mg qd ($P \leq 0.05$) using a CMH test stratified by study.

Source: Ipsen, Integrated summary of efficacy, 2005.[45]

The open-label extension studies of phase II and III trials: febuxostat consistently reduced sUA levels over several years

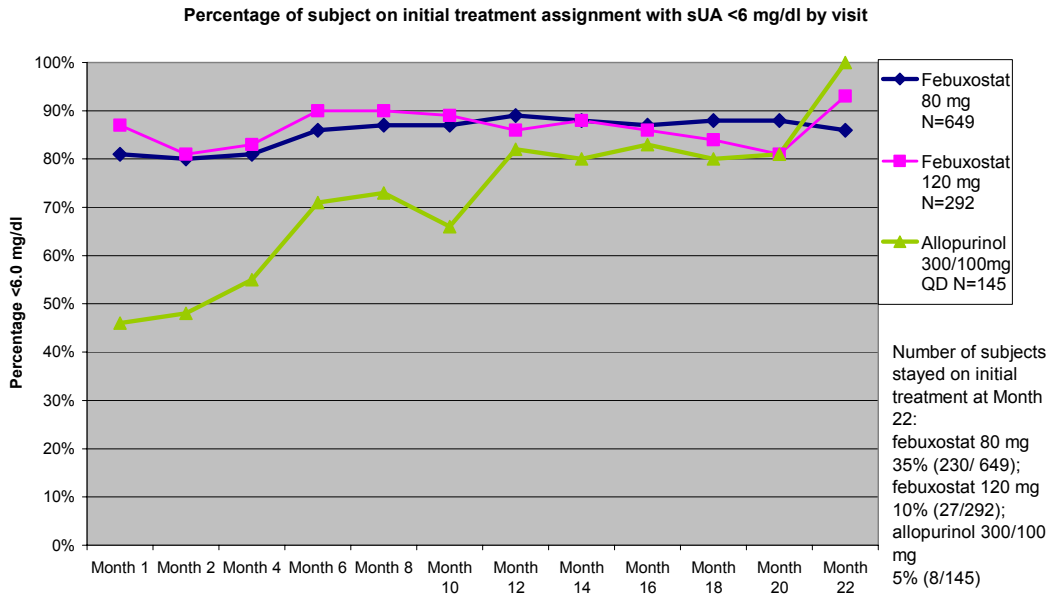
The long-term phase II trial with febuxostat 40 mg, 80 mg and 120 mg showed that the majority of the patients were able to achieve sUA levels of less than 360 µmol/L (6 mg/dL) across a 4-year period.[47] The sUA levels remained consistently below 360 µmol/L (6 mg/dL) after 1 year (78%), 2 years (76%), 3 years (84%) and 4 years (90%).[47,56]

More than half of the patients were able to achieve sUA levels of less than 300 µmol/L (5 mg/dL) across four visits over a 2-year period.[39] The percentage of patients having sUA levels less than 300 µmol/L (5 mg/dL) was between 49% and 65% across weeks 28, 52, 80 and 104 for the febuxostat 80-mg group, the dose used by a majority of the patients (72%).[39] The mean sUA value was less than 300 µmol/L (5 mg/dL) at year 4 (n = 67).[46]

An interim analysis during the ongoing EXCEL trial estimated the percentage of patients on initial treatment (prior to any switch or dose change) with

sUA < 360 µmol/L (6 mg/dL) over 22 months (Figure 5-9). The percentage during the second year was based on few patients in each group due to the time of analysis during the ongoing trial and that the protocol required patients with sUA ≥ 360 µmol/L (6 mg/dL) to switch to other treatment or discontinue the study. The allopurinol group contained only 8 subjects at month 22, with only responders, which explains the 100% rate of response.

Figure 5-9. Percentage of subjects on initial treatment with sUA < 360 µmol/L (6 mg/dL) by visit up to two years (EXCEL)



sUA = serum uric acid. Interim analysis of ongoing trial. The number of subjects in each time interval reflects the subjects exposure to date prior to switch or change in dose.
Source: Ipsen, Integrated summary of efficacy, 2005.[45]

5.5.4 Results of the secondary efficacy endpoint: percentage reduction in sUA levels from baseline

The combined phase III trials: febuxostat significantly reduced sUA levels (< 360 µmol/L [6 mg/dL]) when compared with allopurinol and placebo

An analysis of the combined phase III trials (APEX and FACT) showed a significantly greater mean reduction of sUA from baseline with febuxostat compared to allopurinol. (Table 5-23).

Table 5-23. Mean percentage change from baseline in sUA levels at final visits—ITT patients (phase III pivotal studies)

	Placebo		Febuxostat 80 mg qd		Febuxostat 120 mg qd		Allopurinol 300/100 mg qd	
Actual value (mg/dL) Baseline	n = 134	9.80 (SD 1.67)	n = 517	9.88 (SD 1.29)	n = 519	9.86 (SD 1.24)	n = 519	9.84 (SD 1.22)
Actual value (mg/dL) Final visit	n = 127	9.45 (SD 1.61)	n = 502	5.40 (SD 1.88)	n = 507	4.77 (SD 2.03)	n = 505	6.53 (SD 1.60)
Percentage change from baseline								
Final visit	–2.99% (SD 13.28)		–44.98% (SD 18.61)		–51.71% (SD 18.91)		–33.36% (SD 15.02)	
P value vs. placebo or allopurinol	n/a		P ≤ 0.05		P ≤ 0.05		n/a	

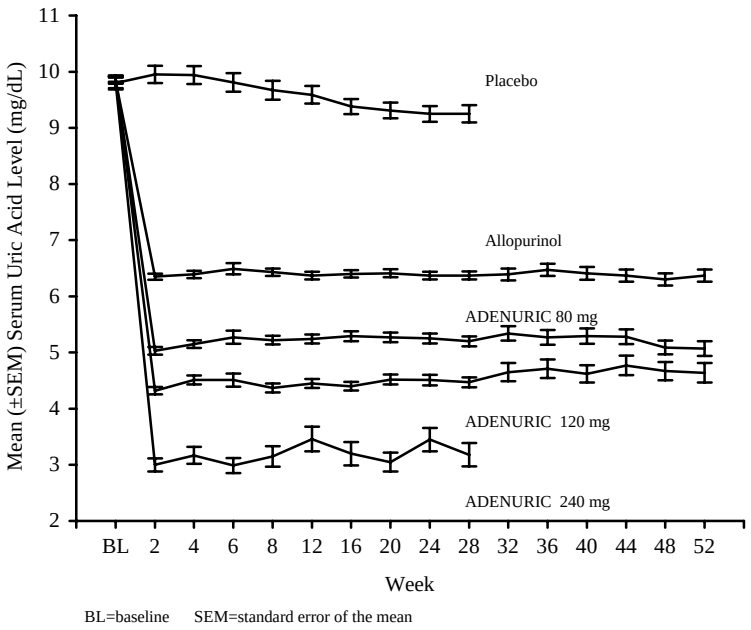
ANOVA = analysis of variance; ITT = intention to treat; n/a = not applicable; qd = once daily; SD = standard deviation; sUA = serum uric acid

P value using 2-Way ANOVA with treatment and study as factors.

Source: Ipsen, Integrated summary of efficacy, 2005.[45]

The mean post-baseline sUA levels were consistent over time within each treatment group and ranged around 540 µmol/L (9 mg/dL) for placebo, 300 µmol/L (5 mg/dL) for febuxostat 80 mg, for febuxostat 120 mg, 180 µmol/L (3 mg/dL) for febuxostat 240 mg, and 360 µmol/L (6 mg/dL) for allopurinol (Figure 5-10). Placebo and febuxostat 240 mg qd was only studied for 28 weeks in the APEX study.

Figure 5-10. Mean sUA levels, combined phase III studies



sUA = serum uric acid.
Source: Ipsen, Integrated summary of efficacy, 2005.[7]

5.5.5 Subgroup analysis results based on baseline sUA levels

An analysis for the combined phase III trials (APEX and FACT) also showed that febuxostat was significantly more effective than placebo and allopurinol in decreasing sUA levels to less than 360 µmol/L (6 mg/dL) in patients with baseline sUA concentrations of less than 540 µmol/L (9 mg/dL), in patients with baseline sUA between 540 and 600 µmol/L (9 and 10 mg/dL), and even in patients whose baseline sUA levels were 600 µmol/L (10 mg/dL) or greater (Table 5-24).[47]

Table 5-24. Proportion of patients with sUA levels less than 360 µmol/L (6 mg/dL) at the final visit, by baseline sUA—ITT patients (phase III pivotal studies)

Baseline sUA mg/dL	Placebo n/N (%)	Febuxostat 80 mg qd n/N (%)	Febuxostat 120 mg qd n/N (%)[a]	Allopurinol 300/100 mg qd n/N (%)
All	1/127 (1%)	368/502 (73%)[a,b]	402/507 (79%)	190/505 (38%)
< 9	1/32 (3%)	114/132 (86%)[a]	124/141 (88%)	79/140 (56%)
9 to < 10	0/50 (0%)	122/163 (75%)[a,b]	139/157 (89%)	70/173 (40%)
≥ 10	0/45 (0%)	132/207 (64%)[a]	139/209 (67%)	41/192 (21%)

ITT = intention to treat; qd = once daily; sUA = serum uric acid. Final visit: Assess the effect of febuxostat and allopurinol prior to drug or dose switch, or discontinuation.

[a] Statistically significant difference versus allopurinol 300/100mg QD ($P \leq 0.05$) using a CMH test stratified by study.

[b] Statistically significant difference versus febuxostat 120mg qd ($P \leq 0.05$) using a CMH test stratified by study.

Source: Ipsen, Integrated summary of efficacy, 2005.[45]

5.5.6 Secondary endpoint: analysis of tophi resolution

The combined phase III trials showed a correlation of reduction of sUA level and reduction of tophi size.

Among patients with a primary palpable tophus at baseline in the combined phase III trials, an analysis of the percent reduction in primary tophus size determined by physical measurement showed a trend towards larger median percentage reductions in the primary tophus size from baseline with febuxostat compared to allopurinol (Table 5-25).[45] At week 52 and at the final visit, greater reductions (median percentage from baseline) were observed in the febuxostat 80-mg (83% and 44%, respectively) and 120-mg (66% and 44%, respectively) groups, when compared with the allopurinol group (50% and 25%, respectively).

Table 5-25 Mean percentage change of primary tophi from baseline at week 52 and at final visit —ITT patients (phase III pivotal studies)

	Placebo		Febuxostat 80 mg qd		Febuxostat 120 mg qd		Allopurinol 300/100 mg qd	
	N	Median Actual value (mm^2) (25^{th} p, 75^{th} p)	N	Median Actual value (mm^2) (25^{th} p, 75^{th} p)	N	Median Actual value (mm^2) (25^{th} p, 75^{th} p)	N	Median Actual value (mm^2) (25^{th} p, 75^{th} p)
Baseline	29	840 (300, 2310)	98	806 (323, 2209)	106	636 (270, 1900)	109	625 (300, 1575)
Week 52	-	-	32	186 (0, 935)	26	290 (64, 864)	30	272 (100, 1482)
Final Visit	26	388 (121, 1000)	92	445 (3, 1287)	101	323 (40, 1200)	105	320 (100, 1184)
Percentage change from baseline								
Week 52		-		-83% (-100%, -16%)		-66% (-85%, -39%)		-50% (-96%, 0.0%)
Final visit		-40% (-62%, -16%)		-44% (-99%, 0.0%)		-44% (-85%, -0.0%)		-25% (-67%, 0.0%)

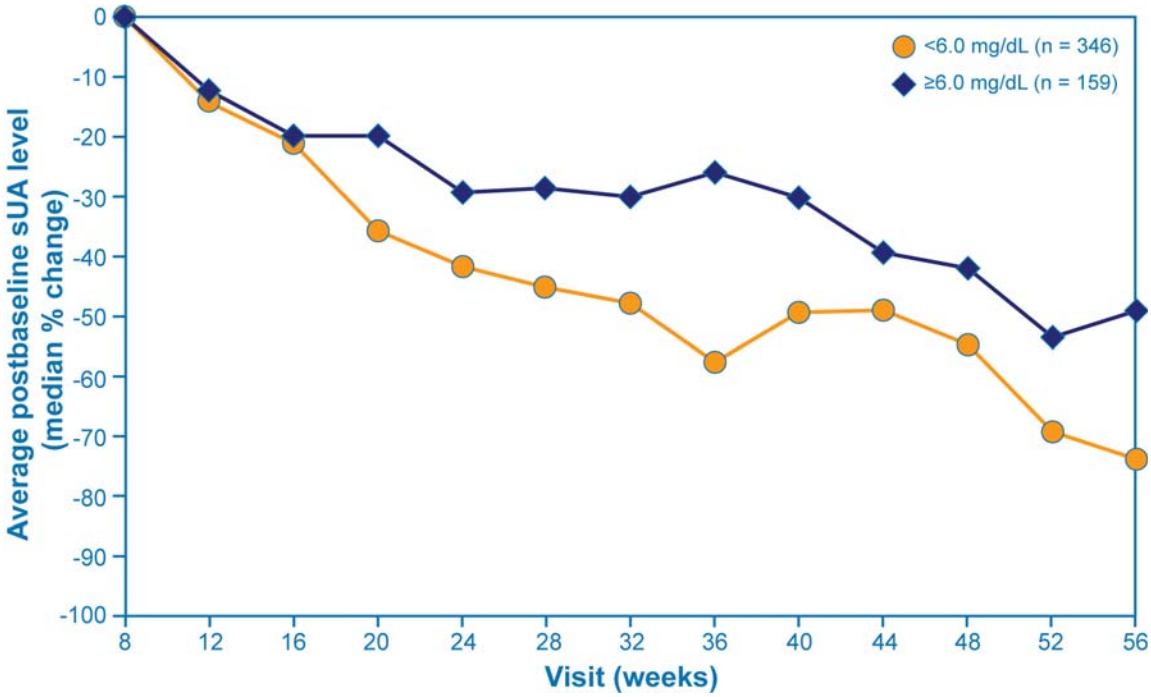
ITT = intention to treat; qd = once daily; 25^{th} p = 25^{th} percentile, p = 75^{th} percentile. Final visit: Assess the effect of febuxostat and allopurinol prior to drug or dose switch or discontinuation.

Source: Ipsen, Integrated summary of efficacy, 2005.[45]

An analysis of change of reduction by average sUA level showed that among patients who achieved an average sUA level of less than 360 µmol/L

(6 mg/dL), a significantly greater reduction in the primary tophus size was noted at the final visit (51%) compared with patients who achieved an average sUA level of 360 µmol/L (6 mg/dL) or greater (24%) ($P \leq 0.05$ using the Wilcoxon rank-sum test) (Figure 5-11).[45]

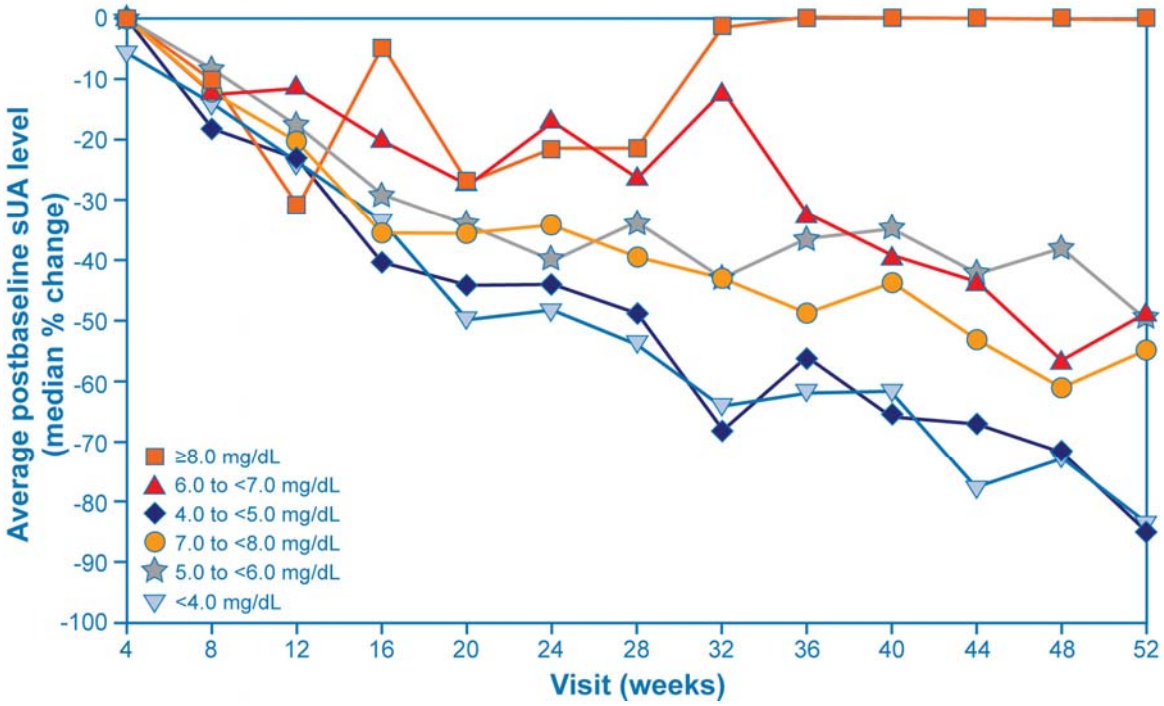
Figure 5-11. Median percentage change from baseline in primary tophus size by average postbaseline sUA level (less than 360 µmol/L [6 mg/dL] and 360 µmol/L [6 mg/dL] or greater)—ITT patients with a primary tophus at baseline (phase III pivotal studies)



ITT = intention to treat; sUA = serum uric acid.
Source: Ipsen, Integrated summary of efficacy, 2005[45]

The decrease in tophus size was directly related to the reduction in sUA level. The median percentage reduction from baseline in primary tophus size was greater in the groups that achieved an average postbaseline sUA level of less than 300 µmol/L (5 mg/dL) by week 20 compared with the groups with higher average postbaseline sUA levels (Figure 5-12). For patients with sUA levels greater than 480 µmol/L (8 mg/dL), an increase in size of tophi was observed.[45]

Figure 5-12. Median percentage change from baseline in primary tophus size by average postbaseline sUA level—ITT patients with a primary tophus at baseline (phase III pivotal studies)



ITT = intention to treat; sUA = serum uric acid.
Source: Ipsen, Integrated summary of efficacy, 2005.[45]

A significant difference in reduction of total number of tophi was seen between the febuxostat 120-mg qd patients (mean -0.8; n = 68) compared with the febuxostat 80-mg qd patients (mean -0.3; n = 66), and the allopurinol 300/100-mg patients (mean -0.2; n = 84) at week 28, respectively ($P \leq 0.05$ using Wilcoxon rank sum test).[45]

The open-label extension studies of phase II and III trials showed a reduction of number of tophi over time.

In the long-term extension of the phase II trial with febuxostat, tophi were not measured; however, the presence or absence of tophi was noted on physical examination. Twenty-six patients entered the study with a palpable tophus, and 20 (77%) of these patients had no tophus present at one or more examinations during the study period of up to 48 months. [45,56]

A subset of patients completing either the FACT trial or the APEX trial were enrolled in an open-label extension study, EXCEL, for more than 24 months.[15] Tophi were present at baseline in 214 (19.7%) of the 1,086 patients.

At the final visit prior to any switches in drug or dosages, the percentages of patients with 100% resolution of tophi with the initial treatment assignments were 38% for the febuxostat 80-mg qd group, 36% for the febuxostat 120-mg qd group and 17% for the allopurinol 300/100-mg qd group. Fifty percent (4/8) of patients followed until month 24 treated with febuxostat 80 mg qd had a complete (100%) resolution of a primary tophus. The percentages of patients with at least a 50% reduction in primary tophus size were 65% for the febuxostat 80-mg qd group, 71% for the febuxostat 120-mg qd group and 57% for the allopurinol 300/100-mg qd group.[45]

5.5.7 Secondary endpoint analysis: analysis of gout flares

The long-term phase II trial showed consistent reduction of flare rates during 5 years of febuxostat treatment

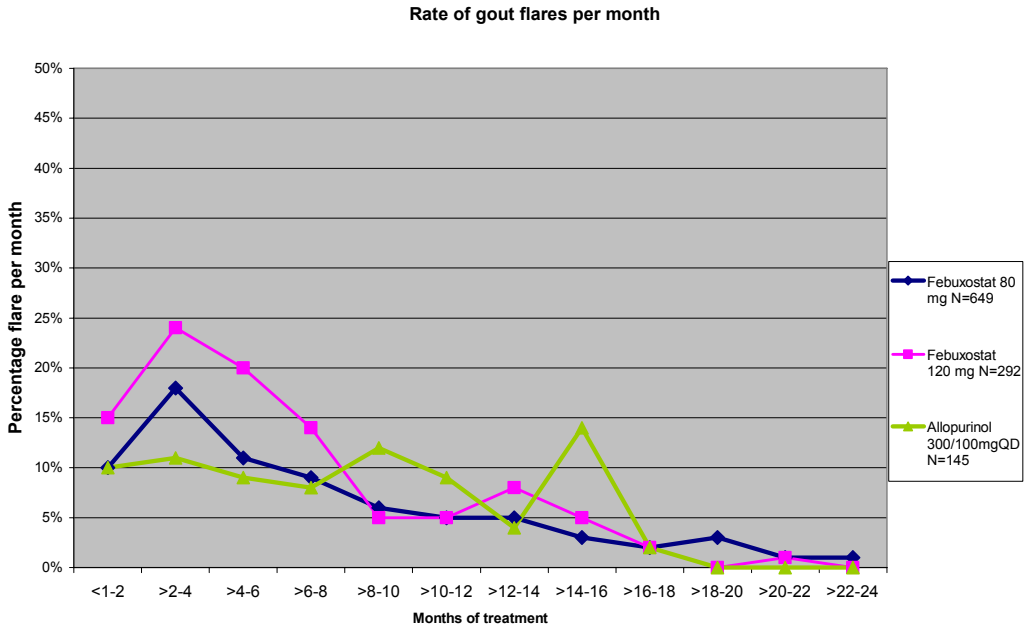
The long-term phase II trial showed fewer than 10% of all patients received treatment for a gout flare after the first year of febuxostat treatment. The overall incidence of gout flares gradually declined over 4 years of febuxostat treatment, with the greatest reduction noted with febuxostat 80 mg treatment. After the first year of stable treatment, patients had, on average, less than one gout flare per year. This rate continued to decrease over time, up to 4 years of treatment.[47,56]

The number of gout flares by subject exposure year decreases by each year on febuxostat treatment (Figure 5-13). During the fourth to fifth year no flares occurred in the febuxostat 80 mg qd treatment group of 19.5 exposure years.[56]

The open-label extension studies of phase II and III trials showed a consistent reduction of gout flares over time.

At the end of month 6 of the open-label extension study (EXCEL), patients were titrated to a stable dose of the study drug; cases with sUA levels at 6 mg/dL (360 µmol/L) or greater were discontinued (Ipsen, Integrated summary of efficacy, 2005). Therefore, based on the study design, only patients who achieved sUA levels of less than 6 mg/dL continued to participate in the study long term. An interim analysis during the trial showed after month 14 on febuxostat, fewer than 2% of patients experienced a gout flare; after month 22, there were no patients with gout flares (Figure 5-14).

Figure 5-14. Rate of gout flare per month by treatment in up to 2 years of continued treatment in patients with sUA levels less than 360 µmol/L (6 mg/dL) at 6 months



Interim analysis of ongoing trial. Treatment group is a subject's initial assigned treatment. Only gout flares occurred during the initial treatment are summarized. Subjects who reported 2 or more gout flares were only counted once in each interval. The number of subjects in each time interval reflects the subjects' exposure to date.
Source: Ipsen, Integrated summary of efficacy, 2005.[45]

For each year on febuxostat treatment, the number of gout flares by number of exposure subject year decreases (Figure 5-15). During the second to third year no flares occurred in the febuxostat 120 mg qd treatment group of 23.61 exposure years.[45]

Figure 5-15. Number of gout flares per exposed subject-year by up to 3 years of continued treatment

5.6 Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest, consideration should be given to using indirect/mixed treatment comparisons. This analysis indirectly compares the proposed technology with the main comparator by comparing one set of RCTs in which participants were randomised to the intervention/common reference with another set of RCTs in which participants were randomised to the main comparator/common reference. The common reference is often placebo, but may be an alternative technology.

Before comparing the proposed technology with the main comparator, the comparability of the two sets of RCTs must be established. If the RCTs have not been described in the previous sections the methodology and results from the RCTs included in the analysis should be summarised using the format described in sections 5.3 and 5.4 Highlight any potential sources of heterogeneity between the RCTs included in the analysis.

Give a full description of the methodology used and provide a justification for the approach.

No indirect comparison was conducted; two large, phase III, head-to-head randomised controlled trials are available.

5.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

5.7.1 Adverse events in clinical trials

Febuxostat in doses of 80 mg and 120 mg is safe and well tolerated, as is febuxostat 240 mg, representing two times the maximum clinical dose.[1,2]

Febuxostat is not associated with clinically significant side effects. In the phase III clinical trials evaluating doses of 80 mg, 120 mg and 240 mg, the most common adverse events reported were upper respiratory tract infection, nasopharyngitis, diarrhoea, arthralgia, headache, pain in an extremity, influenza, back pain, nausea, hypertension, and alanine aminotransferase and aspartate aminotransferase increases. The incidence of adverse events was similar across treatment groups and is displayed in Table 5-22.[1,2,47]

Cardiac disorders were the most common serious adverse events and were the only serious adverse events occurring at an incidence of 1% or more. These results were consistent for all treatment groups, including allopurinol. The majority of patients who had a cardiovascular syndrome adverse event had a history of cardiovascular disease or cardiovascular risk factors.

A total of 12 deaths were reported during the clinical program, none of which was considered related to the study drug. Six of the 12 deaths were a result of cardiovascular conditions. In the combined pivotal phase III and long-term

extension studies, the overall death rate per 100 person-years was 0.43 in the febuxostat total group and 0 in the allopurinol group. Since the exposure to febuxostat (2,792 person years) was greater than exposure to allopurinol (479 person years), the upper limits of the 95% confidence intervals for death rate were similar in the febuxostat total group (0.751) and the allopurinol (0.770) group. A specific review of these deaths showed no statistically significant increase in cardiovascular adverse events or deaths in the febuxostat groups versus the allopurinol group. Mortality rates remain consistent with those observed in populations with cardiovascular risk factors and/or hyperuricaemia.[47]

Table 5-22. Treatment-related adverse events occurring in 2% or more of patients in any treatment group (pivotal phase III studies)

MedDRA High-Level Term/ MedDRA Preferred Terms	Treatment Group n (%)					
	Placebo	Febuxostat				Allopurinol
	(n = 134)	All Doses (N = 1,177)	80 mg qd (n = 523)	120 mg qd (n = 520)	240 mg qd (n = 134)	300/100 mg qd (n = 521)
Total patients with at least 1 adverse event	31 (23%)	267 (23%)	119 (23%)	109 (21%)	39 (29%)	101 (19%)
Diarrhoea (excluding infective)	6 (4%)	37 (3%)	16 (3%)	12 (2%)	9 (7%)	12 (2%)
Diarrhoea	6 (4%)	37 (3%)	16 (3%)	12 (2%)	9 (7%)	12 (2%)
Headaches NEC	0	25 (2%)	7 (1%)	12 (2%)	6 (4%)	12 (2%)
Headache	0	25 (2%)	7 (1%)	12 (2%)	6 (4%)	12 (2%)
Nausea and vomiting symptoms	1 (< 1%)	25 (2%)	12 (2%)	7 (1%)	6 (4%)	5 (< 1%)
Nausea	1 (< 1%)	24 (2%)	11 (2%)	7 (1%)	6 (4%)	4 (< 1%)
Vomiting	0	3 (< 1%)	3 (< 1%)	0	0	2 (< 1%)
Neurological signs and symptoms NEC	1 (< 1%)	18 (2%)	8 (2%)	4 (< 1%)	6 (4%)	2 (< 1%)
Dizziness	1 (< 1%)	14 (1%)	7 (1%)	3 (< 1%)	4 (3%)	2 (< 1%)
Dysgeusia	0	4 (< 1%)	1 (< 1%)	1 (< 1%)	2 (1%)	0
Gastrointestinal and abdominal pains (excluding oral and throat)	3 (2%)	12 (1%)	3 (< 1%)	4 (< 1%)	5 (4%)	3 (< 1%)
Abdominal pain	1 (< 1%)	6 (< 1%)	1 (< 1%)	1 (< 1%)	4 (< 1%)	1 (< 1%)

MedDRA High-Level Term/ MedDRA Preferred Terms	Treatment Group n (%)					
	Placebo	Febuxostat				Allopurinol
	(n = 134)	All Doses (N = 1,177)	80 mg qd (n = 523)	120 mg qd (n = 520)	240 mg qd (n = 134)	300/100 mg qd (n = 521)
Abdominal pain lower	0	1 (< 1%)	1 (< 1%)	0	0	1 (< 1%)
Abdominal pain upper	2 (1%)	5 (< 1%)	1 (< 1%)	3 (< 1%)	1 (< 1%)	1 (< 1%)
Liver function analyses	1 (< 1%)	40 (3%)	18 (3%)	18 (3%)	4 (3%)	19 (4%)
ALT increased	1 (< 1%)	9 (< 1%)	5 (< 1%)	4 (< 1%)	0	5 (< 1%)
AST increased	0	9 (< 1%)	4 (< 1%)	5 (< 1%)	0	4 (< 1%)
Bilirubin increased	0	2 (< 1%)	0	2 (< 1%)	0	0
Hepatic enzyme increased	0	11 (< 1%)	7 (1%)	3 (< 1%)	1 (< 1%)	8 (2%)
LFT abnormal	0	17 (1%)	6 (1%)	8 (2%)	3 (2%)	6 (1%)
Transaminases increased	0	1 (< 1%)	0	1 (< 1%)	0	0
Peripheral vascular disorders NEC	1 (< 1%)	6 (< 1%)	0	3 (< 1%)	3 (2%)	1 (< 1%)
Flushing	1 (< 1%)	4 (< 1%)	0	2 (< 1%)	2 (1%)	1 (< 1%)
Hot flush	0	2 (< 1%)	0	1 (< 1%)	1 (< 1%)	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFT = liver function test; NEC = not elsewhere classified; QD = once daily.

5.7.2 Drug interactions

Febuxostat does not result in significant drug interactions with other treatments commonly used in conjunction with gout, such as colchicine, indomethacin, naproxen, desipramine or warfarin.[5] This is in contrast to allopurinol, which can prolong the half-life of warfarin.[20,21] In addition, administration of allopurinol with thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.[48]

5.7.3 Febuxostat does not require complex dosage adjustments.

Febuxostat does not require dosage adjustment in patients with mild or moderate renal impairment, whereas allopurinol dosing must be modified for patients with renal impairment. [8,9] No dosage adjustments are necessary based on safety, pharmacokinetics, pharmacodynamic endpoints or mild hepatic impairment.[9,10] No dosage adjustments are required for febuxostat with regard to gender or for elderly patients.[49]

For allopurinol, the risk of allopurinol-related toxicity is increased in gout patients with significant renal impairment given a daily allopurinol dose equal to or exceeding 300 mg. Allopurinol dosing needs to be based on creatinine clearance in patients with renal impairment in order to reduce the incidence of clinically important adverse reactions.[21]

5.8 Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The level of detail provided should be the same as for RCTs and where possible more than one independent source of data should be examined to explore the validity of any conclusions. Inferences about relative treatment effects drawn from observational evidence will necessarily be more circumspect from those from RCTs.

5.8.1 Summary of methodology of relevant non-RCTs

No non-RCTs have been conducted with febuxostat.

5.8.2 Critical appraisal of relevant non-RCTs

Not applicable

5.8.3 Results of the relevant non- RCTs

Not applicable.

5.9 Interpretation of clinical evidence

The therapeutic goal in gout is to treat the underlying metabolic disorder, i.e., hyperuriceamia, to prevent acute attacks of gout and deposition of urate crystal masses (tophi) in connective tissues and parenchymal organs. The long term benefit offered to patients by a more effective treatment to maintain a low sUA throughout the years is prevention of disabling and painful gout arthritis. The decision problem is whether febuxostat-containing regimens should become incorporated into standard practice as an alternative treatment option for men and women suffering from gout, given current treatment approaches based on the use of allopurinol. In particular, as allopurinol is known to have a limited efficacy and is poorly tolerated, and contrindicated, for many patients.

- Two large phase III trials and one phase II study involving 1,433 patients (trials C-02-009, C-02-010 and TMX-00-004) with two extension trials of 1,202 of these patients over up to 4 years (C02-021

and TMX-00-005) have directly demonstrated benefits of effective urate lowering therapy in the prevention of gout flares, reduction and resolution of tophi over a time-period of up to 4 years. These studies confirm the ability of febuxostat to reduce and maintain patients below target levels of sUA over a longer-term.[2,3,4,38,39]

- In a pooled analysis of the trials FACT and APEX, statistically significant reductions of sUA to the BSR target level of 300 µmol/L (5.0 mg/dL) occurred at an early 2 week assessment point and this was maintained to the final visit in 47% of the patients treated with the recommended dose of febuxostat 80 mg compared to 13% with allopurinol 300/100 mg ($P < 0.05$). These data strongly support a significant therapeutic and tolerability advantage over allopurinol.[45]

- Maintaining a low urate level is a chronic therapy for gout were clinical benefits are gained after several years of long-term therapy. The long-term studies with febuxostat indicate that maintaining a low sUA over time decreased the risk for gout flare to virtually zero flares per subject year with febuxostat 80 mg qd after 4 years of therapy. Among 26 subjects with tophi, 77% (20/26) of the tophi resolved during the study.[56]

Therefore, the clinical data supports a clear role for the use of febuxostat in patients who have failed to achieve adequate sUA levels, remain intolerant to alternative treatment options, or who have existing tophi and painful gout arthritis symptoms and flares

The regimens with febuxostat have been compared to allopurinol and are representative of current standard care in the UK.

5.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice

The evidence submitted supports the efficacy of febuxostat within the indication in which it is expected to be used in clinical practice; treatment of hyperuricaemia in patients with gout.

- The treatment of gout has both short-term and long-term treament objectives, given the chronic nature of the disease. To address this, the pivotal clinical trials of febuxostat have included significant extension phases (based on the EXCEL study) to assess longer-term tolerability and

also the ability of febuxostat, and allopurinol, to achieve a maintained clinical response and control of gout symptoms.

- The clinical trial data present primary and secondary outcomes based on the proportion of patients achieving a pre-specified threshold for sUA levels, reductions in sUA, and also the proportion of patients achieving reductions in acute flares and tophi. All these outcomes are directly related to the assessment of patients in clinical practice. In clinical practice the objective of treatment is to maintain patients over the longer term on a tolerable treatment that can reduce sUA levels and avoid, or reduce severity of, gout symptoms.

The trial populations were representative of the population expected to be eligible for the intervention, with the exception that patients in the trial were more obese than the general UK gout population.

- Comorbidities were similar in all treatment groups and were controlled for through randomization. The efficacy results of the pooled phase III studies are robust regardless of the attributes of the study population.
- Pooled subset analyses of the primary endpoint of febuxostat 80mg and 120mg were shown to remain statistically significantly superior to allopurinol 300/100mg after adjusting for demographic and disease characteristics (e.g., baseline sUA and baseline palpable tophi), concomitant diseases and medications, BMI, alcohol use, tobacco use, or overall compliance.

The high dose of febuxostat 120 mg was initiated without titration in the clinical trials. The EULAR and BSR guidelines propose to start with a low dose and increase the dose slowly if needed. This will likely decrease the incidence of gout flares if all patients initiate therapy with febuxostat 80mg, and if needed at sUA ≥ 6 mg/dl after 2 to 4 weeks, increase the dose to 120mg.

In the extension trial EXCEL, the initial urate lowering therapy was only continued if the sUA level was below 6 mg/dL. If the sUA level was 6 mg/dL or above the patient had to switch to a higher dose or an alternative therapy. Thus, the long term treatment effect observed were attributed to the urate lowering effect of therapy.

5.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

Current guidelines in the UK and Europe recommends flare prophylactic treatment with colchicine and, if colchicine is not tolerated, use of an non-steroidal anti-inflammatory drug for *up to 6 months* upon initiation of urate-lowering therapy.[6,14] The febuxostat trials were conducted before the new treatment guidelines were adopted, and these trials prescribed only colchicine or naproxen for the first 8 weeks, which was not sufficient to prevent an increase of flares during the first 6 months. Using flare prophylactic treatment over the first 6 months reduces the initial spike of flares at initiation of urate lowering treatment that was seen in the clinical trials. The increase of initial flares seems to be directly related to the urate-lowering effect. This may bias the results in an unfavourable direction for febuxostat as febuxostat induce a greater reduction of sUA than allopurinol.

The recently issued guidelines from the British Society of Rheumatology use a target sUA level of 300 µmol/L (5 mg/dL) instead of sUA ≤ 360 µmol/L (6 mg/dL) that was used a a primary endpoint in the trials. Febuxostat consistently demonstrated better efficacy in decreasing sUA levels below 300 µmol/L (5 mg/dL) (47% and 65% with febuxostat 80 and 120 mg, respectively) and below 240 µmol/L (4 mg/dL), in comparison with allopurinol 300 mg (13%) in the pooled trials. Even when using this more challenging target sUA level, the clinical efficacy results further enforce the conclusion that febuxostat is superior to allopurinol in lowering sUA.

The dose finding trial TMX-00-004 provides the evidence base for the SPC-specified dose. The two phase III trials FACT and APEX used the SPC-specified dose febuxostat 80 mg qd and 120 mg qd in providing the evidence for this submission.

6 Cost-effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

Electronic and manual literature searches were conducted to identify published and unpublished economic cost-utility studies of febuxostat used as a urate-lowering treatment for gout. The most recent literature search was undertaken on 11 November 2007.

A protocol was prepared for the literature search, detailing inclusion and exclusion criteria and search terms, search dates, and data span searched. Articles were identified in electronic database searches of Medline, Embase, and the Cochrane Library using a predetermined search strategy (Table 6-1 to Table 6-3). Broad search terms ensured that no analyses were inadvertently excluded.

The literature search spanned 1950 to 2007 (inclusive). The complete search strategies included all the search terms—Textwords (free text), Subject Index Headings (e.g., MeSH)—and the relationship between the search terms (e.g., Boolean). The records identified were checked if they matched following inclusion/exclusion criteria.

Inclusion criteria:

- Studies including the clinical effect of febuxostat on gout across at least 12 weeks.
- Economic evaluations of febuxostat on gout.

Exclusion criteria:

- Phase I studies on healthy volunteers.
- Preclinical studies.
- Studies not including effect on gout.

- Studies not including economic evaluations.

The complete search strategies are presented in Table 6-1 to Table 6-3.

Table 6-1. MEDLINE (PubMed) Search Strategy

Search String	Description	Number of records
1	"febuxostat"[Text Word] OR "febuxostat "[Substance Name]	54
2	"Gout"[Mesh] OR "gout"[Text Word]	9500
3	Search "Costs and Cost Analysis"[Mesh] OR cost*[Text Word] OR "cost"[Text Word] OR "costs"[Text Word] OR "costing"[Text Word] OR "Economics"[Mesh] OR "Gout/economics"[Mesh] OR economic*[Text Word] OR "Economics, Pharmaceutical"[Mesh] OR pharmacoeconomic*[Text Word] OR model*[Text Word] OR "modeling"[Text Word] OR "modelling"[Text Word] OR "value"[Text Word] OR "Quality-Adjusted Life Years"[Mesh] OR "qaly"[Text Word] OR "quality adjusted life year"[Text Word] OR "quality adjusted life years"[Text Word]	2,320,965
4	Search #1 AND #2 AND #3	4
		None of the records above met the inclusion/exclusion criteria

Table 6-2. EMBASE Search Strategy

Search String	Description	Number of records
1	febuxostat	82
2	gout	6663
3	cost! or cost or costs or costing or economic? or pharmacoeconomic? or pharmacoeconomics! or model or models or modeling or modelling or value or qaly or quality()adjusted()life()year?	2,110,065
4	S1 AND S2 AND S3	12
		None of the records above met the inclusion/exclusion criteria

Table 6-3. Cochrane Library Search Strategy (including DARE, NHS EED, and HTA)

Search String	Description	Number of records
1	"febuxostat"	7

Search String	Description	Number of records
2	MeSH descriptor Gout explode all trees	98
3	(gout)	234
4	(#2 OR #3)	240
5	(#1 AND #4)	6
	Cochran reviews	0
	Other Reviews	0
	Clinical trials	4 (3 unique records)
	Methods studied	0
	Technology Assessments	2
	Economic Evaluations	0
		None of the records above met the inclusion/exclusion criteria

The electronic literature searches were supplemented with information from internal company data sources to identify any unpublished studies. No published or unpublished economic studies of febuxostat were identified in the search. The published and unpublished clinical trials of febuxostat identified in the search are described in section 5.

6.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

No economic analyses have been reported that estimate the cost-effectiveness of febuxostat.

6.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost-effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Attribute	Reference case	Section in 'Guide to the methods of technology appraisal'	Compliance with reference case
Comparator(s)	The comparator that has been specified in the decision problem	5.3.2	Allopurinol is the recommended urate-lowering therapy in the UK
Perspective costs	NHS and Personal Social Services	5.3.3	Yes
Perspective benefits	All health effects on individuals	5.3.3	Yes
Form of economic evaluation	Cost-effectiveness analysis	5.3.4	Yes and cost-utility analysis
Time horizon	Sufficient to capture differences in costs and outcomes	5.3.5	Yes
Synthesis of evidence	Systematic review	5.4.1	Yes
Outcome measure	Quality-adjusted life years (QALYs)	5.5	Yes
Health states for QALY measurement	Described using a standardised and validated instrument	5.5	Yes, EQ-5D is a standardized and validated instrument
Benefit valuation	Time trade-off or standard gamble	5.5	No
Source of preference data	Sample of public	5.5	Yes, observation study of gout patients in the UK
Discount rate	Health benefits and costs – both 3.5%	5.7.2	Yes
Equity	No additional weighting to QALYs	5.9.7	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	5.9.3	Yes

6.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

The indication examined in the model comprised the planned indication for febuxostat i.e., treatment of hyperuricaemia in patients with gout. Continuous use of febuxostat at the recommended dose of 80 mg once daily, or a higher dose of 120 mg daily, was compared to continuous use of allopurinol 300/100mg mg daily. The model assumed that treatment was given from day 1 and that no attrition of patients assigned to treatment occurred during the modelled treatment time of 2 years.

The model allowed for treatment with flare prophylaxis of 250 mg of naproxen twice daily or 0.6 mg of colchicine once daily during the initial 8 weeks of treatment derived from the clinical trial data. The costs of flare prophylaxis were excluded from the model since they applied equally to all comparators. However, a prophylaxis of 6 months will be recommended in the label.[5]

6.2.2. Patients

6.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The economic model evaluated a patient population based on the IMS observational study conducted in the UK, France, and Germany, which includes patients with gout visiting a primary care physician (Section 4.1). The utilities by serum uric acid (sUA) level were derived from the IMS observational study population, which included mostly men (78%) at an average age of 61.4 years with comorbidities of obesity (16.5%) and renal impairment (13.3%). This population reflects the indication that is defined as treatment of hyperuricaemia in patients with gout.[11,13]

The clinical effect of febuxostat and allopurinol was provided from head-to-head clinical trial data. The clinical trial patient population was defined as men and women with gout and with an sUA level of at least 480 µmol/L (8.0 mg/dL) at baseline. The subjects met the American College of Rheumatology criteria for the diagnosis of gout. The clinical trial population included mostly men

(96%) at an average age of 51.8 years with comorbidities of obesity (62%) and renal impairment (35%) and with a mean sUA level of 585.48 µmol/L (9.84 mg/dL) (41% had sUA greater than 600 µmol/L [10 mg/dL]).[1] The model assumed that the clinical effect of the febuxostat and allopurinol on lowering sUA is the same in the observational study as in the clinical trial population.

6.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

No subgroup analysis was undertaken in this economic evaluation because the patient group represent a fairly homogenous group when defined by age, gender and disease severity (Section 5). A multivariate logistic regression analysis of pooled subset analyses of the primary endpoint showed remained statistically significantly superiority of febuxostat 80mg and 120mg compared to allopurinol 300/100mg after adjusting for demographic and disease characteristics.

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

Subgroup analysis considered in the phase III studies and the long-term extensions include:

- Patients with renal impairment,
- Non-responders to allopurinol 300 mg
- Patients with severe disease (e.g., presence of tophi and/or sUA level at baseline)
- Patients defined by age and gender.

The subgroup analysis showed the response rate of the primary efficacy endpoint increased with age, in female, in caucasians (versus non-caucasian), in improved renal function, in lower baseline sUA and presence of tophus [7] This increase of response rate by subgroup occurred in all treatment groups and does not change statistically significantly superiority of febuxostat 80 mg and 120 mg to allopurinol 300/100 mg. Therefore, no subgroup analyses were conducted as the size of subgroups did not allow for any power to detect any differences of treatments between the subgroups that were clinical relevant relative to differences of treatments provided by the full treatment groups (see section 5.4.7 Table 5-16; Figure 5-8; Table 5-17; Section 5.5.5 Table 5.24).

6.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

All patients entered the analysis at the start of their uric acid-lowering therapy and did not exit the assigned treatment in the model, regardless of the treatment regimen. The model assumed that the patient remained on treatment even if only a partial effect on lowering uric acid level was achieved.

6.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

Allopurinol is considered the standard of urate-lowering therapy in the UK (see Section 4.6.1). The NICE remit and scope document states that comparisons should be made with allopurinol; or (1) with alternative standard care (including sulphinpyrazone, benzbromarone, probenecid, or a combination of these medications) for adults unresponsive or hypersensitivity to allopurinol; or (2) with allopurinol (dose adjusted according to glomerular filtration rate), benzbromarone, or a combination of these medications for adults with renal impairment. Clinical opinion and market research data suggest that allopurinol is the most commonly used regimen in the UK and is received by up to 99% of patients receiving sUA-lowering therapy.[11,12,37] Alternative standard care of sulphinpyrazone, benzbromarone, probenecid, or a combination of these medications is rarely used in clinical practice, because of limitations in efficacy, safety profile and contraindications. No head-to-head trials have been reported that directly compare febuxostat with sulphinpyrazone, benzbromarone, or probenecid as these drugs are rarely prescribed (less than 1%).[11]

Allopurinol was selected as the active comparator in the febuxostat clinical development program. The results of the trials provide data of the efficacy of febuxostat relative to allopurinol. Patient-level data from this trial were available to the analyst, and this trial forms the basis of the economic analysis of febuxostat presented here.

The dose of allopurinol in the trials was selected at 300 mg based on allopurinol SPC and clinical practice. This dose reflects the real life use according to two recent studies in the UK; allopurinol dose of ≤ 300 mg is used in 81% of gout patients in primary practice;[37] 97.9% of the GP patients in the UK are prescribed doses of allopurinol ≤ 300mg.[11]

6.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The study reflected the NICE reference case. The evaluation was considered from the perspective of the National Health Service (NHS) in England and Wales. Direct costs to the NHS, including costs for hospital and primary care were included.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

The economic model was based on pooled data from a 28-week RCT (APEX study) and a 52-week RCT (FACT study).[1,2,3] This data was also supported using data from a 2-year randomised open label extension study (EXCEL) which demonstrated a sustained treatment effect. The time horizon of the cost-effectiveness model was limited to an extrapolation of the clinical results out to 2 years (supported by EXCEL). The results of the model outcomes were available at both 1-year and extended 2-year time points. As a set of secondary economic analysis the model also extrapolated beyond the clinical trial data to 3, 4 and 5 year endpoints. This is informative, as gout is a long-term chronic condition, but carries appropriate caveats as this is beyond the clinical trial experience with febuxostat.

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

6.2.6.1 Please provide the following.

- **A description of the model type.**
- **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**
- **A list of all variables that includes their value, range (distribution) and source.**
- **A separate list of all assumptions and a justification for each assumption.**

Model type

A decision tree model in Microsoft Excel was developed to estimate costs and outcomes for patients with gout after initiation of urate-lowering therapy with febuxostat 80 mg or 120 mg, or allopurinol 300 mg daily. The model was designed to run over a time horizon of up to 2 years and was populated and analysed from a UK NHS payer perspective. Extrapolation was also provided for 3, 4 and 5 years based on an assumption of continued treatment effect whilst under treatment.

A mixed cohort of both men and women with gout and with a baseline sUA level of 480 µmol/L (8 mg/dL), or higher, entered the model after initiation of urate-lowering therapy. Effective urate-lowering therapy has a well documented initial effect of exacerbating and increasing the frequency of gout flares during the first months, probably due to a rapid fall of serum uric acid, which cause urate crystals to shed from crystal aggregates.[4] The 'flare-triggering' effect appears to be related to the clinical effect of lowering uric acid levels, i.e., the lower the uric acid levels that are achieved, the higher the rate of initial flares.[1] Prophylactic treatment with colchicine prevents the initial increase of flares, and over the long term, the urate-lowering therapy prevents flares and promotes crystal dissolution.[4] The clinical trial protocol required flare prophylactic treatment with naproxen or colchicine during the first 8 weeks. However, more recent BSR recommendations propose up to 6-months flare prophylactic treatment with colchicine or up to 6 weeks with NSAIDs.[14] The febuxostat SPC recommends 6 months flare prophylactic treatment with colchicine or NSAIDs.[5] The model included an algorithm to calculate the reduction of initial flare rate with prolonged flare prophylactic treatment. The effect of flare prophylactic treatment is based on a 6-months controlled study of colchicine versus placebo when initiating urate-lowering treatment in gout.[4,50]

The model was split into two time periods because of the initial flare-triggering period:

1. An initial period of 3 months, during which patients may, or may not, suffer from a treatment-initiated flare.
2. A treatment maintenance period from months 4 to 24, during which patients were grouped into four subgroups according the clinical effect achieved i.e., sUA level:
   - ≤ 360 µmol/L (6 mg/dL)
   - > 360 µmol/L (6 mg/dL) and ≤ 480 µmol/L (8 mg/dL)

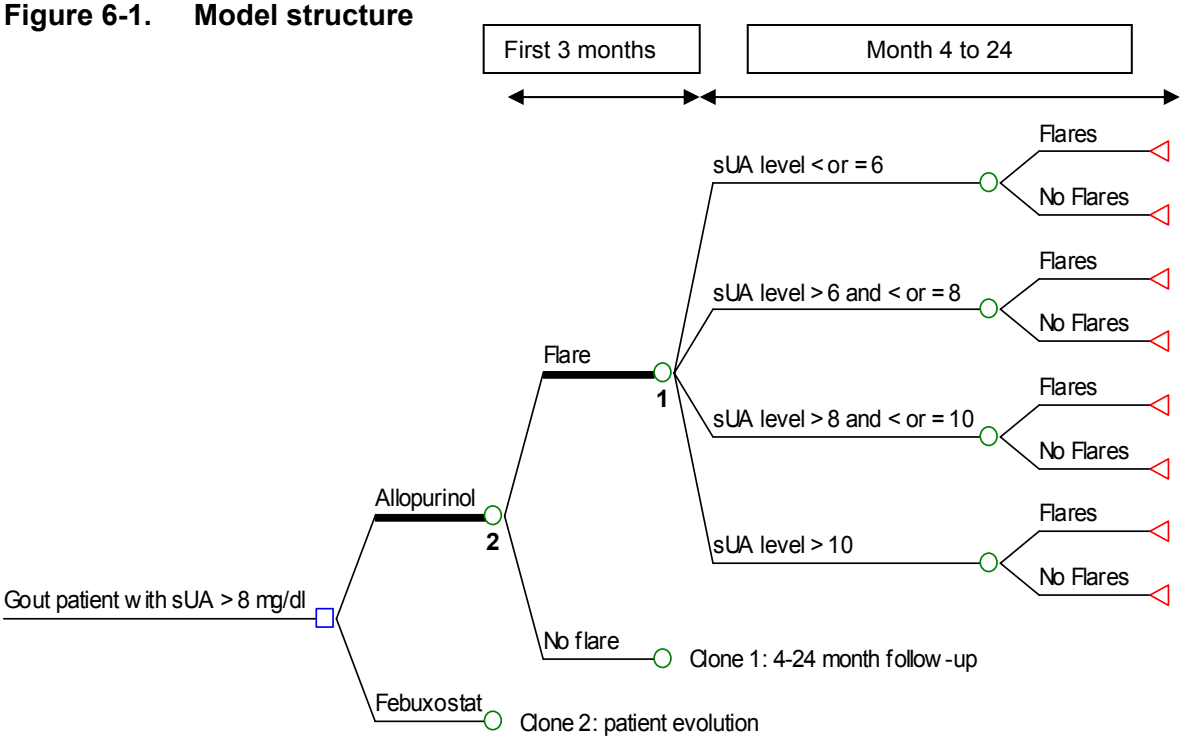
- > 480 µmol/L (8 mg/dL) and ≤ 600 µmol/L (10 mg/dL)
- > 600 µmol/L (10 mg/dL)

The premise of the model is that in achieving an improved level of sUA patients are entering into a disease severity state that can be strongly correlated with health-related quality of life (Table 6-7), which in turn can be directly assessed using a standard and UK validated method of quality-adjusted life-years accounting for long-term effect of maintaining the patient at a low uric acid level to prevent flares, prevent and resolve tophi.

The model is therefore designed to generate an economic evaluation based on a cost utility analyses (CUA), driven by treatment and flare related costs and the overall cost and quality of life associated with disease severity states (measured using sUA) (Table 6-7). Decrements to quality of life were also applied to acccount for the short-durations of acute gout flares.

The structure of the model is presented in Figure 6-1, and key model parameters are summarised in following subsections. A full description and justification for the selection of model parameters is provided in the IMS report.[12]

Figure 6-1. Model structure



The economic model was based on a multi-country model framework that was populated with UK sterling costs for drugs, flares, maintenance and indirect costs (although indirect costs were not used in the analyses).

Results were reported as cost (in £ per quality-adjusted life-years gained (QALYG) at 3 months, 12 months, and 24 months. Country-specific discount rates (UK = 3.5%) were applied on future costs and effects. Extrapolation of clinical data was also possible in the model out to a 5-year time horizon.

Euro conversions were applied to the model to return to GBP values. Euro values were used as the model was based in a wider suite of European-based versions of the model. This submission have used the conversion rate from October 2007 of 1 £ = 1.436€ unless else is stated.

The pooled clinical trial results (n = 724) from a 28-week RCT (APEX study) and a 52-week RCT (FACT study) were applied in the model (Schumacher et al 2005c).[1,2,3, 49] When available, distributions were entered into the model to allow for a probabilistic analysis. The primary endpoint of the clinical trial was to achieve an sUA of less than 360 µmol/L (6 mg/dL) at the last three monthly measurements. A significantly higher proportion of patients treated with febuxostat reached the primary endpoint than patients treated with allopurinol (Section 5.4.1, Figure 5-4, Table 5-12, Figure 5-5, Table 5-13; Section 5.5.2, Table 5-21).

Clinical parameters

Day 1 to 3 months – flare rate

The model accounted for flare rate during the first 3 months. These were derived from the pooled clinical trial data[2,3] and applied in the model (Table 6-4).

Table 6-4. Descriptive statistics of the distribution of the estimated number of flares during the first 3 months after treatment initiation, per drug

	Allopurinol 300 mg	Febuxostat 80 mg	Febuxostat 120 mg
Mean (95% CI)	0.917 (0.782-1.051)	1.121(0.964-1.279)	1.546 (1.365-1.727)
Minimum	0.000	0.000	0.000
Maximum	13.000	14.000	15.000
Mean with 6-month prophylactic treatment[a]	0.2016	0.2467	0.3402

CI = confidence interval.

[a] Six-month flare prophylactic treatment reduces flare rate with 78 % based on colchicine flare rate of 0.52 and placebo flare rate of 2.91.[4]

Week 2 to 24 months—proportion of patients in each sUA category

From week 2 after treatment initiation and up to 12 months, the proportion of patients per sUA level per treatment was derived from the results of the pooled clinical trial data.[2,3] For each patient, the average sUA test value during the period covering week 2 until month 12 was calculated. Patients were classified into one of four sUA categories based on this average value (Table 6-5). These values were maintained in the model during the second year.

Table 6-5. Proportion of patients in each sUA category, by drug (allopurinol vs. febuxostat)—week 2 to month 12

	Allopurinol		Febuxostat 80 mg		Febuxostat 120 mg	
sUA level	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
≤ 6 mg/dL	0.4159	0.0235	0.7340	0.0219	0.8498	0.0177
> 6 and ≤ 8 mg/dL	0.4614	0.0238	0.1970	0.0197	0.1010	0.0150
> 8 and ≤ 10 mg/dL	0.1023	0.0144	0.0567	0.0115	0.0443	0.0102
> 10 mg/dL	0.0205	0.0067	0.0123	0.0055	0.0049	0.0035

sUA = serum uric acid.

Month 4 to 24 months—monthly number of flares per sUA level for the overall population

The model applied the average monthly number of flares per sUA level derived from the IMS study for the overall population (includes patients with and without flares). This monthly number of flares was estimated by multiplying the probability for experiencing flare(s) by the monthly number of flares in patients who experienced flares. In Table 6-6, the mean number of flares per month for each sUA level is shown. These mean values are applied in the model, together with their standard error (SE) for the probabilistic sensitivity analysis.

According to the multivariate analysis, there was no significant difference between sUA levels for the yearly number of flares within the group of patients who experienced at least one flare during their observation period (6 to 24 months). Therefore, the average monthly number of flares for the whole population was used (IMS data only). The average number of flares per month was 0.1354 (SE = 0.0073).

Table 6-6. Probability of experiencing flare(s) per sUA level, and calculated monthly number of flares, as at month 4 after treatment installment

		Estimated monthly number of flares in the overall population[a]	
sUA level	**Prob. flare(s)**	**Mean**	**SE**
≤ 360 µmol/L (6 mg/dL)	0.6456	0.0874	0.00473
> 360 µmol/L (6 mg/dL) and ≤ 480 µmol/L (8 mg/dL)	0.7304	0.0989	0.00535
> 480 µmol/L (8 mg/dL) and ≤ 600 µmol/L (10 mg/dL)	0.8011	0.1085	0.00587
> 600 µmol/L (10 mg/dL)	0.8569	0.1161	0.00628

sUA = serum uric acid.

[a] Includes patients who did not experience flare(s) during the observation period.

Utilities

The utility data applied in the model were derived from the EQ-5D quality-of-life assessment from the IMS study in patients with gout.

The model assigned a utility penalty associated with experiencing one flare and a baseline utility per sUA level:

Table 6-7. Baseline utility per sUA level

sUA level	Mean utility	SE
sUA ≤ 6 mg/dL		
sUA > 6 mg/dL and ≤ 8 mg/dL		
sUA > 8 mg/dL and ≤ 10 mg/dL		
sUA > 10 mg/dL		

sUA = serum uric acid.

Direct costs

Cost of one flare

The cost of one flare in the UK applied in the model was (SE = The cost was derived from the limited IMS study population in the UK and includes the costs of hospitalisation, diagnostics, and outpatient visits for a flare.

Maintenance cost of gout treatment

The maintenance cost of gout treatment in the model was per month (SE = regardless of uric acid level, and was derived from the limited IMS study population in the UK. The maintenance costs included costs for outpatient visits, diagnostic laboratory tests (e.g., sUA and serum creatinine), procedures (e.g., x-rays and joint aspiration), and hospitalisation due to complications of gout (e.g., renal stones and urinary tract infection).

Drug costs

The drug costs in the model were expressed in UK £ per day according the daily doses used in the clinical trial. Ipsen provided the anticipated daily price for febuxostat. The 2007 British National Formulary [51] provided unit costs for allopurinol. The drug cost data applied in the model are represented in Table 6-8.

Table 6-8. Mean daily drug costs in UK

Allopurinol 300 mg/day[a]	Febuxostat 80 mg/day	Febuxostat 120 mg/day
£0.065	£0.870	£0.870

[a] Source UK: British National Formulary.[51]

Assumptions for the model

The economic model was based on the following set of assumptions:

- Patients entered the model with a sUA level of 480 µmol/L (8 mg/dL) or higher. This assumption was based on the clinical trial inclusion criteria.

- The primary time horizon of the model was set to 2 years, but was extrapolated out to a 5-year horizon in secondary analyses. This assumption was based on limited access to long-term data of comparative data of febuxostat and allopurinol therapy.
- Patients with gout have an increased risk of flares during the first 6 months after treatment initiation with urate-lowering therapy. The rate of flares was based on clinical trial data. The febuxostat SPC and recent BRS guidelines require flare prophylactic treatment up to 6 months. The base case analysis assumed a 6-month flare prophylactic treatment with colchicine which reduces the flare rate with 78%.[4,50] The reduction of 78% is based on the mean relative flare of 0.22 with colchicine versus placebo 0.52/2.91 = 0.18[4] and 0.13/ 0.49 = 0.26[50] (in < 386.8 µmol/L [6.5 mg/dL]).
- The impact of adverse events on costs and utility was included only for the increase of flares triggered by urate-lowering therapy during the initial 3 months of treatment. This is important to capture as it is inversely related to the efficacy of the treatment. The impact of other adverse events was assumed to be similar between the groups and to be negligible.
- The model assumed that the level of sUA achieved after 3 months of treatment is persistent over time as long as patients remain on therapy. Long-term data of up to 2 years of treatment from the FACT and the Excel study support this assumption (Figure 5-10 and 5-11 in section 5.5). Therefore, when a patient was assigned to a subgroup by sUA level, the patient remained in that subgroup throughout the time horizon of the model.

- After 3 months, the incidence of flares is dependent on the sUA level.

- The maintenance costs of gout were assumed to be the same regardless of disease severity and uric acid level. This assumption is based on the IMS study which showed a high variability and no correlation between UK non-flare costs and sUA level.[12]
- Discounting was applied on costs and effects in the second year after treatment initiation, applied at standard reference case rates.
- Mortality was not accounted for since the time horizon is only 2 years and there is no increased mortality related with gout. The mortality was assumed to be the same in both treatment groups.
- The drug costs were assigned according to intention to treat and assumed that all patients took their assigned drug daily without any attrition over 2 years. This may overestimate drug costs in the real-world setting. The randomised subset of the open-label EXCEL trial resulted in 76% of the patients on febuxostat 80 mg (n = 299), 71% on febuxostat 120 mg (n = 291) and 40% on allopurinol 300/100 mg (n = 145) remained on initial treatment after more than 24 months.[15]
- All sUA groups had an associated risk of experiencing flare(s). This risk increased with the sUA level. This was based on results from the IMS observational study[12].
- Adverse events during the treatment period were assumed to be similar between the groups and were not accounted for in the model. This was based on results from the phase II and phase III clinical trials (see Section 5).
- The model assumed that the clinical effect of febuxostat and allopurinol on lowering sUA is the same in the observational study population as in the clinical trial population. This is based on consistent results of sUA levels from different trial populations in the phase II and the two phase III clinical trials (see Section 5).
- The model assumed that the patient remained on treatment even if only a partial effect on lowering urate level was achieved.

6.2.6.2 Why was this particular type of model used?

A decision model framework was selected as a simple method of estimating the beneficial effect of urate-lowering therapy on utility over time to prevent

progression of gout. The decision tree also estimated costs during the treatment period and the impact of flare rates over time.

6.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

Justification of structure

The clinical trial data provided results of the effect of febuxostat on lowering sUA, but did not collect any data on EQ-5D or any other QoL data that could be used to estimate utilities. Therefore, a large cross-sectional study was conducted by IMS [12] on patients with gout in three different countries to collect data on QoL and number of flares, in order to provide utility values and flare rate by level of sUA. A simple decision tree model structure was constructed to account for the increased number of flares during the first 3 months that is triggered by urate-lowering therapy, before the patient adjusts to the stabilised lower sUA levels. Clinical trial data has shown that once a patient has reached his individual level of sUA, the level is consistent over time as long as the urate-lowering therapy is continued.

The second part of the model accounts for the differences in utility and flare rate that is differentiated by sUA level. This approach allowed us to focus on the key features of the model, that is, the extrapolation of maintaining low sUA levels beyond the period of trial follow-up. Combining the clinical trial data from North America with cross-sectional data based on the gout population in Europe provides results that have high internal validity and are generalizable to the UK population.

Representation of the course of the disease/condition

Clinical trial data were provided for a 1-year time period and and a further 2-year extended periodt which the model estimates the results of maintained sUA levels for an additional year. This should be considered as a relatively short time period for estimating the costs of a preventive therapy in a chronic disease, but fits closely with the clinical data. In addition, the model was not able to fully account for the reduction in tophi and prevention of progression and complications of gout over time, which will be an important analysis to do in the future.

Other model structures that were considered

A Markov model with progression of disease states from infrequent gout flares to development of tophi and disabling gout arthritis was considered. However, a structured literature search did not identify any data to provide estimates of probabilities of progression of gout disease by sUA levels over the long term that could be used in such a model.

6.2.6.4 What were the sources of information used to develop and inform the structure of the model?

Gout flare

The number of flares during the first 3 months after treatment initiation was derived from the two phase III clinical trials.[1,2,3, 49] The patient data referring to the first 3 months after treatment initiation were analyzed per drug. The results of this analysis are represented in Table 6-10.

Table 6-10. Descriptive statistics of the distribution of the estimated number of flares during the first 3 months after treatment installment, per drug

	Allopurinol	Febuxostat 80 mg	Febuxostat 120 mg
Mean			
95% CI for mean			
Median			
Std. deviation			
Std. error			
Minimum			
Maximum			

The odds of a flare by sUA level at 4 months and forward were calculated by logistic regression of the data provided in the limited IMS population (n = 213). The odds were defined as probability of experiencing flare(s) divided by probability of not experiencing flare(s). The sUA level, considered as an ordinal variable, with exclusion of patients for which the sUA level was unknown (“unclassified”), was categorized into following four subgroups in the analysis:

1. Patients with sUA ≤ 360 µmol/L (6 mg/dL)
2. Patients with sUA > 360 µmol/L (6 mg/dL) and ≤ 480 µmol/L (8 mg/dL)

3. Patients with sUA > 480 µmol/L (8 mg/dL) and ≤ 600 µmol/L (10 mg/dL)
4. Patients with sUA > 600 µmol/L (10 mg/dL)

The details of the significant association between the odds of experiencing flares and sUA level are represented in Table 6-11. Per increase in sUA-category (from 1 to 4), the increase in odds ratio (OR) for experiencing flares in the IMS data were estimated to be 1.487 (95% CI: 1.048, 2.111).

Table 6-11. Description of the significant association between odds of experiencing a flare and sUA level as an ordinal variable (logistic regression), IMS data only

		Parameter Estimates	
Parameter		**sUA level per each 1 level of increase**	**Constant**
Odds ratio			
Std. error			
P-value			
95% CI	Lower		
	Upper		

Full details of this analysis are provided in the IMS report.[12]

Utility

Utility weights were derived from an observational study in three European countires conducted by IMS between May 2005 and May 2007.[12] The study obtained QoL data from EQ-5D questionnaires completed by patients with gout who were visiting a physician (n = 417). The EQ-5D is a standardised instrument to measure health outcome in a wide range of health conditions and treatments. The EQ-5D provides a simple descriptive profile and a single index value for health status. The descriptive system consists of five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problem, some problem, or extreme problem. Subjects are asked to check the level most descriptive of their current level of function or experience for each dimension. The five dimensions, each with three levels, yield 243 possible distinct health states, which can be assigned UK standardised scores. The scores are derived from a “tariff” system of weights from a community sample of persons who valued health states using the time trade-off method in the UK.

6.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

Yes, the model reflects the costs and utilities associated with gout flare and utilities with maintaining a low uric acid level over time to prevent progression of disease.

6.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The time frame of the model was 2 years, divided up into two parts: one initial treatment period of 3 months and a continuous treatment period from 4 months to 24 months. This was selected by the model designer as a reasonable time period because of the limited comparative long-term clinical trial data on sUA levels for both allopurinol and febuxostat. Ideally, a longer time frame of at least 5 years should be evaluated, and the long-term flare rate from extension of the clinical trials should been used. The flare rate appears to diminish over time (with lowering sUA levels). The sUA-lowering effect on preventing the gout complications of tophi and gout arthritis were not accounted for in the 2-year model. The observed stability in sUA levels beyond 3 months of treatment justified the use of a decision tree based approach and therefore the model did not require a discrete time based structure beyond the 3-month time point.

6.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction is not applicable in a decision tree model.

6.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

The costs and clinical outcomes were extrapolated for only 1 year as a reasonable time period for a model, based on the limited, comparative long-term data on sUA levels for both allopurinol and febuxostat treatment from clinical trials. Further extrapolations were conducted of a 5-year horizon, as a set of secondary analyses.

b) Non-model-based economic evaluations

6.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

Not applicable.

6.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Not applicable.

6.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not applicable.

6.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not applicable.

6.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Not applicable.

6.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

6.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The baseline risk of disease progression is not applicable when using a decision tree model.

6.2.7.2 How were the relative risks of disease progression estimated?

The relative risk of disease progression is not applicable when using a decision tree model.

6.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Yes, immediate outcome measures of sUA levels derived from the clinical trial were linked to final outcomes of utility by sUA level to calculate QALY, as described in Section 6.2.6.1.

6.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost-effectiveness of this technology?

Health effects on flare rate and maintaining QALY by lowering the sUA level was accounted for in the model. Adverse effects by treatment were assumed to be the same and were not accounted for in the model. The flare rate, after an initial increase at urate-lowering treatment initiation, appears to diminish over time, when sUA levels are maintained at less than 360 µmol/L (6 mg/dL) in long-term extension trials of febuxostat (see Section 5.2); however, the sUA-lowering effect on preventing the gout complications of tophi and gout arthritis was not accounted for in the 2-year model. A model over a longer time frame accounting for prevention of gout complications over the long term may show a decrease in the incremental cost per QALY of febuxostat compared with allopurinol.

6.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

No expert opinion was used to estimate clinical parameters. The medical department at IPSEN and an advisory board reviewed the structure and design of the decision model.

6.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

A list of assumptions and justifications for the model is presented in Section 6.2.6.1. The model did not account for the higher attrition rates for allopurinol patients. In a recent report published after the model was developed, a greater percentage of patients changed from allopurinol to febuxostat (57%) than from febuxostat to allopurinol (18% [80 mg], 8% [120 mg]) due to lack of efficacy—defined as sUA levels > 360 µmol/L (6 mg/dL) at 6 months.[15] Using only allopurinol for treatment of gout resulted in a larger percentage of

untreated patients and consequently higher sUA levels and higher rates of gout complications in the long term. The current decision model therefore represents a conservative analysis of the impact of febuxostat on preventing gout complications.

6.2.8 Measurement and valuation of health effects

6.2.8.1 Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

During the first 3 months of treatment flare rates were recorded in the case report form by the investigators in the clinical trial. This captured any increased flare rate associated with the initial flare-triggering effect of urate-lowering treatment, but no formal assessment was made of a relationship to an initial flare-triggering treatment effect.

The effects of febuxostat compared with allopurinol on sUA at 4 to 12 months of therapy and adverse events were assessed in the clinical trial and reported in the case report form by the investigator.

The sUA and flare rate in the IMS observational study were assessed by retrospective chart review covering 6 months up to 36 months of patient follow-up for gout and were reported in a case report form by the treating physician. In addition to the retrospective chart review, each of the included patients completed questionnaires with ED-5D questions to assess quality of life (see Sections 6.2.6.1 and 6.2.6.4).

6.2.8.2 Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

The impact on QoL of the adverse events associated with the initial flare-triggering effect of urate-lowering treatment during the first 3 months was estimated in the decision tree by combining estimates of the utility decrement for the event, the duration of the event, the probability of occurrence, and the mean number of episodes experienced per patient who suffered the event. The utility decrement (expressed in QALYs) was subtracted from the baseline utility at the end of the initial treatment period (3 months). Other adverse events were not accounted for as they were assumed to be similar in both groups.

The health effects of sUA-lowering therapy with febuxostat compared with allopurinol included a lower rate of flare in the long term and maintaining the patient at a lower sUA level, the goal of which is to prevent gout complications such as tophi and gout arthritis. The health effects at a low sUA level were measured as QoL with the EQ-5D. The EQ-5D results were used to calculate QALYs gained as described in Section 6.2.6.4.

6.2.8.3 Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?

Yes, the health effects measured with EQ-5D and converted to QALY linked to sUA levels is consistent with NICE's reference case.

6.2.8.4 Were any health effects excluded from the analysis? If so, why were they excluded?

The model lacks long term data on health consequences and was not able to fully account for the reduction in tophi and prevention of progression and complications of gout over time; therefore, it underestimated the beneficial effect of febuxostat in prevention of gout-associated disability.

6.2.8.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Not applicable.

6.2.9 Resource identification, measurement and valuation

6.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

Details of the resources included, how they were measured, and the sources are presented in Table 6-12 to Table 6-17.

Hospitalisations

Hospitalisations due to gout flare or complication related to gout during the observation period was reported and costed with the official Diagnosis Related Groups (DRG) costs for the corresponding indication (Table 6-12).

Table 6-12. Reasons for hospitalisations and corresponding unit cost

Reason for hospitalisation	Count (N = 422)	Percentage of total	Unit cost UK
Gout flare	50		
Urinary tract related	6		
Urinary tract infection	2		
Renal stones	3		
Hydronephrosis	1		
Musculoskeletal	1		
Olecranon bursitis	1		

Source: IMS (2007).[12]

Costs

Cost of one flare

The cost of one flare in the UK applied in the model was .The cost was derived from the limited IMS study population in the UK and includes the costs of hospitalisation and out-patient visits for a flare.[12]

Maintenance cost of gout treatment

The maintenance cost of gout treatment in the model was per month (SE), regardless of uric acid level, and was derived from the limited IMS study population in the UK. The maintenance cost included costs for outpatient visits, diagnostic laboratory tests (e.g., sUA and serum creatinine), procedures (e.g., x-rays and joint aspiration), and hospitalisation due to complications of gout (e.g., renal stones and urinary tract infection).Table 6-13 through Table 6-16 show the details for the diagnostic tests, outpatient visits, and interventions performed in the UK and the corresponding unit cost adapted from the National Health Service.[52]

Table 6-13. Laboratory tests during observation period: UK (6 months)

Laboratory test	Unit cost (£)
Serum uric acid (sUA)	4.4
Serum creatinine	4.4
Haematology	4.4
Chemistry	4.4
Renal function	4.4
Liver function	4.4
Cholesterol	4.4
Triglycerides	4.4
Creatinine clearance	4.4

Source: IMS (2007).[12]

Table 6-14. Diagnostic tests during observation period: UK (6 months)

Diagnostic test	Unit cost (£)
X-ray hand	28.73
X-ray foot	28.73
X-ray knee	28.73
ECG	28.35
Joint aspiration (foot, knee, wrist, ankle, finger)	Included in costs for outpatient visit

Table 6-15. Outpatient visits during observation period: UK (6 months)

Type of practitioner	Unit cost (£)
Rheumatologist	182.1
General practitioner	29.8
General practitioner home visit	88.0
Cardiologist	144.8
Nephrologist	183.6
Lung specialist	189.5
Gastroenterologist	173.1
Endocrinologist	168.6
Urologist	128.3
Neurologist	238.8
Orthopaedic surgeon	122.4
Surgeon	132.8
Dietician	52.2
Physiotherapist	47.8

Source: IMS (2007).[12]

Physicians were asked to report on interventions during the observation period. The most commonly reported intervention was a local steroid injection (Table 6-16).

Table 6-16. Most important interventions for the overall population (6 months)

Intervention	UK unit costs
Excision of olecranon bursa	£454
Dialysis	£176
Local steroid injection	£61
Lithotripsy of renal stones	£1,135

Source: IMS (2007).[12]

Drug costs

The drug costs in the model are expressed in UK £ per day according the daily doses used in the clinical trial. Ipsen provided the anticipated daily price for febuxostat. The 2007 British National Formulary[51] provided unit costs for allopurinol. The drug cost data applied in the model are represented in Table 6-17.

Table 6-17. Mean daily drug costs in the UK

Allopurinol 300 mg/day[a]	Febuxostat 80 mg/day	Febuxostat 120 mg/day
£0.065	£0.870	£0.870

[a] Source UK: British National Formulary (2007).[51]

6.2.9.2 How were the resources measured?

Medical resource use costs were collected retrospectively through a chart review for each patient during an observation period of at least 6 months and up to 3 years.

Resource use included in the evaluation was collected through the IMS observational study.[12] Physicians were asked to collect data on patient characteristics and resource use by a retrospective chart review. In addition to IMS, another recruitment company, Medimix, was involved in recruiting patients in the UK and France to improve the recruitment rate. Medimix was asked to recruit mostly patients currently having tophi, patients with a sUA level > 600 µmol/L (10 mg/dL), and allopurinol- intolerant patients to achieve an adequate number of patients (n ≥ 60), to conduct prespecified subgroup analyses. The subgroups were select on bases that these patients are most challenging to treat in the clinic. Pooled data from both recruitment groups were used for providing estimates of resource use and costs. Patient charts for 422 patients were reviewed by 71 physicians. Altogether, 153 of the patients were British, 150 were German, and 119 were French. Table 6-18 provides characteristics of the patients and the two recruitment groups.

Table 6-18. Patient characteristics

	Total		IMS		Medimix	
Characteristic	N	% of total	N	% of total	N	% of total
Recruiting physicians	71	100	38	53.5	33	46.5
Included patients	422	100	230	54.5	192	45.5
Per country						
UK	153	36.3	51	22.2	102	53.1

Characteristic	Total		IMS		Medimix	
	N	% of total	N	% of total	N	% of total
Germany	150	35.5	150	65.2	0	0
France	119	28.2	29	12.6	90	46.9
Sex = male	332	78.7	173	75.2	159	82.8
Age (years)	61.6	12.7	61.2	12.6	61.9	12.8
Time since gout diagnosis (years)	3.7	7.8	3.3	9.0	4.2	6.2
Length of observation period (days)	739.2	431.4	752.2	411.6	723.6	454.5

Source: IMS (2007).[12]

Patients were classified into the following subgroups (Table 6-19):

- By sUA level at the end of or during the observation period.
- Presence of tophi at the time of inclusion.
- Allopurinol intolerant at the time of inclusion.
- Renal impairment, defined as serum creatinine level > 1.5 times the upper limit of normal at the time of inclusion.

Table 6-19. Patient classification: subgroups

Patient subgroup	Overall	
	Number (N = 422)	Percentage of total
sUA level		
< 6 mg/dL		
6-8 mg/dL		
8-10 mg/dL		
> 10 mg/dL		
Undefined		
Presence of tophi		
Allopurinol intolerant		
Renal impairment		

Source: IMS (2007).[12]

Hypertension, obesity, and/or hypercholesterolemia were the most common comorbidities among this patient population. Table 6-20 gives an overview of the distribution of comorbidities in the population. A single patient could have more than one comorbidity.

Table 6-20. Comorbidities

Comorbidity	Overall	
	Number (N = 422)	Percentage of total
Hypertension		
Obesity		
Hypercholesterolemia		
Low back pain		
Polyarthritis		
Type II diabetes		
Monoarthritis		
Osteoarthrosis		
Angina pectoris		
Myocardial infarction		
Heart failure		
Kidney stones		
Metabolic syndrome		
Chronic renal insufficiency		

Source: IMS (2007).[12]

The high rate of comorbidities in the IMS gout population agrees overall with comorbidity and demographic data found in the other independent UK data base studies.[11,13]

6.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Yes, the same sources were used.

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

The resource use data were collected and costed for 2006.

6.2.9.5 What source(s) of information were used to value the resources?

National Health Service Diagnosis Related Group costs for hospitalisation, laboratory, and diagnostic procedures.

British National Formulary for drug cost of allopurinol and Ipsen's anticipated price per unit for febuxostat.

6.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?

The anticipated unit cost for febuxostat is £0.870 (€1.25) /day.

6.2.9.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes, the resources were measured and valued in a manner consistent with the reference case.

6.2.9.8 Were resource values indexed to the current price year?

No, the prices for 2006 are provided.

6.2.9.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

Not applicable.

6.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes, the costs and health benefits are discounted by 3.5%.

6.2.11 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.11.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

A sensitivity analysis was conducted to explore the effect of

- Extrapolating the results of the model to 3, 4, and 5 years.
- Reduction of 3-month flares due to prophylaxis: 0%
- Reduction of 3-month flares due to prophylaxis: 100%
- Discounting cost and effects: both 0%
- Discounting cost and effects: both 6%
-

-
- Utility decrease with each sUA point (0.02)
- Utility decrease with each sUA point (0.05)
- Proportion of patients < 360 umol/L in months 4-24 for febuxostat (0.7)

6.2.11.2 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Yes, a Monte Carlo analysis was performed by running the model 1000 times.

Table 6-21 contains the list of model parameters that have associated sampling uncertainty and hence are included in the model's probabilistic sensitivity analysis (PSA). For each type of parameter, the type of distribution, mean, and SE are reported.

Table 6-21. Parameters applied in the probabilistic sensitivity analysis - distribution, mean and SE

Parameter	Distribution	Mean	SE
Clinical data			
First 3 months after treatment initiation			
Incidence of flares (N flare/ 3 month)			
From month 4 after treatment initiation			
Proportion of patients in sUA level ≤ 6 mg/dL			
Monthly number of flares, by sUA level			
Utility data			
Flare penalty: utility decrease per experienced flare			
sUA ≤ 6 mg/dL			
Decrease in utility per sUA level:			
Cost data (UK)			
Allopurinol (£)	Gamma	0.065	0.0098
Febuxostat (£)			
Cost of 1 flare (£):			

Source: IMS (2007).[12]

6.2.11.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

Uncertainty associated with structural uncertainty has been investigated through the sensitivity analysis described in the section above.

6.2.12 Statistical analysis

6.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

Corrected values for cost of resource use and flare rates derived from the IMS observational study were calculated with bivariate and multivariate regression analysis. See the IMS report for details.[12]

6.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The flare rate currently used in the model is based on clinical trial data during the first year of use. The flare rate may need a longer time than 4 months to 12 months to reach a steady state that can be projected into the second and subsequent years. The incidence of gout flares in the last 4 weeks (weeks 49 through 53) of therapy in the FACT study was numerically lower in the febuxostat groups: 8% for febuxostat 80 mg, 6% for febuxostat 120 mg, and 11% for allopurinol.[1] This was not accounted for in the model in order to keep the model simple.

6.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

All data entries and formulas were checked by a modeler at IMS not involved in the model building.

6.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY

- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves
- scatterplots on cost-effectiveness quadrants.

6.3.1 Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

The UK discount rates for both costs and health outcomes are set to 3.5%. The reduction of 3-month flares due to prohylaxis is set to 78%.Table 6-22 presents the results of the cost-effectiveness analysis by time period from a health care payer's perspective. The 2-year ICER for febuxostat is £15,565 per quality-adjusted life-year gained (QALYG). This is below the threshold applied by NICE of £20,000.

Table 6-22. Cost and effectiveness results: UK setting, health care payer's perspective

Treatment	Total cost	Incremental cost	QALY	QALYG	ICER £/QALYG
12 months horizon					
Allopurinol	£1,314		0.709		
Febuxostat (80 mg + 120 mg pooled)	£1,592	£278	0.726	0.017	£16,574
24 months horizon					
Allopurinol	£2,605		1.395		
Febuxostat (80 mg + 120 mg pooled)	£3,146	£540	1.430	0.035	£15,565

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; QALYG = quality-adjusted life-year gained.

Results of the probabilistic sensitivity analysis

A Monte Carlo analysis was performed by running the model 1000 times. In Table 6-23, the mean costs and effects and the 95% confidence intervals (CI) are shown for febuxostat versus allopurinol at 24 months.

Table 6-23. Cost and QALY based on Monte Carlo analysis at 24 months in the UK

		95% CI			95% CI	
Treatment	**Cost**	**Lower**	**Upper**	**QALY**	**Lower**	**Upper**
Allopurinol	£2,606	£2,102	£3,223	1.399	1.291	1.510
Febuxostat	£3,145	£2,612	£3,770	1.432	1.346	1.510
Incremental	£539	£347	£776	0.033	-0.017	0.083
ICER	£16,324	£6,281	£239,928	-	-	-

QALY = quality-adjusted life-year.

In 63% of the runs, the cost-effectiveness of febuxostat was below the threshold value of £20,000. This is shown in the scatterplot (Figure 6-2) and cost-effectiveness acceptability curve (Figure 6-3) that can be drawn based on the Monte Carlo analysis.

Figure 6-2. Scatterplot: UK setting (Euro)

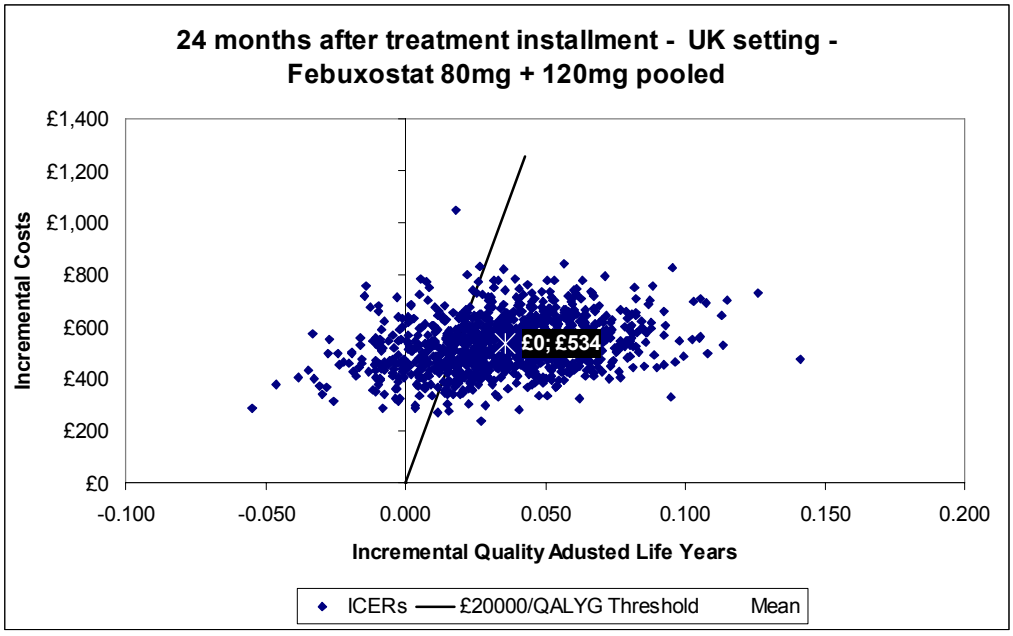
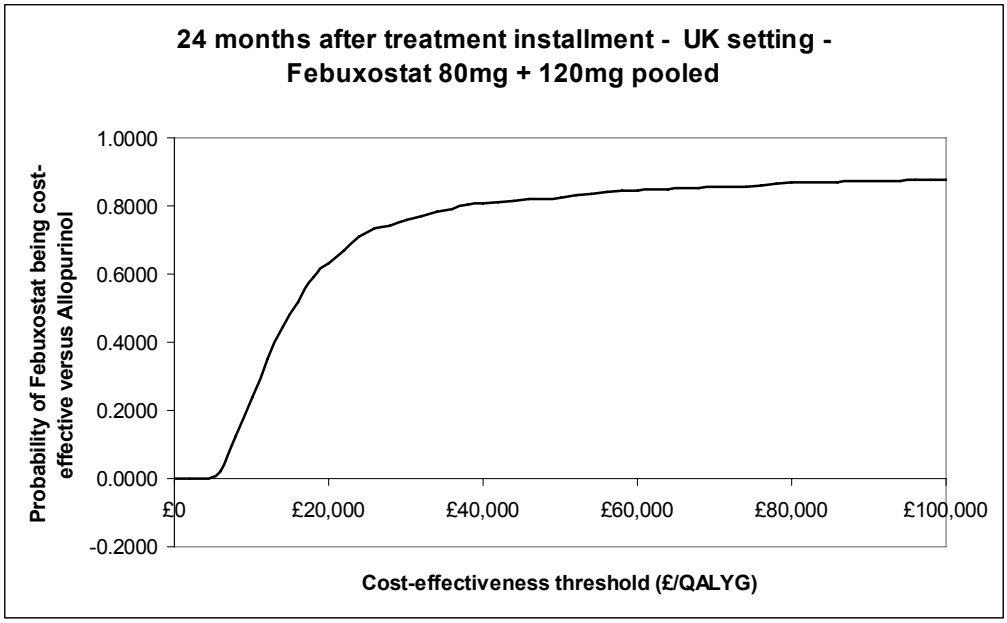


Figure 6-3. Cost-effectiveness acceptability curve: UK setting



6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

No subgroup analyses were conducted (see discussion Section 6.2.2.2-3).

6.3.3. Sensitivity analyses

6.3.3.1 What were the main findings of the sensitivity analyses?

The ICER remained stable over time when extrapolating the results up to 5 years. The impact on the ICER of varying the reduction of 3-month flares due to prophylaxis to 0% increase the cost per QALY to £18,826 which remains under the acceptable threshold for cost-effectiveness represented in Table 6-24. Discounting has only a marginal effect on the ICER. As expected the drug price have an impact on the ICER, lowering the price by just over 40% to 0.50 decreases the ICER to £7,949 / QALY and increasing the price to 1.25 increases ICER to £23,386 / QALY.

Table 6-24. Univariate sensitivity analysis ICER

Parameter changed	Allopurinol	Febuxostat	Difference
36 months			
Cost (£)	£3,851	£4,652	£801
QALY	2.056	2.108	0.052
ICER (cost per QALY)			**£15,403**
48 months			
Cost (£)	£5,053	£6,114	£1,061
QALY	2.695	2.763	0.069
ICER (cost per QALY)			**£15,438**
60 months			
Cost (£)	£6,213	£7,533	£1,320
QALY	3.311	3.395	0.085
ICER (cost per QALY)			**£15,552**
3-months Flare prophylaxis 0%			
Cost (£)	£2,802	£3,410	£608
QALY	1.388	1.420	0.032
ICER (cost per QALY)			**£18,826**
3-months Flare prophylaxis 100%			
Cost (£)	£2,550	£3,071	£521
QALY	1.397	1.432	0.035
ICER (cost per QALY)			**£14,725**
Discount rate 0%			
Cost (£)	£2,652	£3,205	£553
QALY	1.420	1.455	0.035
ICER (cost per QALY)			**£15,631**
Discount rate 6%			
Cost (£)	£2,573	£3,103	£531
QALY	1.377	1.411	0.034
ICER (cost per QALY)			**£15,520**
Febuxostat unit cost, (£0.50)			
Cost (£)	£2,605	£2,881	£276
QALY	1.395	1.430	0.035
ICER (cost per QALY)			**£7,949**
Febuxostat unit cost, (£1.25)			
Cost (£)	£2,605	£3,417	£812
QALY	1.395	1.430	0.035
ICER (cost per QALY)			**£23,386**

Parameter changed	Allopurinol	Febuxostat	Difference
Utility decrease with sUA (0.02)			
Cost (£)	£2,605	£3,146	£540
QALY	1.416	1.437	0.021
ICER (cost per QALY)			**£26,018**
Utility decrease with sUA (0.05)			
Cost (£)	£2,605	£3,146	£540
QALY	1.372	1.422	0.05
ICER (cost per QALY)			**£10,786**
Proportion of patients with sUA < 360 umol/L (0.7)			
Cost (£)	£2,605	£3,156	£551
QALY	1.395	1.417	0.022
ICER (cost per QALY)			**£24,645**
Base-case			
Cost (£)	£2,605	£3,146	£540
QALY	1.395	1.430	0.035
ICER (cost per QALY)			**£15,565**

6.3.4 Interpretation of economic evidence

6.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No published cost or economic evaluations are available for febuxostat. Only one cost-effectiveness study of allopurinol in gout was identified in the literature search.[53] This study evaluated the cost effectiveness of urate lowering therapy on prevention of flare in gout patients without tophi in a Canadian health care setting over one year horizon. The results of the study are in line with the Ipsen model as it showed urate-lowering therapy is cost-effective in gout patients. However, the study is not relevant to this STA submission as it is dated and conducted in gout patients without tophi over a short time period of one year in a non-UK gout population.

6.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Yes, the results of the economic evaluation are relevant and generalizable to all groups of patients in the UK who would potentially use the technology, i.e., patients with gout in need of hyperuricaemia treatment.

6.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the evaluation is that it is based on the results of a head–to-head trial of febuxostat compared with allopurinol, which is the current standard of reference for the long-term treatment of gout, and that the utilities for the gout populations at different sUA levels and resource use are based on a European population, where UK patients make up one-third of the study population.

Overall, the current model provides a conservative estimate of the cost and beneficial effect of febuxostat compared with allopurinol. A general weakness is extrapolating data out beyond 2 years and these results need to be viewed with caution. The model does not account for the reduction in tophi and gout complications—like joint deformation and disability—over the long term. This is significant as establishing a lower sUA level could be related to avoided severe physical complications much later in life.

6.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further analyses could include long-term data on the sUA levels and flare rates based on up to 4 years of clinical data for febuxostat treatment in the phase II and phase III extension studies. Another useful data input would be to have rates of longer-term complications that could be related to high sUA levels.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

Acceptability, appropriateness, and preference

Febuxostat offers to general practitioners an alternative treatment which has demonstrated superior efficacy in lowering sUA levels in the global gout

population, as well as in sub-populations for which current therapies have limitations (patients with mild to moderate renal impairment, patients with tophi, patients with elevated sUA levels, patients not responding to allopurinol). Most patients will reach the EULAR-recommended target sUA level (< 6 mg/dL [360 µmol/L]), and about half of the patients will achieve the BSR-recommended target sUA level (< 5 mg/dL [360 µmol/L]) with 80 mg administered once daily, compared to 38% and 13% respectively with allopurinol 300 mg. After 2 to 4 weeks of treatment, sUA levels should be checked. If the target sUA level has not been reached the dose may be increased to 120 mg.

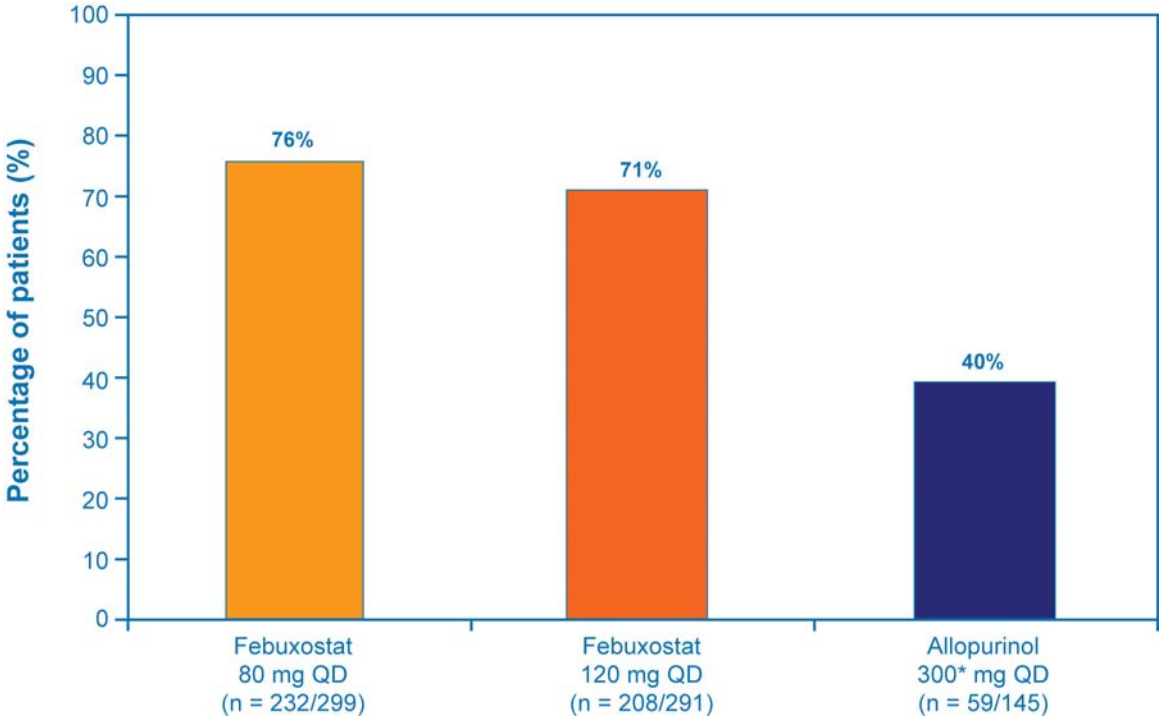
Compared with allopurinol, febuxostat is effective and safe to use in middle-aged and older gout patient populations with comorbidities and concomitant medications. Febuxostat does not interact with other drug treatments commonly used in conjunction with gout, such as colchicine, indomethacin, naproxen, desipramine or warfarin.[5] Febuxostat does not require complex dosage adjustments as allopurinol does. No dosage reduction from 80 mg is necessary based on safety, pharmacokinetics, or pharmacodynamic endpoints in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 ml/min)[5] or mild hepatic impairment.[5] No dosage adjustments are required for febuxostat with regard to gender or for elderly patients.[49]

Up to one-fifth of patients cannot tolerate allopurinol and may discontinue therapy. Some patients develop a rare but potentially fatal allopurinol hypersensitivity syndrome.[21,27,54,55] In one small study, 8 patients with gout and sUA levels greater than 480 µmol/L (8 mg/dL), who had been intolerant to allopurinol (i.e., a history of a reaction precluding rechallenge), were entered into an open-label extension trial and treated with febuxostat 80 mg (titration to 40 mg or 120 mg possible). The patients maintained sUA levels less than 360 µmol/L (6 mg/dL), and six of the patients continued treatment for 2 years or more.[9]

A long term study (EXCEL) showed febuxostat is the preferred treatment; patients remained on febuxostat treatment for a longer time than allopurinol and more patients switched from allopurinol to febuxostat than vice versa. A subset of patients (n = 735) completing either the FACT trial or the APEX trial were enrolled in an open-label extension study, EXCEL, for more than 24 months. Changes in treatment were permitted in the first 6 months to maintain sUA levels between 180 µmol/L (3 mg/dL) and 360 µmol/L (6 mg/dL). Patients with sUA levels of 360 µmol/L (6 mg/dL) or greater at 6 months were

considered therapeutic failures and were discontinued from the study. Most patients initially assigned to febuxostat treatment remained on febuxostat throughout the study as shown in (Figure 7-1).[15] Among the patients initially assigned to allopurinol, 57% changed from initial treatment due to lack of efficacy compared to 18% with febuxostat 80 mg and 8% with febuxostat 120 mg.[15]

Figure 7-1. Percentage of patients who remained on initial therapy during the EXCEL study



QD = once daily.
* 141 patients received allopurinol 300mg, 4 received 100 mg based on renal function.
Source: Becker et al. (2007) [15].

7.1 What is the estimated annual budget impact for the NHS in England and Wales?

7.1.2 Method

We present an analysis of the budget of febuxostat treatment for gout with elevated uric acid levels in England and Wales assuming an increasing market share of febuxostat from 2.3% the first year and reaching up to 27.8% the fourth year.The market is based on the expected population with gout currently taking allopurinol and is assumed to remain the same over the modelled 5-year period, i.e the allopurinol market share will decrease with the corresponding percentage increase of febuxostat market share. The analysis was conducted from the perspective of the NHS for the entire England and

Wales population. The budget impact was estimated for each year between 2008 and 2012 inclusive.

Outcome measures of the model include annual total cost based on data from the IMS observational study and costs in the UK.[12] To establish an average cost for a given population receiving febuxostat, the model developed in the cost-effectiveness analysis was used to estimate the costs of resource use (Table 7-1). The model provided total annual drug and health care budget estimates.

Table 7-1. Budget impact parameters used in the model

Number of treatment-eligible patients currently on allopurinol in England and Wales	**446,031**
Market share of febuxostat	
Year 1	
Year 2	
Year 3	
Year 4	
Year 5	
Proportion of patients in sUA level ≤ 6mg/dL	
Allopurinol	
From week 3 after treatment initiation	
From month 4 to 12 after treatment initiation	
From month 13 to 60 after treatment initiation	
Febuxostat	
From week 3 after treatment initiation	
From month 4 to 12 after treatment initiation	
From month 13 to 60 after treatment initiation	
Monthly number of flares in sUA level ≤ 6mg/dL	
Year 1-5	

Costs were reported for the following agents and activities:

- Urate-lowering agents (pooled febuxostat 80 mg and 120 mg versus allopurinol 300 mg); febuxostat was initially dosed 80 mg daily and increased to 120 mg after 2-4 weeks if sUA was higher than 360 µmol/L (6 mg/dL)
- Cost of flare
- Maintenance cost of gout treatment

Estimates of the cost of managing adverse events were assumed to be the same between the treatments and were not accounted for in the analysis, except for the cost for managing the initial increase in flare rate at initiation of treatment. The clinical trials provided gout flare prophylactic treatment with colchicine or NSAIDs during the first 8 weeks of urate-lowering therapy. These drugs were not costed in the model as they are the same for both treatment groups. Likewise, the cost of a prolonged flare prophylactic treatment according to the recent BSR-recommended time period of up to 6 months was not accounted for as the costs are the same in both treatment groups. The costs and health benefits were derived from the cost-utility analysis described in Section 6. Costs were not discounted in the model and were all based on 2007 prices.

7.1.3 Results

The cost element of the cost-effectiveness model was used to calculate the budget impact of gradually introducing febuxostat to the England and Wales market. No discounting was applied for the budget impact calculations, as these are not appropriate in this form of economic analyses. The 5-year budget impact of introducing febuxostat to the England and Wales market is represented in Table 7-2 and Table 7-3. The 5-year horizon was selected to reflect a typical health budget planning horizon. The model assumes at least 3 months of flare prophylactic therapy with colchicine (flare reduction set to 78%).

The overall budget increase during the fifth year for the health care payer is estimated to be attributed to the higher cost of febuxostat combined with cost-savings of flare costs Table 7-3 provides a cumulative year-on-year view of the nudget increases expected with febuxostat. Over 5-years the additional budget is estimated at just under.

Table 7- 2. Within-year incremental population-based budget impact results per year for febuxostat on the England and Wales market.

Year	Total cost	Drug cost	Flare cost	Follow-up cost	Market share
Year 1					
Year 2					
Year 3					
Year 4					
Year 5					

Assumes a total population of 406,189 treated gout patients. The febuxostat costs are combined for 80 mg and 120 mg doses.

Table 7- 3. Cumulative year-on-year incremental population-based budget impact results per year for febuxostat on the England and Wales market.

Year	Total cost	Drug cost	Flare cost	Follow-up cost	Market share
Year 1					
Year 2					
Year 3					
Year 4					
Year 5					

Assumes a total population of 406,189 treated gout patients. The febuxostat costs are combined for 80 mg and 120 mg doses.

Overall flares and follow-up costs represent 98% of the total estimated budget for gout. The drug element of the estimated budget represents approximately 2%. Over the 5-year budget horizon, the £xxxx additional budget represents an approximate increase of 4% compared to the current estimated 5-year budget based on using only allopurinol (£xxxx). The BI model assumes no difference in the follow-up cost of complication to gout (£xxxx) which stands for 75% of the major total budget costs (Table 7-4). The budget impact calculations are restricted to undiscounted direct costs only.

Table 7-4. Cumulative overall 5-year budget compared between only allopurinol and the introduction of febuxostat.

	Total Cost	Drug cost	Flare cost	Follow-up cost	Market share
Allopurinol					

	Total Cost	Drug cost	Flare cost	Follow-up cost	Market share
Febuxostat					
Incremental					

Note: Assumes that the total gout population (N = 406,189) uses either allopurinol or febuxostat. Febuxostat costs are combined for 80 mg and 120 mg doses.

As previously discussed, the cost-effectiveness model that underpins the budget impact calculations, includes data showing an initial increase in flare rate which is treatment initiated for patients new to treatment. This effect is present in the first 3 months of treatment but is reduced using an anti-inflammatory prophylaxis treatment, such as colchicine, as newly recommended in the BRS guidelines.

7.2 What number of patients were assumed to be eligible? How was this figure derived?

The number of gout cases in England and Wales was estimated by multiplying the prevalence of gout (1.35%)[11] by the total population of England and Wales during 2007. The estimated number of patients on allopurinol in the UK was based on the IMS Disease Analyzer study (delivered at the end of 2006) and gout population. The estimates are provided in Table 7-5. It was assumed that the size of this population would remain constant over the 5 years included in the budget impact calculations.

Table 7-5. Estimated number of patients on allopurinol, England and Wales

Total population in England and Wales[a]	53,728,800
Estimation of number of patients with gout	
Patients included in the Disease Analyser study	2,514,806
Patients with gout	34,071
Estimated prevalence	1.35%
Estimated total population with gout in England and Wales	725,339
Estimation of number of patients on allopurinol	
Proportion of patients on allopurinol in the Disease Analyser study	56%
Estimated total population on allopurinol	**406,189**

[a] Source: UK: www.statistics.gov.uk

7.3 What assumption(s) were made about current treatment options and uptake of technologies?

The budget impact model is based on a market forecast with following assumptions:

- Febuxostat will be available on the market year 2008.
- Labelled indication will remain unchanged from described earlier in the STA
- Febuxostat will be commercially successful
- No other competitors will enter the market during this time period.

The model was intended to assess the budgetary consequences of replacing allopurinol with febuxostat. Therefore, it was assumed that any market share increase of febuxostat was associated with an equal market share decrease in allopurinol. Thus, the total market of treated patients was assumed to not increase.

7.4 What assumption(s) were made about market share (where relevant)?

The estimated market share of febuxostat during the first 5 years after introduction to the market was provided by Ipsen (Table 7-6.).

Table 7-6. Estimated market share of febuxostat, UK

Year	Market Share (%)
Year 1	
Year 2	
Year 3	
Year 4	
Year 5	

7.5 What unit costs were assumed? How were these calculated?

The drug costs in the model were expressed in cost per day. The drug doses were based on the expected recommended doses of febuxostat, 80 mg and 120 mg, in the SPC. The most commonly used dose of allopurinol in the UK is 300 mg, according to observational research.[11,12] These doses are also the doses used in the clinical trials providing the clinical evidence for the cost-effectiveness model and budget impact model. The drug costs in the model refer to the daily drug dose of febuxostat 80 mg and febuxostat 120 mg and applied in this setting. For allopurinol, unit costs were derived from the British National Formulary. For febuxostat, the anticipated daily price was provided

by Ipsen. The drug cost data applied in the model are represented in Table 7-7.

Table 7-7. Daily drug costs used in the model, UK

Allopurinol 300 mg/day[a]	Febuxostat 80 mg/day	Febuxostat 120 mg/day
£0.065	£0.870	£0.870

[a] Source UK: British National Formulary (2007).[51]

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime—for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

All the costs and resource use are based on the IMS observational study[12] which should reflect the treatment of gout in the UK in general.

7.7 Were there any estimates of resource savings? If so, what were they?

Within the 5-year time frame of the model, cost savings of £xxxx are expected from a reduction in gout flare.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The cost savings expected from long term use of febuxostat leading to maintained low sUA levels and prevention of gout arthritis with reduced numbers of tophi and disability from gout arthritis were excluded from the analysis because they are uncertain within the 5-year time frame of the model. Similarly, health benefits in terms of QALYs gained over patient lifetime were not accounted for. The maintainence costs from gout treatment are the same for both groups in the model because there are no data to quantify the decrease in maintenace cost with decreasing sUA level. These costs are likely to decrease with sUA level over time and induce additional costs savings.

Additional societal cost-savings with maintained productivity and less absence from work due to gout flares can be expected.

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9 Appendices

9.1 Appendix 1:Summary of Product Characteristics

9.2 Appendix 2: Search strategy for Section 5 and Section 6