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Review Article

Febuxostat, a Non-Purine Selective Xanthine Oxidase Inhibitor in The Management of Hyperuricemia and Chronic Gout: A Systematic Review

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ABSTRACT

Febuxostat is a novel, potent, non-purine selective xanthine oxidase inhibitor which got approved for marketing in the year late 2009 by Central Drugs Standard Control Organization (CDSCO), India. Systematic search of trials/studies from PubMed and Cochrane database lead to 11 trials which demonstrated its superior ability to lower and maintain serum urate levels below 6 mg/dl compared with conventionally used doses of allopurinol for gout. Almost 45% of studies were of high quality according to Jadad score which proves the studies to be more authentic and reliable. The most common adverse reactions reported were abnormal liver function tests, headache, and gastrointestinal symptoms which were usually mild and transient. However, hepatotoxicity becomes a limitation in the use of febuxostat. Febuxostat seems to be a promising alternative for prescribing in primary care patients who are intolerant to allopurinol or to whom allopurinol is contraindicated but it should be associated with further long term surveillance for its safety and efficacy.

Keywords: Febuxostat, Xanthine oxidase inhibitor, Serum urate level, Clinical trial, Hyperuricemia, Gout

1. INTRODUCTION

Gout is an increasingly common disorder [1-3] characterized by hyperuricemia (serum urate concentration (sUA) exceeding 6.8 mg/dL, the limit of urate solubility) and by acute and chronic consequences of urate crystal deposition: episodic gout flares, deforming gouty arthropathy, tophi, and urolithiasis [4]**.** Gout affects about 2% of men (>30 years) and women (>50 years) and accounts for about 3.9 million annual physician visits, with more than two-thirds occurring at the primary care practitioner's office [5, 6]. Long-term management of recurrent or progressive gout focuses on urate-lowering therapy (ULT) aimed at maintaining sUA in a sub-saturating range, often chosen as <6.0 mg/dL [7-10].

The most frequently used pharmacologic urate lowering strategies involve reducing urate production with a xanthine oxidase inhibitor and enhancing urinary excretion of uric acid with a uricosuric agent. Urate-lowering agents are limited, however, in number, availability, and effectiveness [11]. Allopurinol, a xanthine oxidase inhibitor, is the most commonly prescribed of these agents. The average dose is 300 mg per day, although dosing recommendations range from 100 to 800 mg per day, titrated to serum urate and creatinine clearance. The side effects of allopurinol, although uncommon, may be severe or life-threatening and occur more often in patients with renal insufficiency. Long-term management of chronic gout often requires urate-lowering therapy that includes xanthine oxidase (XO) inhibitors, uricosuric agents, and recombinant urate oxidases. XO inhibitors decrease the production of UA, whereas uricosuric agents and recombinant urate oxidases increase the elimination rate of UA [12-15].

Febuxostat(2-[3-cyano-4-isobutoxyphenyl]-4-methylthia-zole-5-carboxylic acid) is an orally administered, novel, potent, non-purine, selective inhibitor of XO that has activity against both the oxidized and reduced forms of XO [16, 17]. Absorption of febuxostat is rapid (t_{max} of approximately 1 h), and C_{max} and AUC exhibit dose proportionality over the dose range of 10 to 120 mg. Febuxostat is highly bound (>99%) to plasma proteins [18] and undergoes extensive phase 1 and phase 2 metabolism to its acyl-glucuronide metabolite and to hydroxylated metabolites. Less than 5% of the dose is excreted unchanged in urine [19]. Short-term pharmacokinetic studies performed in non-gouty subjects with impaired renal function suggest that febuxostat dose adjustment may not be required in these patients [20, 21]. Allopurinol had been the mainstay of urate-lowering therapy for about 40 years until febuxostat was approved in 2009 for treatment of chronic hyperuricemia in conditions where urate depression has already occurred

(including a history, or presence of tophus and/or gouty arthritis) [22]. This article aims to critically review the clinical trial data, safety profile and the role of febuxostat for the management of hyperuricemia and gout.

2. MATERIAL AND METHODS

2.1. Search Strategy

Pertinent studies were searched in PubMed (updated January 2012) by two of the investigator using the term "Febuxostat" by initiating limits to only randomized controlled trials, controlled clinical trials, comparative study, clinical trial (Phase I-IV), practice guidelines in humans for full texts and abstracts. The search strategy was developed according to Biondi-Zoccai [23, 24]. The language restriction was enforced to English and the search strategy was set to an end on month of January 2012.

The Cochrane Controlled Trial Register (Cochrane Library) without language restriction was searched using term "Febuxostat" and advanced search was carried out through the entire Cochrane library.

2.2. Inclusion criteria

All randomized trials, comparative studies, controlled clinical trials with free full texts and abstracts that evaluated febuxostat in management of gout were potentially eligible for systematic review. Studies or trials were included if all participants were greater than 18 years of age and the drug was given in comparison with allopurinol, placebo or no treatment. Studies showing pharmacokinetic interactions and dose escalation of febuxostat were also included in this review. The enrolled patients were required to meet the American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout [25]. The primary outcome measure for assessment was proportion of reduction of sUA levels and gout flares at the predefined dosages of febuxostat and other groups (placebo, allopurinol etc) included for comparison, while, secondary outcome measure was to have safety assessment through evidence of various adverse drug events amongst the respective groups.

2.3. Data extraction and analysis

All titles and abstracts were screened independently by the reviewers and irrelevant studies were discarded. The full text of the remaining studies was assessed to determine if the inclusion criteria were met. The included studies were all assessed for trial quality without blinding to author of source. Any discrepancies in quality assessment were resolved in discussion. The quality items assessed were allocation concealment, blinding, intention to treat analysis, loss of follow up, measurement of outcome and outcome assessed. Data were extracted onto standard pre-prepared forms.

Jadad scale [26] is one of the methods implemented to assess the quality of a clinical trial as they provide quantitative estimates of quality that could be replicated easily and incorporated formerly into the peer review process and into systematic review. The Jadad scoring of trials was performed with the help of medical online calculator [27].

3. RESULTS

3.1. Literature search

The results obtained from search strategy using both PubMed and Cochrane Library databases for the term "Febuxostat" is depicted in Figure 1.

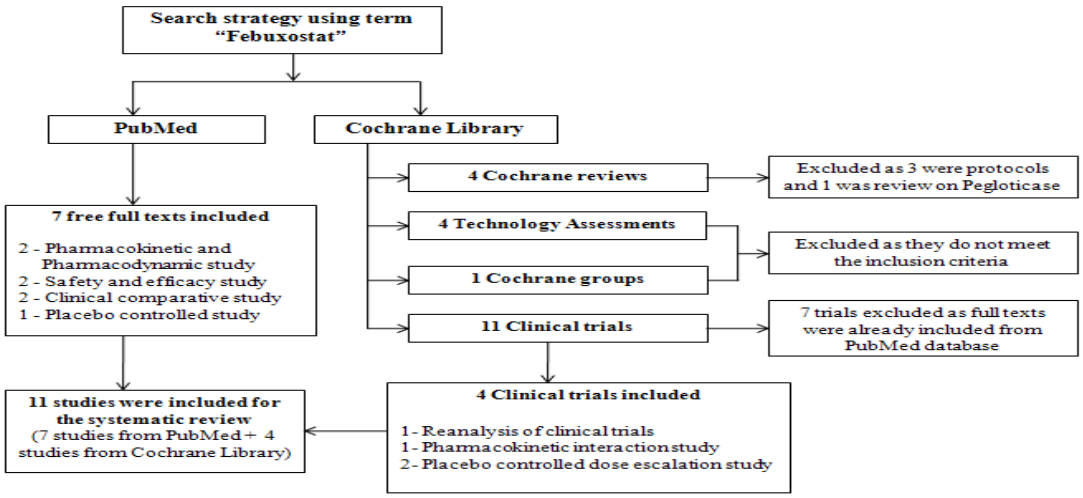

Figure 1: Search strategy adopted for the systematic review

Upon extensive search we found 7 studies available as free full text from PubMed database while 20 studies available as abstracts from Cochrane database. Studies from Cochrane database include 11 clinical trials, 4 cochrane reviews, 4 technology assessments and 1 was cochrane groups. All reviews, technology assessments and cochrane groups were excluded as they did not meet our inclusion criteria. Among the 11 cochrane clinical trials, 4 were included for the systematic review as rest of the studies were already included as full text from PubMed database. Thus, 11 studies were included for the systematic review which includes 7 studies from PubMed and 4 studies from Cochrane Library database. There was no disagreement between the reviewers regarding the inclusion of trials. The requested information to allow inclusion of these trials could not be obtained from the authors.

3.2. Study characteristics

The characteristics of the 11 trials involving a total of 8766 subjects were shown in Table 1. Three trials were available showing comparison of Febuxostat with placebo (n= 319 subjects) [28-30], two trials compared Febuxostat with Allopurinol and Placebo (n= 5173 subjects) [31, 32], two trials compared Febuxostat with Allopurinol (n= 3030 subjects) [33, 34] and only one study was found where febuxostat was compared with its various doses 40 mg, 80 mg and 120 mg (n=116) [35]. Among the remaining three studies, two were PK-PD (Pharmacokinetic- Pharmacodynamic) studies [36, 37] and one was pharmacokinetic interaction study (n=128) [38]. There were 5 trials wherein healthy subjects and 6 trials wherein patients with hyperuricemia and gout were enrolled for the conduct of study.

3.3. Study Quality

Study quality was assessed using Jadad scale. Out of 11 studies, only 5 (45.45%) were of High quality in the range of 3-5 Jadad score (Table 4 and Figure 2). All 11 studies mentioned randomization except one study [35] out of which only 3 studies had adequate allocation concealment and 6 studies were double blinded. Three studies reported no loss to follow up and other trials had a total loss of 9.1% (Table 2).

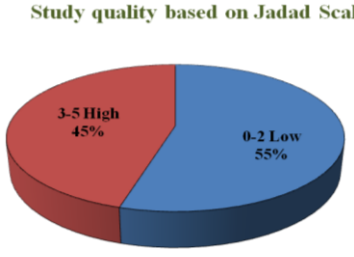

Figure 2: Summary showing the clinical trials study quality based on Jadad Scale

The retrieved information was also screened for safety profile of febuxostat in patients with hyperuricemia and gout. Out of 11 studies, 8 studies mentioned the adverse drug events profile of febuxostat during the trial period. Table 3 summarizes the adverse events (AEs) of febuxostat in patients with hyperuricemia and gout in various studies.

4. DISCUSSION

Grabowski B et al conducted a PK-PD study taking 36 healthy subjects who received single doses of febuxostat 80mg alone and febuxostat 80mg+hydrochlorothiazide 50 mg, separated by 7 days in an open-label, randomized, crossover fashion. Study medication was administered following an overnight fast (at least 10 h) and subjects continued to fast for 4 h post-dose. In each period, blood samples for the determination of febuxostat plasma concentrations were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dose. Blood samples for the determination of sUA were collected pre-dose and at 6, 12, 18, 24, and 48 h post-dose. Urine samples for the determination of UA were collected and pooled between 0 and 12 h post dose and between 12 and 24 h post-dose. Safety was monitored through AE recording, vital signs, physical examination and laboratory evaluations. This study demonstrated that the overall rate and extent of absorption of a single dose of febuxostat 80mg was not affected by co-administration with a single dose of hydrochlorothiazide 50 mg which suggests that febuxostat may be a viable option for hyperuricemia and gout patients who require diuretics. Also there is no requirement of dose adjustment of febuxostat when it is co-administered with hydrochlorothiazide [36].

Another PK-PD Phase I study was conducted by Khosravan R et al showing the effect of food and antacid on PK-PD of febuxostat. Healthy adult male and female subjects between the ages of 18-55 years with normal creatinine clearance (79–149 ml/min) and a body mass index $<30\ kgm^{-2}$ were recruited. Studies were designed as randomized, single centre, two-way crossover studies. Administration of febuxostat with food caused a delay in t_{max} and was associated with a lower maximum and total exposure to febuxostat, indicating a decrease in the absorption rate constant and an increase (21–24%) in the oral clearance (i.e. CL/F) of febuxostat. Administration of febuxostat under nonfasting conditions (i.e. high-fat meal) did not appear to affect the apparent terminal phase elimination half-life of febuxostat. Following administration of febuxostat with antacid, there was also a delay in febuxostat t_{max} and a decrease in febuxostat C_{max}. However, these changes in febuxostat AUC was neither statistically nor clinically significant. Therefore, based on the pharmacokinetic and pharmacodynamic, febuxostat can be administered without regard to food or antacid intake. The incidences of treatment-related AEs were higher under fasting conditions compared with nonfasting conditions. However, all

events were self-limiting and probably the result of the act of fasting itself [37].

Khosravan R [29] et al and Becker MA et al [30] conducted a phase I multiple-dose, placebo-controlled, dose-escalation study of febuxostat ranging from 10 to 240 mg in 12 and 154 healthy adults respectively. During the course of the study, blood and urine samples were collected to assess the pharmacokinetics of febuxostat and its metabolites, and its pharmacodynamic effects on uric acid, xanthine and hypoxanthine concentrations. Febuxostat was well tolerated at once-daily doses of 10 mg to 240 mg. There appeared to be a linear pharmacokinetic and dose-response (percentage decrease in serum uric acid) relationship for febuxostat dosages within the 10 mg to 120 mg range.

A multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial of once-daily oral febuxostat (40 mg, 80 mg, or 120 mg) in reducing sUA levels in adult patients with gout and hyperuricemia (sUA >8.0 mg/dl) conducted by Becker MA et al. Subjects receiving urate-lowering therapy underwent a 2-week washout period preceding randomization and were weekly followed up throughout the study. The mean percentage reductions in sUA from baseline levels at each visit were significantly greater in each febuxostat group than in the placebo group, with the greatest reductions in the febuxostat group receiving 120 mg/day. There were no significant differences between febuxostat and placebo groups with regard to treatment related AEs [28].

Wortmann RL et al [31] conducted analysis of three phase III trials and Schumacher Jr HR et al [32] conducted phase III, randomized, double blind, allopurinol- and placebo-controlled clinical trial involving 1072 and 4101 gout and hyperuricemic subjects respectively. Postbaseline sUA and AEs were assessed. Patients were followed up monthly. Flare prophylaxis for up to 6 months during the initiation of febuxostat appeared to provide greater benefit than flare prophylaxis for 8 weeks, with no increase in AEs [31]. Febuxostat effectively reduces sUA in subjects with hyperuricemia and gout and that these effects are significantly greater than those produced by the commonly used doses of allopurinol or by placebo [32].

FOCUS study conducted by Schumacher Jr HR et al assessed urate-lowering and clinical efficacy and safety of long-term febuxostat therapy in 116 gout subjects of 145 subjects completing the 28-day Phase II trial. Each subject initially received febuxostat 80mg daily for 4 weeks. In the period between Weeks 4 and 24, the dose of febuxostat could be titrated among doses of 40, 80 or 120mg daily in order to maintain sUA between 3.0 and <6.0 mg/dl, to respond to an AE, or at the discretion of the investigator. Study visits occurred at Weeks 2 and 4, and then every 4 weeks through Week 56. AEs were reported by 91% (106/116) of the subjects during the study. Serious AEs were reported by 18% (21/116) of the subjects; the majority resulted in hospitalization. The investigators did not found any of the serious AEs to the study drug. This study indicates that treatment with febuxostat for up to 5 yrs results in a sustained reduction in sUA and subjects that maintain an sUA <6.0 mg/dl have infrequent gout flares and reduction in the presence of tophi [35].

Becker MA et al conducted two randomized double blind study [33, 34] taking 762 and 2268 subjects (the CONFIRMS trial) [33] with gout respectively comparing various doses of febuxostat with 300 mg of allopurinol. Bimonthly visits of patients were scheduled for follow up. The end points were sUA conc. <6.0 mg/dL and safety assessments included blinded adjudication of each cardiovascular (CV) adverse event and death with reduction in the incidence of gout flares and in tophus area. Febuxostat, at a daily dose of 80 mg or 120 mg, was more effective than allopurinol at the commonly used fixed daily dose of 300 mg in lowering serum urate. Adjudicated (APTC) CV event rates were 0.0% for febuxostat 40 mg and 0.4% for both febuxostat 80 mg and allopurinol. One death occurred in each febuxostat group and three in the allopurinol group [33] while reductions in gout flares and tophus area occurred in all treatment groups [34].

A Pharmacokinetic interaction study of febuxostat and NSAIDs includes indomethacin and naproxen in healthy subjects using febuxostat 80 mg once daily or twice daily, indomethacin 50 mg and naproxen 500 mg twice daily dosing showed no effect of febuxostat on the plasma pharmacokinetics of indomethacin and naproxen. Similarly, indomethacin had no effect on the plasma pharmacokinetics of febuxostat. Thus, based on the plasma pharmacokinetic data in healthy subjects, febuxostat may be administered with indomethacin or naproxen with no dose adjustments for febuxostat, indomethacin, or naproxen [38].

5. CONCLUSION

Febuxostat was found to be an effective anti-hyperuricemic agent for the dose ranges from 80 mg to 120 mg when compared with well established drug allopurinol 300 mg as stated by the clinical trials and various other studies. Administration of febuxostat along with food or antacid does not affect its bioavailability. Almost 45% of studies were of high quality according to Jadad score which proves the studies to be more authentic and reliable. The most common adverse reactions reported were abnormal liver function tests, headache, and gastrointestinal symptoms which were usually mild and transient. However, hepatotoxicity becomes a limitation in the use of febuxostat. Febuxostat seems to be a promising alternative for prescribing in primary care in-patients who are intolerant to allopurinol or to whom allopurinol is contraindicated. Further clinical post marketing surveillance studies required for proving its safety and efficacy in patients with hyperuricemia and gout.

Table 1: Characteristics of studies using febuxostat in patients with Hyperuricemia and Gout

Study (Reference)	Population	No. of patients (n)	Drug and Doses given to respective groups (mg)					Follow up
Grabowski B, USA, 2010[36]	Healthy adult subjects	36	n=34 Febuxostat 80mg alone			n=35: Febuxostat 80mg + Hydrochlorothiazide 50 mg		24 hrs
Becker MA, Multicenter study, 2010[33]	Subjects with gout and sUA ≥ 8.0 mg/dL	2268	n= 757: Febuxostat 40 mg daily	n= 756: Febuxostat 80 mg daily	n= 755: Allopurinol 200/300 mg daily			Bimonthly
Schumacher Jr HR, Multicenter study, 2009[35]	Subjects with gout	116	n= 8: Febuxostat 40 mg daily	n= 79: Febuxostat 80 mg daily	n= 29: Febuxostat 120 mg daily			Weeks 2, 4 and then every 4 weeks through Week 56. Visits during yrs 2–5 occurred every 8 weeks
Schumacher Jr HR, Multicenter study, 2008[31]	Subjects with gout, hyperuricemia and normal or impaired renal function	1072	n= 267: Febuxostat 80 mg	n= 269: Febuxostat 120 mg	n= 132: Febuxostat 240 mg	n= 268: Allopurinol 300 mg	n= 134: Placebo	4 week
Khosravan R, USA, 2007[37]	healthy subjects	92	40 mg (single dose), 80 mg (multiple doses) or 120 mg (single dose) of Febuxostat			80 mg (single dose) of Febuxostat alone and with an antacid [i.e. 800 mg Mg(OH)2 +900 mg Al(OH)3]		6 days
Becker MA, Multicenter study, 2005[34]	adult subjects with gout and with sUA of at least 8.0 mg/ dl	762	n=257 : Febuxostat 80 mg/day	n=251 : Febuxostat 120 mg/day	n= 254: Allopurinol 300 mg/day			15 days
Becker MA, Multicenter study, 2005[28]	Patients with gout and hyperuricemia (sUA ≥8.0 mg/dl).	153	n= 37: febuxostat 40 mg /day	n= 40: febuxostat 80 mg /day	n= 38: febuxostat 120 mg /day	n=38: Placebo		Weekly
Wortmann R, Multicenter Study, 2010[32]	Patients with gout	4101	Febuxostat or allopurinol for 6 months or 1 year and flare prophylaxis with colchicine 0.6 mg/d or naproxen 250 mg BID for 8 weeks or 6 months			Placebo for 6 months or 1 year flare prophylaxis with colchicine 0.6 mg/d or naproxen 250 mg BID for 8 weeks or 6 months		4 week intervals
Khosravan R, USA, 2006[38]	Healthy subjects	Not mentioned	febuxostat 80 mg once daily, indomethacin 50 mg twice daily, or both			febuxostat 80 mg, naproxen 500 mg twice daily, or both		Day 5 and Day 7
Khosravan R, USA, 2006[29]	Healthy subjects	12 subjects (10 Febuxostat + 2 Placebo)	10, 20, 30, 40, 50, 70, 90, 120, 160, 180 and 240 mg Febuxostat dose groups					17 days
Becker MA, USA, 2004[30]	Healthy volunteers	154	Daily febuxostat doses in the range 10 mg to 120 mg			Placebo		2-week

Indicates studies from PubMed database Indicates studies from Cochrane Library database

Table 2: Quality assessment of trials included in the systematic review of febuxostat in patients with Hyperuricemia and Gout

Study (Reference)	Allocation concealment used?	Blinding?	Intention to treat?	Loss to follow up	Measurement of Outcome	Outcome assessed
Grabowski B, USA, 2010[36]	Inadequate	Open label	Not stated	3 subjects	Plasma concentrations of febuxostat and urinary and serum concentrations of uric acid	Following febuxostat + hydrochlorothiazide co-administration and febuxostat alone; the respective peak plasma concentration mean values (Cmax) were 2.9 and 2.9 mg/ml. Both treatments were bioequivalent with respect to maximum and total systemic exposure to febuxostat. sUA conc. at 24 and 48 hrs were higher with febuxostat and hydrochlorothiazide than with administration of febuxostat alone.
Becker MA, Multicenter study, 2010[33]	Adequate	Double blind	Stated	n= 125:with Febuxostat 40 mg n= 158: with Febuxostat 80 mg n= 135: with Allopurinol 200/300 mg	sUA conc. <6.0 mg/dL , renal impairment (mild/moderate) and, Safety assessments includes assessment of cardiovascular (CV) adverse event and death	sUA <6.0 mg/dL were achieved 45.2%, 67.1%, and 42.1% in the Febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups, respectively. Among subjects with renal impairment, the UL response rate in febuxostat 80 mg group (71.6%) significantly exceeded those observed in the febuxostat 40 mg (49.7%) and allopurinol (42.3%) groups. Rates of AEs did not differ across treatment groups.
Schumacher Jr HR, Multicenter study, 2009[35]	Non randomized	Open label	Not stated	n= 6: with Febuxostat 40 mg n= 41:with Febuxostat 80 mg n= 11: with Febuxostat 120 mg	Gout flares were recorded and sUA, baseline tophi and safety were monitored	Overall, 47% (55/116) of subjects reported gout flares that required treatment while on their maintenance dose. At 5 yrs, 93% (54/58) of the remaining subjects had sUA <6.0 mg/dl, In 26 subjects with a tophus at baseline, resolution was achieved in 69% (18/26) by last visit on study drug. There were no deaths reported during the study. There was nearly complete abolition of gout flares in patients completing the study. Baseline tophi resolved in a majority of subjects.
Schumacher Jr HR, Multicenter study, 2008[31]	Adequate	Double blind	Stated	n= 93, 69, 48, 57, 33 : Febuxostat 80 mg, 120 mg, 240 mg, Allopurinol 300 mg , Placebo respectively	Serum urate levels <6.0 mg/dl	Significantly ($P < 0.05$) higher percentages of subjects treated with febuxostat 80 mg (48%), 120 mg (65%), and 240 mg (69%) attained the primary end point of last 3 monthly serum urate levels <6.0 mg/dl compared with allopurinol (22%) and placebo (0%)
Khosravan R, USA, 2007[37]	Inadequate	Not mentioned	Not stated	3 subjects	Effects of food or antacid on the pharmacokinetics and pharmacodynamics of febuxostat	Food caused a decrease in C_{max} (38–49%) and AUC (16–19%) of febuxostat at different dose levels following single or multiple oral dosing with febuxostat. Antacid caused a decrease in C_{max} (32%), but had no effect on AUC of febuxostat.

Table 2: Continued….

Study (Reference)	Allocation concealment used?	Blinding?	Intention to treat?	Loss to follow up	Measurement of Outcome	Outcome assessed
Becker MA, Multicenter study, 2005[34]	Adequate (computer generated randomization)	Double blind	Not stated	n= 2, 1, 3 : Febuxostat 80 mg, 120 mg, Allopurinol 300 mg respectively	sUA concentration of <6.0 mg/ dl, Reduction in incidence of gout flares and in tophus area	sUA was reached in 53 % of patients receiving 80 mg febuxostat, 62 % of receiving 120 mg of febuxostat, and 21 % of those receiving allopurinol. Similar reductions in gout flares and tophus area occurred in all treatment groups.
Becker MA, Multicenter study, 2005[28]	Inadequate	Double blind	Stated	n= 1, 3, 2, 2: Febuxostat 40 mg, 80 mg, 120 mg, Placebo respectively	sUA level <6.0 mg/dl, Gout flares, Incidences of treatment related AEs	Targeted sUA level was attained on day 28 in 0%, 56%, 76%, 94% of those taking placebo, febuxostat 40 mg, 80 mg and 120 mg respectively. Gout flares occurred with similar frequency in the placebo (37%) and 40-mg febuxostat (35%) groups and with increased frequency in the higher dosage febuxostat groups (43% taking 80 mg; 55% taking 120 mg). Incidences of AEs were similar with febuxostat and placebo.
Wortmann RL, Multicenter Study, 2010[32]	Inadequate	Double blind	Not stated	4 subjects	Plasma concentrations of febuxostat and urinary and serum concentrations of uric acid	Following febuxostat + hydrochlorothiazide co-administration and febuxostat alone; the respective peak plasma concentration mean values (Cmax) were 2.9 and 2.9 mg/ml. Both treatments were bioequivalent with respect to maximum and total systemic exposure to febuxostat. sUA conc. at 24 and 48 hrs were higher with febuxostat and hydrochlorothiazide than with administration of febuxostat alone.
Khosravan R, USA, 2006[38]	Inadequate	Not mentioned	Not stated	None	Plasma concentration (Cmax) and area under the curve (AUC)	Febuxostat had no effect on the plasma pharmacokinetics of indomethacin and naproxen. Similarly, indomethacin had no effect on the plasma pharmacokinetics of febuxostat. It may be administered with indomethacin or naproxen with no dose adjustments for febuxostat, indomethacin or naproxen.
Khosravan R, USA, 2006[29]	Inadequate	Non blinded	Not stated	None	Blood and urine samples were collected to assess the pharmacokinetics and pharmacodynamics of febuxostat and its metabolites	Febuxostat was well tolerated at once-daily doses of 10-240 mg. There appeared to be a linear pharmacokinetic and dose-response (percentage decrease in serum uric acid) relationship for febuxostat dosages within the 10-120 mg range.
Becker MA, USA, 2004[30]	Inadequate	Double blind	Not stated	None	sUA, plasma concentrations and AUC	Daily febuxostat doses resulted in proportional mean sUA ranging from 25% to 70% and proportional increases in maximum febuxostat plasma concentrations and AUC. AEs were mild and self-limited and no deaths or serious AEs were observed. Febuxostat is a safe and potent hypouricemic agent in healthy humans.

Table 3: Summary of adverse events of febuxostat in patients with Hyperuricemia and Gout in various studies

Study (Reference)	Adverse events observed
Grabowski B, USA, 2010[36]	Vision blurred(3%), Dyspepsia, eructation(6%), Abdominal pain(6%), Nausea and vomiting(14%), Upper respiratory tract infections(11%), Sunburn(3%), Abnormal liver function test(3%), Myalgia(3%), Muscle cramp(3%), Somnolence(6%), Headache(17%), Dizziness(17%), Menstruation with increase bleeding(3%), Vaginal laceration(3%), Contact Dermatitis(3%), Orthostatic hypotension(6%)
Becker MA, Multicenter study, 2010[33]	**Febuxostat (40 mg, 80mg):** URTIs(9.4%, 7%), liver function analysis(8.3%, 6.9%), Rash(5.8%, 5.6%), Diarrhoea(5.9%, 6.2%), Musculoskeletal and connective tissue signs and symptoms NEC(5.7%, 5%), Non fatal myocardial infarction (0%, 0.13%), Non fatal stroke(0%,0.26%). Angina(0.26%, 0%), Coronary revascularization(0.13%, 0%), Transient ischemic attack(0.13%, 0%), Venus and peripheral arterial vascular thrombotic event(0%,0.26%), CHF(0.26%, 0%), Arrythmia(0.4%, 0.53%). No CV death
Schumacher Jr HR, Multicenter study, 2009[35]	URTIs (53%), Musculoskeletal and connective tissue signs and symptoms(36%), Joint-related signs and symptoms(28%), Diarrhoea(21%), Influenza(17%), Limb injuries(17%), Headache(16%), Paresthesias and dysesthesias(14%), LRTIs(13%), Liver function analyses(13%), Vascular hypertensive disorders(13%), GI and abdominal pains(12%), Rashes, eruptions and exanthems(12%), Skin injuries(11%) Osteoarthropathies(11%), Oedema (10%), Pain and discomfort(10%), Non-site-specific injuries(10%), Tendon disorders(10%)
Schumacher Jr HR, Muticenter study, 2008[31]	**Febuxostat (80mg, 120 mg, 240 mg):** URTI(15%, 19%, 20%), Musculoskeletal and connective tissue signs and symptoms(9%, 9%, 10%), Diarrhoea(6%, 7%, 13%), Joint-related signs and symptoms(6%, 9%, 5%), Headache(5%, 55, 9%), Abnormal LFTs(6%, 4%, 4%), Influenza viral infections(4%, 5%, 5%), Nausea and vomiting(4%, 4%, 6%), Non site specific injuries(4%, 3%, 7%), Hypertension(5%, 2%, 4%), GI and abdominal pain(2%, 3%, 6%), Dizziness(2%, 2%, 7%). No death
Khosravan R, USA, 2007[37]	**Febuxostat 40 mg single dose (Fasting, Non fasting):** Headache (13%, 4%), Nausea(8%, 0%) **Febuxostat 40 mg single dose (Fasting, Non fasting):** Somnolence(13% each), Abdominal pain(8%, 4%), Nausea(8%, 4%), Diarrhoea(8%, 0%), Headache(0%, 9%), Arthralgia(8%, 0%), Myalgia(0%, 9%)
Becker MA, Multicenter study, 2005[34]	**Febuxostat (80mg, 120 mg):** Abnormal LFTs(4%, 5%), Diarrhoea(3% each), Headache(1%, 2%), Joint related signs and symptoms(<1%, 2%), Musculoskeletal and connective tissue signs and symptoms(2%, 1%), GI disorders(2%, <1%), Nausea and vomiting(2%, 1%), Dizziness(2%, 1%), Asthenic condition(2%, <1%), GI signs and symptoms(2%, <1%), Erythema(<1% each), Peripheral oedema(2%, <1%)
Becker MA, Multicenter study, 2005[28]	**Febuxostat (40mg, 80 mg, 120 mg):** Abdominal pain(3%, 3%, 3%), Diarrhoea(0%, 10%, 8%), Abnormal LFTs(5%, 3%, 3%)
Wortmann RL, Multicenter Study, 2010[32]	Not mentioned
Khosravan R, USA, 2006[38]	Not mentioned
Khosravan R, USA, 2006[29]	Not mentioned
Becker MA, USA, 2004[30]	No deaths or serious adverse events were observed

Table 4: Jadad Score for predicting the study quality of febuxostat in patients with Hyperuricemia and Gout

Study (Reference)	Jadad score- Study quality (based on Jadad Scale)*
Grabowski B, USA, 2010[36]	1-Low
Becker MA, Multicenter study, 2010[33]	5-High
Schumacher Jr HR, Multicenter study, 2009[35]	1-Low
Schumacher Jr HR, Multicenter study, 2008[31]	5-High
Khosravan R, USA, 2007[37]	1-Low
Becker MA, Multicenter study, 2005[34]	5-High
Becker MA, Multicenter study, 2005[28]	3-High
Wortmann RL, Multicenter Study, 2010[32]	3-High
Khosravan R, USA, 20062[38]	0-Low
Khosravan R, USA, 2006[29]	0-Low
Becker MA, USA, 2004[30]	2-Low

6. REFERENCES

1. Arromdee E, Michet CJ, Crowson CS, O'Fallon WM, et al. *J Rheumatol*, 2002; **29:** 2403-2406.
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, et al. *Arthritis Rheum*, 2008; **58:** 26-35.
3. Roddy E, Zhang W, Doherty M. *Nat Clin Pract Rheumatol*, 2007; **3:** 443-449.
4. Terkeltaub RA. *N Engl J Med*, 2003; **349:**1647-1655.
5. Choi HK, Curhan G. *Curr Opin Rheumatol*, 2005; **17:** 341-345.
6. Krishnan E, Lienesch D, Kwoh CK. *J Rheumatol*, 2008; **35:** 498-501.
7. Becker MA, Chohan S. *Curr Opin Rheumatol*, 2008; **20:** 167-172.
8. Perez-Ruiz F, Liote F. *Arthritis Rheum*, 2007; **57:** 1324-1328.
9. Li-Yu J, Clayburne G, Sieck M, Beutler A, et al. *J Rheumatol*, 2001; **28:** 577-580.
10. Shoji A, Yamanaka H, Kamatani N. *Arthritis Rheum*, 2004; **51:** 321-325.
11. Schlesinger N, Schumacher HR Jr. *Curr Opin Rheumatol*, 2001; **13:** 240-244.
12. Schlesinger N. *Drugs*, 2004; **64:** 2399-2416.
13. Terkeltaub RA. *N Engl J Med*, 2003; **349:** 1647-1655.
14. Fam AG. *Drugs Aging*, 1998; **13:** 229-243.
15. Harris MD, Siegel LB, Alloway JA. *Am Fam Physician*, 1999; **59:** 925-934.
16. Takano Y, Hase-Aoki K, Horiuchi H, Zhao L, et al. *Life Sci*, 2005; **76:** 1835-1847.
17. Okamoto K, Eger BT, Nishino T, Kondo S, et al. *J Biol Chem*, 2003; **278:** 1848–1855.
18. Kondo S, Nishimura S,Mochizuki T, Taniguchi K, et al. *Drug Metab Rev*, 1995; **8:** 56.
19. Becker MA, Kisicki J, Khosravan R, Wu J, et al. *Nucleosides Nucleotides Nucleic Acids*, 2004; **23:** 1111–1116.
20. Hoshide S, Takahashi Y, Ishikawa T, Kubo J, et al. *Nucleosides Nucleotides Nucleic Acids*, 2004; **23:** 1117–1118.
21. Mayer MD, Khosravan R, Vernillet L, Wu JT, et al. *Am J Ther*, 2005; **12:** 22–34.
22. http://www.medlineindia.com/list%20of%20approved%20drugs1.html (date of access: 14th Feb. 2012).
23. Biondi-Zocci GG, Agostoni P, Abbate A, Testa L, et al. *Int J Epidemiol*, 2005; **34:** 224-225.
24. Panda BK, Pawar A, Patel C, Marne SR, et al. *American Journal of PharmTech Research*, 2012; **2(1):** 287-303.
25. Wallace SL, Robinson H, Masi AT, Decker JL, et al. *Arthritis Rheum*, 1977; **20:** 895–900.
26. Jadad AR, Moore RA, Carroll D, Jenkinson C, et al. *Control Clin Trials*, 1996; **17:** 1-12.
27. http://doctick.com/medical_calculator/files/jadad-scale.html (date of access: 14th Feb. 2012).
28. Becker MA, Schumacher Jr HR, Wortmann RL, MacDonald PA, et al. *Arthritis Rheum*, 2005; **52(3):** 916–923.
29. Khosravan R, Grabowski BA, Wu JT, Joseph-Ridge N, et al. *Clin Pharmacokinet*, 2006; **45(8):** 821-841.
30. Becker MA, Kisicki J, Khosravan R, Wu J, et al. *Nucleosides Nucleotides & Nucleic acids*, 2004; **23(8-9):** 1111-1116.
31. Schumacher Jr HR, Becker MA, Wortmann RL, Macdonald PA, et al. *Arthritis Rheum*, 2008; **59(11):** 1540–1548.
32. Wortmann RL, Macdonald PA, Hunt B, Jackson RL. *Clin Ther*, 2010; **32(14):** 2386-2397.
33. Becker MA, Schumacher HR, Espinoza LR, Wells AF, et al. *Arthritis Res Ther*, 2010; **12(2):** R63.
34. Becker MA, Schumacher Jr HR, Wortmann RL, MacDonald PA, et al. *N Engl J Med*, 2005; **353(23):** 2450-2461.
35. Schumacher Jr HR, Becker MA, Lloyd E, MacDonald PA, et al. *Rheumatology*, 2009; **48:** 188-194.
36. Grabowski B, Khosravan R, Wu JT, Vernillet L, et al. *Br J Clin Pharmacol*, 2010; **70(1):** 57–64.
37. Khosravan R, Grabowski B, Wu JT, Joseph-Ridge N, et al. *Br J Clin Pharmacol*, 2007; **65(3):** 355–363.
38. Khosravan R, Wu JT, Joseph-Ridge N, Vernillet L. *J Clin Pharmacol*, 2006; **46(8):** 855-866.