

Febuxostat—A new drug for an old disease

Learning Objectives

1. Present an overview of gout and its standard therapy.
2. Highlight febuxostat pivotal trials.
3. Identify febuxostat potential adverse effects and the ramifications in patient's care.
4. Define the place of febuxostat in the treatment of gout.

Epidemiology

Gout, also referred as gouty arthritis, is one of the oldest recognized diseases. It was first identified by the Egyptians in 2640 BC and its legendary association with rich food and excessive alcohol has coined the historic name of "Disease of Kings" or "Rich Man's Disease". It is one of the most common forms of inflammatory arthritis affecting approximately 1% of the general population in Western countries.¹ Although a worldwide disease, the condition is more widespread among African Americans, Pacific Islanders, Filipinos, Taiwanese-Aborigines and Samoans. In the U.S., according to the 1996 National Health Interview Survey, gout was reported by 2.24% of people between the ages of 45-64 years and 3.17% of those 65-74 years of age.² Based on the results of the same survey, and the 2005 population estimates from the Census Bureau, approximately 3.0 million adults in the U.S. were affected in the previous year and over 6.0 million have had gout.³ Both prevalence and incidence of gout are projected to be increasing worldwide.^{4,5} In the U.S., within the last 2 decades, the annual incidence rate increased from 45.0/100.000 in 1977-1978 to 62.3/100.000 in 1995-1996.⁶ The condition is rarely seen in children but affects adults of both sexes. The prevalence is 3 times higher in men than non-menopausal women, although male to female ratio as high as 8:1 has been reported.⁷ The highest prevalence is being observed in middle-aged men and post-menopausal women.⁶ There is a direct correlation between risk of gout and advancing age in both male and female populations.

The Disease

Gout is caused by an abnormality in uric acid metabolism that is clinically characterized by precipitation and deposition of uric acid in the synovial joint spaces, peri-articular structures, or other connective tissues.⁸ Uric acid, a waste product of purine nucleotide catabolism and diet protein, is soluble in the blood at a concentration of approximately 7 mg/dl. At higher concentrations, it generally precipitates with formation of monosodium urate crystals. These typical needle-like crystals trigger a phagocytic process resulting in a highly inflammatory arthritis, gouty arthritis. Contributory factors favoring the development of deposition of intra-articular crystals include intra-articular lower temperature, dehydration, presence of chondroitin, insoluble collagens, and proteoglycans.⁸ The risk of crystal formation also increases with an increase in the serum urate concentration (sUA).

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Table 1: Percentage of Patients Reaching Primary End Point sUA <6 mg/dl

Trial	n	Duration of Trial	Febuxostat				Allopurinol	Placebo
			40 mg	80 mg	120 mg	240 mg		
Phase 2**	153	4 weeks	56%	76%	94%		0%	
FACT *** †	762	52 weeks		53%	62%		21%	
APEX ***	1072	28 weeks		48%	65%	69%	22%	0%
With CrCl<90 ml/min				44%	46%	60%	0%	
CONFIRMS**	2269	24 weeks	45%	67%			42%	
With CrCl<90 ml/min			50%	72%			42%	

† At final visit among patients with renal impairment (CrCl<90 ml/min), 77% of patients on febuxostat achieved primary end point compared to 45% in the allopurinol group.

** At final visit

*** At last three monthly visits

The incidence of crystal formation in healthy male subjects with a urate level neighboring solubility threshold (<7.0 mg/dl) is low (0.1 %) compared to 4.9% in subjects with sUA level \geq 9.0 mg/dl and 0.5% incidence in people with sUA level 7.0-8.9 mg/dl.⁷ Hyperuricemia is defined as sUA level >7 mg/dl in male and postmenopausal women and >6 mg/dl in pre-menopausal female. It is the most important risk factor for gout, although cases of gout with normal sUA have been reported.⁹ Elevated sUA may result either from an imbalance between the intake or production of purine and the elimination of purine by-products or a combination of reduced excretion and overproduction. Up to 70% of urate is eliminated by the kidneys and renal under-elimination accounts for 90% of the incidence of hyperuricemia. Nephropathy due to exposure to low-dose environmental lead and cyclosporine has been found to decrease urate excretion, therefore increasing hyperuricemia and gout incidence. Aspirin at high dose (>3 gm daily) is uricosuric but a low-dose regimen (75 mg/daily) has been shown to decrease uric acid excretion by 15%, leading to an increase in serum urate level and gout incidence. Long-term use of diuretics decreases excretion and increases reabsorption of urate, resulting in an increased risk of gout, however, the findings from a recent case-control study do not support the independent association of diuretics with an increase risk of gouty arthritis.^{10,11} Other potential medications linked to hyperuricemia include levodopa, pyrazinamide, ethambutol, and niacin.⁸ Overproduction of uric acid, leading to increased risk of gout, has been observed in patients with lymphoma or other lymphoproliferative disorders due to augmentation in nucleoprotein turnover and in patients with psoriasis, a disease with high cellular proliferation. Overproduction of uric acid can also be observed in people with excessive alcohol consumption, notably beer, high ingestion of fructose or high intake of animal purine-rich foods (organ meats, anchovies, herring, scallops).^{12,13} Aside from genetic abnormalities, increased age and male gender status, other significant risk factors for the development of hyperuricemia and gout include hypertension, increased body mass index (BMI), obesity, metabolic syndrome, hypercholesterolemia, renal insufficiency and hypothyroidism.⁸

During the first phase of the disease which can last up to 20-30 years, the patient is hyperuricemic but pain free, and asymptomatic.¹⁴ High sUA level is a common biomedical abnormality and is not necessarily an indication for treatment; only 25% of hyperuricemic adults progress to acute gout. The second phase of gout is characterized by a series of attacks, each followed by a period of quiescence. Typically, the first acute gout attack presents at night, with the patient being awakened by a sudden increasing intense pain of the first metatarsophalangeal joint of the big toe of one foot, accompanied by fever, chills and malaise. The joint is tender, red, warm and swollen. This monoarticular acute condition usually subsides spontaneously within a week to 10 days. After a pain free period of quiescence, usually lasting 2-3 years, the patient gets a second attack. Subsequent attacks are closer in time, less intense but last longer and can involve more than 1 joint. Although 50% of the initial attacks involve the first toe, patients with first gouty attacks can also initially present with inflammatory joint of the instep, ankle, knee, elbow, finger or wrist. Sudden change in synovial concentration of urate caused by overindulgence of rich food and alcohol, recent use of thiazide or loop diuretics, serious medical illness, and surgery have been all considered potential triggers for acute gouty attacks. On the average, after a period of 10-12 years of acute intermittent gouty attacks, chronic gouty arthritis sets in. The patient is now in constant pain and has limited joint mobility. This third phase is characterized by the destruction of bone and cartilage with the formation of nodular masses of uric acid crystals, also known as tophi, in the surrounding areas of the joints, bones, or under the skin and are commonly seen in various locations such as the elbow, fingers, knee, ankle, toes, and helix of the ear. Although rare, tophaceous deposits can also develop in the spine or internal organs, such as kidney, pancreas, or heart. Left untreated, long-term chronic gout can lead to urolithiasis and permanent damage to kidneys or joints.¹⁴ Most gout patients have numerous coexisting medical conditions ranging from hypertension, metabolic syndrome, cardiovascular disease, hypercholesterolemia, obesity or diabetes.

A preliminary diagnosis of acute gouty arthritis based on the presence of sudden arthritis of a joint reaching maximum inflammation within 8-12 hours, hyperuricemia, symptomatic swelling and redness of a joint, excruciating pain, chills, fever, shivering, and gnawing pain—must be confirmed by the identification of typical needle-shaped monosodium urate crystals in the synovial fluid, connective tissue tophi or the kidneys.¹⁴ Although most patients are hyperuricemic during an acute attack, hyperuricemia is not a specific or sensitive indicator of acute gout. Up to a third of the patients have a normal serum uric acid value at presentation of the attack and some patients are even hypouricemic.

Current Standard Therapeutic Options

Optimal management of gout involves provision of a quick and safe resolution of inflammation and pain, prevention of recurrent attacks, and prevention of tophi which potentially lead to destructive arthropathy and kidney damage. Treatment of underlying coexisting medical conditions and modification of diet and life style must also be considered.

Oral colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and systemic glucocorticoids have been recognized as effective in rapidly relieving symptoms of acute gout.^{14,15} When given early, at the first sign of the attack, colchicine and NSAIDs are equally effective. Typically the colchicine regimen starts with 0.6 mg-1.2 mg given orally followed by 0.6 mg hourly or 1.2 mg every 2 hours until relief of inflammation and articular pain or until gastrointestinal discomfort and diarrhea occurs.¹⁶ The usual total amount of colchicine needed to abate an attack ranges from 4-8 mg. The only NSAIDs approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute gout are: naproxen 750 mg initially followed by 250 mg three times daily (tid), naproxen sodium 825 mg initially followed by 275 mg tid, non-sustained release indomethacin 50 mg tid and sulindac 200 mg twice daily.¹⁷ Glucocorticoids given orally, intra-articularly, intramuscularly (IM) or intravenously (IV) are good alternatives for patients intolerant or not responding to colchicine or NSAIDs. A second goal in the treatment consists of lowering and maintaining serum uric acid concentration below saturation point to increase the dissolution of formed crystals and prevent further formation of tophi. The usually recommended goal for serum uric acid concentration is less than 6.0 mg/dl. Allopurinol, a xanthine oxidase inhibitor, has been the antihyperuricemic agent of choice for the last 40 years. Typically, 300-400 mg given orally once a day is effective in most patients with hyperuricemia caused by either overproduction or underelimination of urate. The maximum recommended dose is 800 mg/day. Allopurinol is not well tolerated; overall, up to 20% of patients have reported side effects and the treatment-related withdrawal rate is high (5%). Along with potentially severe hypersensitivity syndrome and rash, nephrotoxicity and hepatotoxicity limit the use of this drug. Allopurinol dosage should be individualized in older patients and renally impaired subjects. The treatment of co-existing diseases

Table 2: CONFIRMS Study Cardiac Event Rate

Cardiac Events	Febuxostat		Allopurinol n = 756
	40 mg (n = 757)	80 mg (n = 756)	
APTC pre-defined events:	0 (0%)	3 (0.4%)	3 (0.4%)
Cardiac Death	0 (0%)	0 (0%)	2 (0.26%)
Myocardial Infarction	0 (0%)	1 (0.13%)	1 (0.13%)
Stroke	0 (0%)	2 (0.26%)	0 (0%)
Non-APTC events:			
Unstable angina, transient ischemic attack, congestive heart failure, arrhythmia, coronary revascularization, venous arterial thromboembolism	10 (1.3%)	9 (1.1%)	7 (0.9%)

and life style modification in gouty subjects are beyond the scope of this article.

A New Drug, Febuxostat

The FDA has recently approved febuxostat (Uloric™) for the treatment of patients with chronic hyperuricemia and gout.¹⁸ The approval was based on the results of a dose-ranging study, three phase-3 clinical trials along with two long term extension studies. Febuxostat is a non-purine, xanthine oxidase inhibitor. It inhibits the conversion of hypoxanthine to xanthine and of xanthine to uric acid leading to a lower uric acid serum level in hyperuricemic patients. In contrast to allopurinol, the first xanthine oxidase inhibitor, febuxostat, is selective and does not inhibit other enzymes in the purine and pyrimidine pathways.¹⁹

After oral administration, the estimated absorption is approximately 50% and peak concentrations are reached within 1-1.5 hours. Plasma concentration and area-under-the-curve (AUC) increase proportionally with the dose. Plasma protein binding is high (99%) and the apparent volume of distribution is 0.7 L/kg. The mean terminal elimination half-life is 5-8 hours.²⁰ Febuxostat is mainly metabolized by the hepatic system via conjugation and oxidative metabolism. On the average <5% of febuxostat is excreted in the urine and 12% in the feces as unchanged drug. No dose adjustment is needed with respect to age and gender.²¹ Food and antacids containing magnesium and aluminum hydroxide decrease absorption rate of febuxostat without causing a clinically significant change in the febuxostat hypouricemic effect²². Xanthine oxidase substrate drugs such as azathioprine, mercaptopurine or theophylline are contraindicated in patients treated with febuxostat, due to a potential increase in serum levels of the former drugs.²⁰ No significant pharmacokinetic interaction between febuxostat and indomethacin or naproxen was reported. Naproxen can cause a clinically insignificant increase in febuxostat plasma concentration but no dose adjustment is needed when the drugs are given together.²³ Although febuxostat is primarily metabolized by the hepatic system, no dose adjustment is necessary for patients with mild to moderate liver impairment.²⁴ Renal impairment has little impact on the pharmacodynamics and pharmacokinetics of febuxostat and no dose adjustment is necessary in patients with mild to moderately impaired kidney function.²⁵

Phase-2 Dose-Ranging Trial

The clinical activity of febuxostat was demonstrated in a 28-day phase-2 randomized, double-blind, placebo-controlled, dose-response clinical trial involving a total of 153 adults with gout and hyperuricemia caused by uric acid under-excretion and over-

production.²⁶ The population was predominantly white (87%), male (89%) with an average mean age of 54 years and mean baseline serum urate of 9.65 mg/dl. Hyperuricemia was caused by underexcretion of urate in most cases (77%). The main exclusion criteria were serum creatinine >1.5 mg/dl, active liver disease or hepatic dysfunction. The most frequent co-existing conditions included hypertension, hyperlipidemia, cardiovascular disease, and obesity. Eligible subjects were randomized to receive febuxostat 40 mg, 80 mg, 120 mg or placebo (n = 37, 40, 38 and 38 respectively) orally once a day for 4 weeks. The primary end point was the percentage of patients with sUA <6.0 mg/dl at the last visit day. Colchicine 0.6 mg orally twice a day was given during the 2 week pre-randomization during washout period and for 2 weeks after randomization to prevent gout flares. At 28 days, the percentage of patients reaching sUA <6.0 mg/dl, was statistically higher in all three febuxostat groups when compared to placebo group (56 %, 76%, 94% and 0% respectively for febuxostat 40 mg, 80 mg, 120 mg and placebo (p < 0.001 for all). A dose-dependent response was observed in the febuxostat group. Treatment with febuxostat was associated with a statistically higher reduction from baseline of mean sUA concentration and uric acid urinary excretion when compared to placebo (p < 0.001 for all doses). Compared with the placebo group, the incidence of gouty arthritis flares was the same in the febuxostat 40-mg arm (37% and 35% respectively) but increased in groups given higher dosages (43% and 55%). The majority of the gout flare incidents occurred when colchicine was not being given. The overall pattern of adverse events was not significantly different between febuxostat and placebo, although, a higher incidence of treatment-related mild to moderate increase in liver function tests was reported in all febuxostat groups (1/40 and 1/38 patients in febuxostat 80-mg and febuxostat 120-mg groups and 2/37 patients in febuxostat 40-mg vs. 0/38 in patients receiving placebo). The other most frequently observed side effects included mild to moderate abdominal pain and diarrhea. Drug discontinuation was reported in 1/38 (3%) patients in the placebo, 1/37 (2%) in the febuxostat 40-mg, 2/40 (5%) in the febuxostat 80-mg and 2/38 (5%) in the febuxostat 120-mg groups. A potentially treatment-emergent serious adverse effect, Guillain-Barre syndrome, was reported in 1 patient treated with febuxostat 80 mg. No deaths were reported.

Febuxostat appeared to be well tolerated and superior to placebo in lowering sUA in patients with hyperuricemia and gout.

Pivotal Studies

The efficacy and safety of oral febuxostat was compared with that of allopurinol in a phase-3 randomized non-inferiority trial (FACT study) involving a total of 762 patients with gout or a history of gout and hyperuricemia (sUA ≥ 8.0 mg/dl).^{27,28} Baseline characteristics were adult patients with an average mean age of 51.8 years old, 96% white, BMI ≥ 30 (62.5%), mean baseline sUA 9.84 mg/dl. Preexisting conditions were frequent among eligible patients: hypertension (44%), atherosclerotic cardiovascular disease (10%), mild renal impairment (35.2%—estimated creatinine clearance <80 ml/min per 1.73 m²) and hyperlipidemia (34%). Excluded were patients with estimated creatinine clearance rate <50 ml/minute or serum creatinine >1.5 mg/dl, active liver disease or alanine aminotransferase (ALT) or aspartate aminotransferase

Table 3: Percentage of Patients with Abnormal Hepatic Tests

Trial	n	Febuxostat				Placebo	Allopurinol
		40 mg	80 mg	120 mg	240 mg		
Phase 2	153	5%	3%	3%		0%	
FACT	762		4%	5%			4%
APEX	1072		6%	4%	4%	2%	6%
CONFIRMS	2269	8%	7%				7%

(AST) level 1.5 times above the upper normal limit. After a two-week washout period, eligible subjects were randomized to receive a daily dose of febuxostat 80 mg (n = 256), febuxostat 120 mg (n = 251) or 300 mg fixed-dose allopurinol (n = 253) for 52 weeks. Colchicine (0.6 mg once a day) or NSAID (naproxen 250 mg bid) was given to prevent treatment-initiated gout flares during the washout period and the first 8 weeks of therapy. The primary efficacy end point, defined as a decrease in sUA to <6 mg/dl at the last 3 monthly measurements, was achieved in 136/255 (53%) of patients given the lower dose of febuxostat, 154/250 (62%) in the higher dose and 53/251 (21%) in the allopurinol group (p < 0.001 for each dose of febuxostat compared to allopurinol). By week 52, 74% and 80 % of the patients given febuxostat 80 mg and febuxostat 120 mg, respectively, had lowered their sUA to less than 6 mg/dl compared to 36% in the allopurinol group (p < 0.001). At the end of the trial no significant difference was detected between the febuxostat and allopurinol groups with respect to percentage reduction from baseline of tophus area and number of tophi. During the first 8 weeks of the trial, the incidence of gout flares was significantly higher in patients treated with febuxostat 120 mg compared to the other two groups (36% versus 22% and 21%, p < 0.001 for all) but the difference was no longer statistically significant after week 9. The overall incidence of gout flares during weeks 9 through 52 was 64-70%. There was no significant difference between the three groups regarding the overall incidence of treatment-related adverse events. Mild to moderate increase in liver enzymes was observed in 13/251 patients (5%) on febuxostat 120 mg, 9/256 patients (4%) on febuxostat 80 mg, 11/253 patients (4%) on allopurinol, and led to drug discontinuation in 7, 5 and 1 patients respectively (p = 0.04 for febuxostat 120 mg vs. allopurinol). Diarrhea, the second most common adverse event, was reported in 3% of the patients in each group. Other frequent adverse events included arthralgia, rash and nausea. No statistically significant difference was seen in the incidence of serious adverse events between the three arms. Two deaths, including 1 cardiac death, occurred in both febuxostat groups. No deaths were observed in the allopurinol group (p = 0.31). There was a high discontinuation rate in the study with 88 of 257 subjects receiving febuxostat 80 mg, 98 of 251 subjects receiving febuxostat 120 mg, and 66 of 254 in the allopurinol treatment group (p = 0.003 for febuxostat 120 mg vs. allopurinol). Febuxostat 80 mg and 120 mg were more effective than allopurinol (300 mg) in lowering sUA in patients with hyperuricemia and gout, but there was no difference in the incidence of gout flares or in the reduction of tophus area, and there was a dropout rate of almost 40%.

APEX, the second pivotal trial, compared the safety and efficacy of febuxostat to allopurinol or placebo in 1,072 patients with gout and hyperuricemia (sUA ≥ 8.0 mg/dl).^{28,29} Overall population baseline characteristics, main inclusion and exclusion criteria were similar to that of the FACT study with the exception of the inclusion of a small number of patients (3-4%) with mild to moderate chronic kidney disease (SCr >1.5 and ≤ 2.0 mg/dl) and a

higher percentage of patients with a history of cardiovascular disease (13.8%), hypertension (47%) or carrying multiple risk factors (obesity, diabetes, hyperlipidemia, or elevated BMI). After a 2-week washout period, eligible patients were randomized to receive 28 weeks of daily oral febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, allopurinol (300 mg or 100 mg if serum creatinine >1.5 mg/dl and <2.0 mg/dl) or placebo. Colchicine or naproxen was given to prevent gout flare during the washout period and the first 8 weeks of the treatment. At the last three visits, significantly more patients treated with febuxostat had lowered their sUA to <6.0 mg/dl compared to the allopurinol and placebo counterparts [126/262 (48%), 175/269 (65%) and 92/134 (69%)] for febuxostat 80 mg, febuxostat 120 mg and febuxostat 240 mg compared to 60/268 (22%) and 0/134 (0%) respectively for allopurinol and placebo ($p \leq 0.001$ for all doses of febuxostat compared to allopurinol or placebo and allopurinol compared to placebo). The difference remained statistically significant at the last visit ($p \leq 0.05$). Within the febuxostat groups, a significantly higher percentage of patients on febuxostat 240 mg achieved the goal at the final visit (92% vs. 72% and 79% respectively for febuxostat 80 mg and febuxostat 120 mg; $p \leq 0.05$ for all). Among patients with renal impairment, 4/9 (44%), 5/11 (45%) and 3/5 (60%) patients on febuxostat 80 mg, 120 mg and 240 mg achieved the primary end point compared to zero percent in both the placebo and allopurinol groups ($p \leq 0.001$ for febuxostat 120 mg vs. allopurinol or placebo; $p \leq 0.05$ for febuxostat 240 mg and febuxostat 80 mg vs. allopurinol or placebo). At week 28, there was no between group difference in reduction of number of tophi and percentage reduction of tophus size from baseline with the exception for the mean change in number of tophi in patients treated with febuxostat 120 mg compared to placebo ($p \leq 0.05$). The decrease in sUA level from baseline at week 28 was significantly higher in all patients on febuxostat compared to allopurinol or placebo ($p \leq 0.05$ for all). The occurrence of adverse events was similar among all groups; upper respiratory tract infection is the most common (15-20%) followed by musculoskeletal side effects (9-10%), and diarrhea (6-13%). Patients assigned to febuxostat 240 mg reported a significantly higher incidence of diarrhea (13%) compared to subjects receiving febuxostat 80 mg (6%), febuxostat 120 mg (7%) and allopurinol (6%) ($p \leq 0.05$ for all). The incidence of drug withdrawal related to diarrhea was the highest in the febuxostat 240-mg group (3%) compared to 1% in the febuxostat 80-mg group and <1% in febuxostat 120-mg arm. A higher incidence of mild to moderate abnormal liver function tests was observed across all patients receiving active treatments (4%-6% vs. 2% in the placebo) leading to 1% withdrawal in both febuxostat 120 mg and allopurinol groups and 2% in patients receiving febuxostat 80-mg. Chest pain, coronary artery disease, myocardial infarction and atrial fibrillation were reported in patients of all 5 groups. These rare serious cardiovascular adverse events (<1%) were not considered to be treatment-related but caused 1 patient on febuxostat 80 mg and 2 on febuxostat 120 mg to withdraw. A serious drug-related increase in serum creatinine (up to 1.5 mg/dl) was observed in one patient receiving febuxostat 240 mg, but the level returned to normal limits upon lowering febuxostat dose to 120 mg. Premature withdrawal rates in this study were 25% for placebo, 35% for febuxostat 80 mg, 26% for febuxostat 120 mg, 36% for febuxostat 240 mg and 21% for allopurinol. The febuxostat 80 mg and 240 mg withdrawal rates were significantly higher than allopurinol or febuxostat 120 mg. The febuxostat 80-

mg group also had a significantly higher withdrawal rate than placebo.

The results of this second pivotal trial provide further evidence that febuxostat at doses 80 mg, 120 mg and 240 mg is more effective than allopurinol and placebo in lowering sUA in patients with hyperuricemia and gout. During this relatively short study, there was no significant benefit of febuxostat compared to allopurinol for clinical outcomes related to gout flares or reduction of tophi, but there was a greater premature withdrawal rate with febuxostat.

The third pivotal Trial, CONFIRMS, was a large randomized, double-blind, active-controlled, parallel-group study comparing the safety and efficacy of febuxostat 40 mg or 80 mg to that of allopurinol in over 2,000 patients with normal, mild (creatinine clearance 60-89 mL/min) or moderate (creatinine clearance 30-59 mL/min) renal function with hyperuricemia and gout.³⁰ At the same time, the study addressed the concerns the FDA had during the febuxostat approval process, mainly, the higher incidence of cardiovascular thromboembolic adverse events and deaths compared to the control arms.³¹ At the time of this writing, the study has not been published. Inclusion criteria were similar to the previous 2 pivotal trials (gout or a history of gout and hyperuricemia). Comparable main exclusion criteria were used (CrCl<30 ml/min, active liver disease or ALT or AST 1.5 times higher than the upper limit of normal). Two thousand two hundred sixty-nine subjects were randomized to receive febuxostat 40 mg (n = 757), febuxostat 80 mg (n = 756) or allopurinol 300/200 mg (200 mg if renally impaired, n total = 756) for 6 months. Gout flare prophylaxis (colchicine 0.6 mg/once a day or naproxen 250 mg bid—lansoprazole 15 mg daily) was provided during the 30-day washout period in patients previously on anti-gout therapy and for the duration of the trial in all patients. Overall baseline demographics were similar to previous studies, with the exception of the inclusion of more patients with mild and moderate renal impairment [(1081/2269 (48%) and 402/2269 (18%)]. Study design was also comparable, except for a longer washout period (30 days) in patients previously on anti-gout therapy, a longer prophylaxis of gout flare lasting for the duration of the trial, and the use of lansoprazole (15 mg daily) in conjunction with naproxen for prophylaxis of gout flares. The primary end point was the percentage of patients with sUA <6.0 mg/dl at the final visit. Secondary end points included percentage of renal impaired patients with sUA <6.0 mg/dl, percentage of patients sUA <5.0, <4.0, <6.0 mg/dl at each visit and percentage of sUA level reduction from baseline at each visit. At the final visit, a significantly higher proportion of patients assigned to febuxostat 80 mg achieved the primary end point 507/756 (67%) compared to 342/757 (45%) and 318/755 (42%) respectively for febuxostat 40 mg and allopurinol; $p < 0.001$ for both comparisons. Febuxostat superiority was also observed in patients with impaired renal function; statistically more patients on febuxostat 80 mg achieved the goal when compared to allopurinol or febuxostat 40 mg (360/503 (72%) vs. 212/501 (42%) and 238/479 (50%) respectively for allopurinol and febuxostat 40 mg; $p < 0.001$ for both comparisons). Febuxostat 80 mg/day was statistically also superior to allopurinol in regards to all other secondary end points. Seventy-nine percent (598/756) of patients assigned to receive febuxostat 80 mg completed the study compared to 83% (632/757) and 82% (621/756) in the febuxostat 40-g and allopurinol group. Six percent of patients receiving febuxostat 40 mg discontinued therapy due to adverse events compared to 8% in both the febuxostat 80-mg and

allopurinol groups. The most frequently observed adverse events were the same as in the FACT and APEX study and included mild or moderate upper respiratory tract infection, abnormal liver function tests, diarrhea and arthralgia. The incidence of serious adverse events is higher in the allopurinol group (4.1%) compared to the febuxostat 40-mg and febuxostat 80-mg groups (2.5% and 3.7% respectively). Abnormal liver function tests caused withdrawal in 5.4% (14/757), 8.4% (9/756) and 10.8% (7/756) patients receiving respectively febuxostat 40 mg, 80 mg and allopurinol. The rate of overall cardiovascular adverse events was identical in the febuxostat 80-mg and allopurinol groups (n = 3; 0.40%) and no cardiovascular event was observed in febuxostat 40-mg patients. Two cardiovascular deaths (0.26%) were reported from the allopurinol group compared to none in the febuxostat arms. One nonfatal myocardial infarction occurred in both allopurinol and febuxostat 80-mg arms. Non-fatal stroke was reported in 2 patients (0.26%) on febuxostat 80 mg but none in the other groups. Other cardiovascular events such as angina, revascularization, non-fatal congestive heart failure, arrhythmia or transient ischemic attack occurred in 1.3%, 1.1% and 0.9% of patients on febuxostat 40 mg, 80 mg and allopurinol respectively. None of the differences were statistically significant. In this large trial where the pre-specified Antiplatelet Trialists' Collaboration (APTC) cardiovascular adverse event criteria were used, the incidence of cardiovascular and thromboembolic adverse events was still modest and contrary to the two previous trials, no increase in cardiovascular thromboembolic events was observed when compared to controls (see Table 2). Febuxostat 40 mg is as effective as allopurinol in reducing sUA, febuxostat 80 mg is more effective than allopurinol, and both are superior to allopurinol in patients with mild to moderate renal impairment. Discontinuation of drug therapy due to an adverse event occurred in 49/757 (6%) patients on febuxostat 40 mg, 61/756 (8%) patients on febuxostat 80 mg and 64/756 (8%) patients on allopurinol.

The findings of an open-label 5-year follow-up extension study (FOCUS) in 116 subjects showed that febuxostat 40 mg, 80 mg and 120 mg remained effective in lowering sUA in most patients (up to 82%) with hyperuricemia and gout.³² There was near complete absence of gout flares by the end of the study and tophi were reduced. Premature discontinuation of the study occurred in 58 (50%) of the subjects, 38 discontinued within the first year. Thirteen of the discontinuations were due to an adverse event. No death was reported during the study.

The results of a 40-month long-term open-label study (EXCEL) in 1086 patients concluded that more patients on febuxostat 80 mg (n = 606) and febuxostat 120-mg (n = 388) had a sustained response; 75%-83% compared to 53% for allopurinol (n = 92).³³ Gout flares were essentially eliminated and tophi improved over time. Premature discontinuation rates in this study were 32%, 44%, and 62% for the febuxostat 80-mg, febuxostat 120-mg, and allopurinol treatment groups respectively. The incidence and magnitude of cardiovascular adverse events and abnormal hepatic enzymes test did not increase over time and did not differ significantly between treatments.

Conclusion

The FDA approved febuxostat for the management of chronic hyperuricemia in patients with gout. The recommended starting dose is 40 mg orally daily increased to 80 mg once daily after 2 weeks of therapy if the goal of a serum uric acid of less than 6 mg/dl is not achieved. No dose adjustment is needed in elderly

people or subjects with mild to moderate renal or hepatic impairment. Monitoring of liver function and cardiovascular adverse events is recommended (Tables 2, 3). Of note, current guidelines from the National Institute of Health and Clinical Excellence (NICE) recommend febuxostat (80 mg-120 mg daily) only for patients who are intolerant to allopurinol side effects or for whom allopurinol is contraindicated and at the same time preclude its use in patients with congestive heart failure or ischemic heart disease.³⁴ Febuxostat may provide some therapeutic advance for the management of chronic hyperuricemia and gout, however, more comparative data are needed on long-term safety and on improvements in gout flares and other complications of gout. The studies comparing febuxostat to allopurinol did not use optimized doses of allopurinol, therefore it is difficult to conclude that it is more effective. However, the current practice of dosing allopurinol is most often typical of the fixed study doses of 300 mg, therefore these present studies indicate a need to reconsider dose optimization of allopurinol in practice. Febuxostat appears to be generally well-tolerated and to efficiently lower sUA, but the early discontinuation rates in the trials have been rather high at 30% to 50%. One potential advantage with febuxostat is in the treatment of patients with mild to moderate renal disease, but the amount of data in these patients is limited. No clinical trials have been done comparing it with a non-fixed allopurinol dose and no data are available regarding its use in patients with severe renal or liver disease. Febuxostat is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline. Febuxostat is not recommended for use in patients in whom the rate of urate formation is greatly increased such as with malignant disease and its treatment. The development of febuxostat has highlighted the need for more appropriate management of gout and achievement of optimal treatment goals.

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IDIS/Web Descriptor Lookup Enhancement

Effective July 2009: Descriptor definitions are now available on the *IDIS/Web* descriptor look-up page. To access the definitions in this way click the "Look Up" button at the end of the Descriptor field on the Search page. Then on the Descriptors/Definitions look-up page, click on the descriptor term to view the complete definition. Click on the term again to remove the definition from your page. Descriptor definitions are also available by clicking the Descriptor Definitions link on the left side of the Search page.

ASSESSMENT QUESTIONS



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1. Gout is one of the oldest recognized diseases and:
 - a. Is the most common form of inflammatory arthritis.
 - b. Is two times more common in children than adults.
 - c. Is widespread among Caucasians.
 - d. Its incidence and prevalence are decreasing within the last 2 decades.
2. Gout is caused by precipitation of uric acid and:
 - a. Deposition of urate in internal organs.
 - b. Deposition of urate in synovial joint spaces.
 - c. Deposition of urate in connective tissues.
 - d. All of the above.
3. Gout can be triggered by a sudden change in urate concentration. Potential triggers include:
 - a. Food rich in purine such as scallops or organ meats.
 - b. Surgery and serious illness.
 - c. Use of certain diuretics.
 - d. All the above.
4. Allopurinol has been the cornerstone for the treatment of chronic hyperuricemia and gout. Which of the following statements is true about allopurinol:
 - a. No dose readjustment is needed in patients with renal impairment.
 - b. Usual dose is 600 mg orally daily.
 - c. It is effective in patients with hyperuricemia caused either by overproduction or underexcretion of urate.
 - d. Most people on allopurinol do not experience side effects.
5. Which of the following statements is true regarding acute gouty arthritis:
 - a. Usually the inflammation subsides within weeks.
 - b. The pain cannot be treated with NSAIDs.
 - c. Colchicine is generally given IV.
 - d. Colchicine starting dose (0.6–1.2 mg orally at the first sign of the attack) is usually followed by 0.6 mg hourly until relief of inflammation and pain or sign of gastrointestinal discomfort or diarrhea occurs.
6. Safety concerns identified in two early febuxostat pivotal trials prompting the FDA's request of additional data analysis and trial do not include:
 - a. Stroke
 - b. Cardiac death
 - c. Renal impairment
 - d. Myocardial Infarction
7. One of the most common side effects of febuxostat is abnormal liver function test. Percentage of patients experiencing an increase in liver enzymes level is approximately:
 - a. 10%
 - b. 1%
 - c. 20%
 - d. 3% to 8%
8. Side effects commonly reported by patients on febuxostat do not include:
 - a. Arthralgia
 - b. Diarrhea
 - c. Nephropathy
 - d. Nausea
9. The National Institute of Health and Clinical Excellence recommends the use of febuxostat in patients with hyperuricemia and gout. Which of the following statement is true:
 - a. The dose range is 80-120 mg.
 - b. Patients were previously intolerant to allopurinol.
 - c. Febuxostat is contraindicated in patients with congestive heart failure.
 - d. All of the above.
10. Febuxostat has been approved by the FDA in the treatment of hyperuricemia and gout. Which of the following statements is true:
 - a. The recommended dose is 40 mg daily, increased to 80 mg, if there is no response after 2 weeks.
 - b. The dose needs to be individualized, especially in older patients and subjects with mild and moderate renal impairment.
 - c. The drug is well tolerated and no monitoring of liver function and cardiac adverse effect is necessary.
 - d. Febuxostat is the third xanthine oxidase inhibitor approved by the FDA.

New Molecular Entities & Biologicals

FDA Approvals
May 2009–July 2009

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor 155 FDA APPROVAL PACKAGE in combination with the valid drug term to retrieve these documents from the *IDIS* database.

For some newly approved drugs the FDA Approval Package may not yet be available. If the medication has been reviewed by one of the FDA Advisory Committees you may still access data from pivotal studies, even those that have not been published in peer reviewed literature. These Committee reports are indexed in the *IDIS* database using the descriptor “FDA ADVISORY COMMITTEE 164”. In addition to access to data from pivotal studies, these reports provide critical commentary from the Advisory Committee members, and specific, important questions related to the use and safety of the medication.

Generic Name Trade Name (FDA Review Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Besifloxacin Hydrochloride <i>Besivance</i> (S)	Bausch and Lomb (May 28, 2009)	BESIFLOXACIN 8122036 FDA approved indication (7 citations) Total (7 citations)	Bacterial conjunctivitis. Ophthalmic susp	Conjunctivitis, Acute 372.0
Canakinumab <i>Ilaris</i> (BIOL)	Novartis Pharms (June 17, 2009)	CANAKINUMAB 82000516 FDA approved indication (1 citation) Total (1 citations)	Cryopyrin-associated periodic syndromes (CAPS) Subcutaneous inject	Urticaria NEC 708. Amyloidosis 277.3 Hearing Loss, Sensorineural 389.1
Dronedaron <i>Multaq</i> (P)	Sanofi Aventis US (July 1, 2009)	DRONEDARONE 24040225 FDA approved indication (29 citations) Total (35 citations)	Atrial fibrillation. Oral Tablet	Fibrillation, Atrial 427.3
Prasugrel <i>Effient</i> (P)	Effient (July 10, 2009)	PRASUGREL 20120672 FDA approved indication (47 citations) Total (117 citations)	Acute coronary syndrome being managed with percutaneous coronary intervention. Oral tablet	Infarction, Myocard, Acute 410.
Tolvaptan <i>Samsca</i> (S)	Otsuka America Pharm (May 19, 2009)	TOLVAPTAN 40280035 FDA approved indication (32 citations) Total (70 citations)	Hypervolemic or euvolemic hyponatremia. Oral tablet	Hyposmolality/Hyponatremia 276.1

Review Classification:

S=Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

AA=Accelerated Approval

FT=Fast Track

P=Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL=Biological

O=Orphan



Dr. Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

Selected Bibliography

Besifloxacin

Karpecki P, DePaolis M, Hunter JA, et al. Besifloxacin ophthalmic suspension 0.6% in patients with bacterial conjunctivitis: a multicenter, prospective, randomized, double-masked, vehicle-controlled, 5-day efficacy and safety study. *Clinical Therapeutics*. 2009; 31:514-526. (IDIS Article Number 617306). *An intent-to-treat population of 118 patients with acute bacterial conjunctivitis was randomized to topical besifloxacin ophthalmic suspension (n = 60) or vehicle (n = 58) administered 3 times/day for 5 days. The primary endpoint was clinical resolution and eradication of the bacterial infection by day 8 in culture-confirmed patients. At day 8, clinical resolution of the baseline infection was seen in significantly more patients given besifloxacin ophthalmic suspension compared with vehicle (44/60 [73.3%] versus 25/58 [43.1%], respectively; p < 0.001). Besifloxacin also showed significantly greater rates of bacterial eradication compared with vehicle (53/60 [88.3%] versus 35/58 [60.3%]; p < 0.001). Frequency of adverse events were similar in both groups.*

Canakinumab

Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the Cryopyrin-Associated Periodic Syndrome. *N Engl J Med*. 2009; 360:2416-2425. (IDIS Article Number 619108)

This randomized, double-blind, placebo controlled, 48-week study was conducted in 3 parts. Part 1: Thirty-five cryopyrin-associated periodic syndrome (CAPS) patients received 150 mg canakinumab subcutaneously, and those with complete response went on to part 2. In part 2, patients were randomized to receive 150 mg canakinumab subcutaneously or placebo every 8 weeks for up to 24 weeks. Patients who did not relapse went on to part 3 in which they received at least 2 more doses of the study drug. In part 1, 34 of the 35 (97%) patients had complete response and 31 of these went on to part 2. All 15 patients randomized to canakinumab remained in remission, while 13 of 16 patients given placebo experienced disease flares. At completion of part 3, 28 of the 31 patients (90%) were in remission.

Dronedarone

Davy J-M, Herold M, Hoglund C, et al. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J*. 2008; 156:527e1-527e9. (IDIS Article Number 603830)

In this double-blind, multicenter trial, a total of 174 patients with permanent atrial fibrillation were randomized to oral doses of 400 mg dronedarone (n=85) twice daily, or placebo (n=89), plus standard therapy for 6 months. Results showed that, compared with placebo, dronedarone significantly decreased mean 24-hour ventricular rate, with a mean reduction at day 14 of 11.7 beats per minute (p<0.0001), with reductions sustained throughout the trial. Compared with placebo, mean reduction during maximal exercise was 24.5 beats per minute (p<0.0001). Dronedarone was well tolerated and its rate control effects were additive with other rate control agents.

Prasugrel

Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009; 373:723-731. (IDIS Article Number 613478)

This trial included 3534 ST-elevation myocardial infarction (STEMI) patients from 707 sites in 30 countries. Patients were randomized to receive prasugrel (loading dose = 60 mg, maintenance dose = 10 mg, n = 1769) or clopidogrel (loading dose = 300 mg, maintenance dose = 75 mg, n = 1765). Maintenance doses were given daily for the entire 15 months of the study period, and the primary endpoint was cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. Results showed that at 30 days 115 (6.5%) of patients who received prasugrel had met the primary endpoint, compared with 166 (9.5%) of those assigned to clopidogrel (hazard ratio 0.68 [95% CI 0.54-0.87]; p = 0.0017), and at 15 months 174 (10.0%) of those on prasugrel and 216 (12.4%) of those taking clopidogrel had reached the primary endpoint, (hazard ratio 0.79 [CI 0.65-0.97]; p = 0.0221). Investigators concluded that in patients with STEMI, prasugrel is more effective than clopidogrel and is similar as to risk of excess bleeding.

Tolvaptan

Gheorghide M, Gottlieb SS, Udelson JE, et al. Vasopressin V₂-receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol*. 2006; 97:1064-1067. (IDIS Article Number 552058)

Twenty-eight hospitalized patients with serum sodium <135 mmol/L were randomized to receive oral tolvaptan (n = 17) alone starting at 10 mg/day and increased up to 60 mg/day as needed, or to fluid restriction (1,200 ml/day) plus placebo (n = 11), for up to 27 days with a 65-day follow-up. The primary endpoint was serum sodium >135mmol/L or a ≥10% increase from baseline. Mean inpatient treatment was 7 days ±3.6 days, and at the last inpatient visit, serum sodium had increased by 5.7 mmol/L in the tolvaptan group and 1.0 mmol/L in the placebo group (p = 0.0065). Adverse events were similar in both groups.

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