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VILAZODONE: A NEW TREATMENT FOR MAJOR DEPRESSIVE DISORDER

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Major Depressive Disorder (MDD) is a debilitating disease that affects patient's overall health and quality of life. This disease affects 13% – 16% of Americans through the course of their lifetime. There is an increased risk of MDD in females, middle-aged persons, those that are single, have a low income, or are unemployed or disabled. [1,2] MDD is diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. The average age of onset for this disorder is the late 20s, but onset may occur at any age. [1,2]

Many patients suffering from MDD receive delayed treatment and up to 40% receive no treatment at all.[2] First-line treatment options include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) can also be used to treat MDD, but are usually reserved for those who are unresponsive to other treatments due to their unfavorable side effect profile.[3,4]

Vilazodone (Viibryd®) is a new treatment option for MDD. It was approved on January 21, 2011 by the FDA, licensed by Merek KGaA, and distributed by Forest Labs, Inc.. Vilazodone has a novel mechanism of action: a combination of SSRI and partial agonist of serotonin receptor subtype 1A (5-HT_{1A}). Its only approved indication is for the treatment of MDD. The objective of this article is to provide information on the pharmacology, pharmacokinetics, past clinical trials, adverse events, drug interactions and dosing of vilazodone.

Pharmacology & Pharmacokinetics

The antidepressant effect of vilazodone is not fully understood. Vilazodone binds with high affinity to the presynaptic serotonin reuptake site, preventing the reuptake of serotonin from the neuronal synapse. Vilazodone shows a higher affinity for the serotonin reuptake site compared with other agents used to treat MDD (**Table 1**).[5,6] It also selectively binds to 5-HT_{1A} receptors and has partial agonist activity at this receptor subtype. Buspar®, a 5-HT_{1A} partial agonist, has been used to augment the effect of SSRIs.[7]

The pharmacokinetics have been studied in several Phase 2 trials (**Table 2**).[8] Vilazodone achieves peak plasma concentration in 4 to 5 hours after oral administration. The absorption of vilazodone is significantly affected by food. An approximately 2-fold increase in peak concentration (Cmax) and area under the concentration time curve (AUC) was seen after vilazodone was taken with food. It is important to counsel patients to take this medication with a light meal to ensure adequate drug concentrations. The terminal half is 25 hours allowing vilazodone to be dosed once daily. It is widely distrib-

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Table 1 | Binding affinity of SSRIs [5,6]

Antidepressant	Ki for serotonin reuptake site (nM)
Vilazodone	0.1
Citalopram	9.6 ± 0.5
Escitalopram	2.5 ± 0.4
Fluoxetine	5.7 ± 0.6
Paroxetine	0.34 ± 0.03
Sertraline	2.8 ± 0.8
Fluvoxamine	11 ± 1

Ki = inhibition constant, nM = nanomolar, SSRIs = selective serotonin reuptake inhibitors

uted throughout the body and is highly protein bound. These features lead it to be resistant to removal by dialysis. Vilazodone has the potential to interact with other highly protein bound medications.[8]

Vilazodone is metabolized primarily by cytochrome P450 (CYP) pathways in the liver with the majority of metabolism accomplished by CYP3A4 and minor metabolism from CYP2C19 and CYP2D6.[9] No metabolites have shown serotonergic activity or toxicity.[5] The metabolism by CYP3A4 may lead to drug-drug interactions from CYP3A4 inhibitors or inducers. No dosage adjustment is needed for mild to moderate hepatic impairment, but vilazodone has not been studied in severe hepatic impairment.[9] Only 3% of unchanged drug is excreted in the urine or feces. No dosage adjustment is required in mild to severe renal impairment. There is also no need for dosage adjustment based on the age of the patient.[8]

Clinical Trials

Vilazodone underwent two Phase 3 studies to evaluate its efficacy in MDD (Table 3). Both studies, one by Rickets et al.[10] and the other by Khan et al.[11], were 8 weeks in duration and were randomized, double-blind, placebo-controlled, multicenter trials. The patients randomized to vilazodone were titrated up from 10mg daily to 40mg per day over three weeks. The primary efficacy endpoint for both studies was the mean change in Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to week 8.[10,11] MADRS is a validated method to assess symptom outcome, and is commonly used in studies of MDD. A higher score indicates more severe disease.[12]

Rickets et al. included patients that were 18 to 65 years of age, had a diagnosis of MDD and had a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score ≥ 22 and a HAM-D-17 item 1 score of ≥ 2 at baseline.[10] In addition to MADRS change, the mean change in HAM-D-17, Hamilton Rating Scale for Anxiety (HAM-A), Clinical Global Impressions - Severity of Illness (CGI-S), and Clinical Global Impressions - Improvement (CGI-I) scores from baseline were assessed. In this trial, 410 patients were enrolled and randomized to either vilazodone or placebo. The mean reduction in MADRS score was significantly greater for vilazodone (-12.9) compared to placebo (-9.6, p=0.001). Vilazodone showed significant improvement in HAM-D-17 scores compared to placebo (-10.4 vs. -8.6, respectively; p=0.022), HAM-A (-6.6 v -5.1, p=0.045), and CGI-S scores (-1.4 vs. -1.0, p=0.001). CGI-I scores were also significantly lower in the vilazodone group (2.6 vs. 3.0, p=0.001). The beneficial effect of vilazodone was seen as early as week 1 and continued throughout the duration of the study. The authors concluded that vilazodone was effective for the treatment of MDD due to statistically and clinically significantly reducing depression symptoms.[10]

Khan et al. included 481 patients that were 18-70 years old, had a diagnosis of MDD and a current major depressive episode, and had a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score ≥ 22 and a HAM-D-17 item 1 score of ≥ 2 at baseline.[11] The primary outcome was mean change in MADRS from baseline. The investigators also monitored the mean change from baseline in HAM-D-17, HAM-D-21, HAM-A, CGI-S, and CGI-I. Patients treated with vilazodone showed a significant improvement in MADRS scores from baseline compared to placebo (-13.3 vs. -10.8, respectively; p=0.009). Statistically significant improvements over placebo were also seen for the other measures including HAM-D-17 (-10.7 vs. -9.1, p=0.026), HAM-D-21 (-11.6 vs. -9.9, p=0.029), HAM-A (-7.0 vs. -5.7, p=0.037) and CGI-S (-1.4 vs. -1.1, p=0.004). A significantly better score for CGI-I was

Table 2 | Pharmacokinetics of Vilazodone [5,8,9]

Property	Vilazodone
Tmax	4-5 hours
AUC	1645 ng*h/mL (with food)
Cmax	156 ng/mL (with food)
Terminal ½ life	25 hours
Bioavailability	72% (with food)
Volume of distribution	8 L/kg
Protein Binding	96-99%
Metabolism	CYP3A4 major, CYP2C19 and CYP2D6 minor

AUC = area under the curve, Cmax = maximum concentration, h = hour, kg = kilograms, L = liters, mL = milliliters, ng = nanograms, Tmax = time to peak concentration

also noted (2.5 vs. 2.8, p=0.004). The authors concluded these finding confirmed those of Rickets et al.[10] that vilazodone is effective for treating MDD.[11]

One limitation of these studies is the duration of treatment is only 8 weeks long.[10,11] Treatment duration for antidepressants is typically 6 to 12 months, which is much longer than those studied in these trials. In addition, these studies only assessed symptom reduction but not response or remission, which is the goal of antidepressant therapy.[3,10,11]

The phase III study entitled "A 1-Year, Open-Label Study Assessing the Safety and Tolerability of Vilazodone in Patient with Major Depressive Disorder" assessed the safety of vilazodone over one year.[13] The patients were titrated from 10mg daily up to 40mg per day over three weeks. The primary goal of this study was to assess the rate of adverse events. The researchers also looked at physical and laboratory evaluations, electrocardiograms, sexual function, and effectiveness. During this study, the most frequent adverse events were diarrhea (35.7%), nausea (31.6%), and headache (20.0%). During the study, 20.7% of patients discontinued vilazodone due to adverse events. There were no deaths during the study and most serious adverse events were not judged to be caused by vilazodone. There were no laboratory trends identified using laboratory tests and mean scores for Changes in Sexual Functioning Questionnaire (CSFQ) improved during the course of the study. To evaluate effectiveness, change in MADRS, CGI-S, and CGI-I scores from baseline were measured. Scores for all the questionnaires decreased in all three measures during the course of the study, indicating symptom improvement; however, this was not the primary outcome of the study. Although gastrointestinal side effects were frequent, they were usually mild to moderate in intensity and short in duration. The authors concluded that vilazodone was safe and well tolerated by patients.[13]

Adverse Effects

Vilazodone has a few commonly occurring side effects, the most prevalent being diarrhea and nausea. These seem to be dose related and self-limiting. To reduce the occurrence of unwanted adverse events, slow upward titration of vilazodone should be utilized. Other common adverse reactions are listed in **Table 4**. Sexual dysfunction was identified as a potential adverse event particularly in male patients, which is also seen with other SSRIs. Vilazodone has a Black Box Warning for suicidiality which is present on all antidepressant medications. Similar to the other SSRIs on the market, vilazodone has advisories for increased bleeding risk, activation of mania, and avoiding abrupt discontinuation.

Drug Interactions

Vilazodone has some important drug interactions that the prescriber should be aware of. As with all SSRIs, the use of vilazodone with MAOIs is contraindicated. Caution is advised for concomitant use of vilazodone with other medications that have serotonergic activity due to the risk of serotonin syndrome. Medications that have serotonergic activity include, but are not limited to, SSRIs, SNRIs, trazodone, ergot alkaloids, triptans, buspirone, tramadol, and tryptophan containing products.[9,14] Medications with dopaminergic activity, such as antipsychotics, can also lead to serotonin syndrome.[14] Since vilazodone is primarily metabolized by CYP3A4, other medications that inhibit or induce this enzyme may affect levels of vilazodone. The manufacturer recommends decreasing the dose of vilazodone by 50% to 20mg per day in the presence of strong CYP3A4 inhibitors such as chloramphenicol, conivaptan, dalfopristin/quinupristin, delavirdine, indinavir, itraconazole, ketoconazole, posaconazole, ritonavir, tipranavir.[9,14] Patients' doses should be lowered to 20mg per day if they experience intolerable side effects with concomitant use of a moderate CYP3A4 inhibitor.[9] CYP3A4 inducers, such as carbamazepine, phenytoin or dexamethasone, are likely to lower concentrations of vilazodone, but this effect has not been evaluated and no recommendation exists on dosage adjustments.[9,14] According to *in vitro* studies, vilazodone may inhibit CYP2C19, CYP2D6, and CYP2C8. However, as these effects have not been studied *in vivo* the clinical relevance is unknown.[9]

Table 4 | Common Adverse Reactions with Vilazodone [8,9]

Adverse Reaction	Vilazodone 40mg/day (%)	Placebo (%)
Diarrhea	28	9
Nausea	23	5
Vomiting	5	1
Insomnia	6	2
Abnormal dreams	4	1
Dizziness	9	5
Parasthesia	3	1
Tremor	2	0
Fatigue	4	3
Palpitations	2	< 1
Increased appetite	2	1
Decreased libido	4	< 1
Erectile dysfunction	2	1

Cost

The average retail cost of a 30 day-supply of Viibryd® 40mg is $147.59, with a range of $131.84 - $155.95

Summary

Vilazodone is a new treatment option for MDD. It has a novel mechanism of action since it is both an SSRI and a $5HT_{1A}$ partial agonist.[9] It seems to have similar response rates to other SSRIs, but the trials conducted were only able to evaluate short-term efficacy.[7,10,11] There is potential for drug interactions with vilazodone due to its metabolism by CYP3A4. Vilazodone is titrated up using 10mg daily for 7 days, then 20mg daily for 7 day, then 40mg daily for the duration of treatment. It must be taken with food to achieve therapeutic levels and GI side effects are common.[9] Viibryd® is expensive for a patient with no insurance and may cost up to $155.95 per month, potentially limiting its widespread use as a first line therapy for MDD.

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AN UPDATE ON THE TREATMENT OF GOUT: FOCUS ON FEBUXOSTAT'S ROLE IN THERAPY

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Historically, gout was known as the "Disease of the Kings." Due to its association with excessive alcohol and rich foods, the disease most often affected the affluent.[1] However, now that the high purine diet associated with gout is common amongst many Americans the incidence of gout has dramatically increased.[1,2] Recent NHANES data shows that as of 2008 the prevalence of gout in the US has risen to 3.9%. Currently, it affects approximately 8.3 million patients in the United States.[2] Gout also carries a significant economic burden. It is estimated that the treatment for new acute gout episodes alone in the US costs approximately $27 million per year and this does not include indirect medical costs.[3]

For treatment, there are several options for both acute gout attacks and prevention of gout flares. No new agents were introduced for years until the approval of febuxostat (FBX) in 2009. FBX, or UloricÒ, is purported to have several benefits over existing therapies for lowering serum uric acid (sUA). FBX does not require renal dose adjustment.[4] Additionally, it is

structurally unrelated to allopurinol, so it may provide a useful alternative to patients with allopurinol intolerance.[5] This article will provide an overall review of gout and explore the role of FBX in serum uric acid lowering therapy including the pharmacokinetics, dosing, adverse reactions and clinical data associated with FBX.

Etiology

Gout is a disease associated with high uric acid levels.[6] High levels of uric acid occur because humans lack the enzyme uricase. Uricase degrades uric acid to allantoin, which is more water-soluble and more easily excreted by the kidneys.[7] As body fluids become saturated with uric acid, crystallization occurs. The exact point of crystallization is dependent on a number of factors, such as body pH and temperature.[7] Most people who develop a high sUA never develop gout.[4] It is estimated that patients with a sUA of > 9 mg/dL have a 22% chance of developing gout while patients with a sUA of 7-8 mg/dL have a 3% cumulative risk of developing gout.[6] Patients on medications that raise sUA are at an increased risk for gout (**Table 1**).[7,9]

Gout affects men disproportionately.[2,8] This may be at least partially due to the protective effects of estrogen, as demonstrated by the increased rate of gout in post-menopausal women compared to their pre-menopausal counterparts. While the exact mechanism of the estrogen effect is not known, estrogen is believed to decrease the activity of a uric acid transporter, URAT1, which is responsible for reabsorption of uric acid from renal tubules.[8]

Table 1 | Drugs That Can Affect Gout [9]

Drugs that raise serum urate concentrations	Drugs that lower serum urate concentrations
Thiazide and loop diuretics	Ascorbic acid
Tacrolimus	Benzobromide
Cyclosporine	Calcitonin
Ethambutol	Citrate
Pyrazinamide	Estrogens
Cytotoxic chemotherapy	Fenofibrate
Ethanol	Losartan
Salicylates (low dose)	Probenecid
Levodopa	Salicylates (high doses)
Ribaviron and interferon	Losartan
Teriparatide	
Nicotinic Acid	
Beta-blockers	

Clinical Manifestations of Gout

There are several stages of gout (**Table 2**).[6,8,10-13] According to the American College of Rheumatology, the diagnosis of gout can be made by visualization of monosodium urate (MSU) crystals from synovial joint aspiration or tophi confirmation. However, since aspiration is not always feasible, a diagnosis should be made with high degree of certainty based on the presence of at least six diagnostic criteria (**Table 3**).[14]

Treatment Options

While there currently are no guidelines published regarding the treatment of gout, it is expected that guidelines will be released in early 2012. Preliminary guidelines were made at the American College of Rheumatology (ACR) and Association of Rheumatology Health Professionals Meeting in November 2011.[15] Presently, The European League Against Rheumatism (EULAR) has the most widely accepted recommendations regarding the treatment of gout.[16]

According to EULAR, dietary modifications are important in patients diagnosed with gout. Patients should limit their intake of high fat foods and purines as well as keep co-morbid conditions such as diabetes, hypertension, and hyperlipidemia well controlled. Oral colchicine and non-steroidal anti-inflammatory drugs (NSAIDS) are currently recommended as first line therapy for the acute treatment of gout, while probenecid, allopurinol, colchicine and FBX are used for the prophylactic treatment of gout.[16]

Notably, there has been some controversy over oral colchicine. In 1938, the Food, Drug and Cosmetic Act required all new drugs to be tested for safety before introduction to the market. However, it allowed some medications, like colchicine, that were already on the market to remain there. Until 2009, colchicine marketing was not challenged. But, when the Colcrys® manufacturer, URL Pharma, released new clinical trial data for market approval, the FDA not only gave Colcrys® market approval, but since colchicine had never been formally approved for acute gout flares or gout prophylaxis, it gave URL Pharma three-year marketing exclusivity. Due to lack of market competition, URL Pharma was able to raise its prices from the cost of generic colchicine at $0.09 per tablet to brand Colcrys® at $4.85 per tablet.[17]

There is debate over the choice of specific NSAIDs in the treatment of gout. Traditionally, indomethacin has been used for gout; however all NSAIDs are equal-

Table 2 | Clinical Manifestations of Gout [6,8,10-13]

Stage	When it occurs	Manifestation	Treatment indicated?	Other information
Asymptomatic hyperuricemia	Occurs in many patients before onset of gout	sUA > 6.8 mg/dL No symptoms	No	Patients may never develop gouty arthritis
Acute gouty arthritis	Intermittently; lasts between 3-14 days untreated	Often affects first metatarsalphalangeal joint (podagra) or otherwise monoarticular Rarely polyarticular at first attack (3-14%)	Yes Acute treatment for first attack	Patients often have second attack within six months to two years of first attack
	Common triggers: alcohol, meat or seafood, trauma, or drugs that increase UA levels	Rapid increase in pain over 6-12h, swelling, erythema Fever and chills may be present	Consider UA lowering txy after attack if multiple flares	
Chronic tophaceous gout	Usually transition from acute gout to chronic gout within 10 years in patients who have generally had multiple attacks	Tophi (sodium urate crystals surrounded by mononuclear and giant cells) frequently seen over helix of ear, olecranon processes, on Achilles tendons, on toes or finger joints around the knees or within the pre-patellar bursae	Yes	Common complication due to chronic gout include: uric acid nephrolithiasis (10-40%)
		May lead to joint inflammation, destruction and deformity	Patients with chronic gout should be on UA lowering txy and acute txy	Hyperuricemia may also lead to hypertension[13]

Abbreviations: dL: deciliter; mg: milligram; sUA: serum uric acid; txy: therapy; UA: uric acid

ly efficacious. Certain NSAIDS may be preferred in the setting of renal insufficiency. Sulindac was originally designed as a prodrug in the search for a kidney-sparing NSAID. The active form can be converted to its non-active form (the sulphoxide moiety) by the kidneys, which appears to delineate sulindac's effects on prostaglandin excretion. This has translated clinically to sulindac having much less effect on serum creatinine (SCr) and creatinine clearance (CrCl) than other NSAIDs. Nabumetone has also been compared to ibuprofen and it has been shown to have fewer effects on SCr than other NSAIDs.[18]

For patients who have recurrent gout attacks, sUA lowering therapy is an option. The goal of treatment is to get sUA to a subsaturating level to prevent urate crystal formation and deposition. This is most often defined as a sUA less than 6 mg/dL.[16] However, not every gout patient should be started on sUA-lowering medication. The primary indications for sUA lowering therapy include macroscopic subcutaneous tophi, three or more attacks of gouty arthritis per year, or a documented state of uric acid overproduction.[20] There are several options available for the prevention of acute gout flares. Allopurinol is by far the most commonly used, but there are multiple options available, including the newest agent, FBX. It is important to note that sUA therapy should never be started or stopped during an acute attack as this may actually precipitate or worsen the attack due to mobilization of uric acid stores as sUA begins to decrease.[4,21] **Table 4** reviews the use of allopurinol and probenecid. For gout prophylaxis.[19,22-24]

Table 3 | American College of Rheumatology Preliminary Criteria for Gout [14]

Diagnostic Criteria for Gout
Asymmetric swelling within a joint on a radiograph
First metatarsophalageal joint is tender or swollen (i.e., podagra)
Hyperuricemia
Maximal inflammation developed within one day
Monoarthritis attack
More than one acute arthritis attack
Redness observed over joints
Subcortical cysts without erosions on a radiograph
Suspected tophi
Synovial fluid culture negative for organisms during an acute attack
Unilateral first metatarsophalangeal joint attack
Unilateral tarsal joint attack

Table 4 | Medications Used in Gout Prophylaxis [17,20-22]

Medication	Dosing	Action	Cautions and Special Considerations	Cost
Allopurinol (Zyloprim)	300 mg daily for CrCl > 90 mL/min 200 mg daily for CrCl >60 mL/min 100 mg daily for CrCl >30 mL/min 50-100 mg daily for CrCl <30 mL/min May increase up to 800 mg/day	Decreases the production of uric acid by prevention the conversion of xanthine to uric acid (xanthine oxidase inhibitor)	Must dose adjust in renal impairment	100 mg: $0.24/tablet 300 mg: $0.64/tablet
Probenecid	Initially, 250 mg twice daily; gradually increase to 250-1000 mg twice daily with maximal dose used based on extent of UA lowering	Enhances elimination of UA through urinary excretion	Avoid in patients with 24h urine UA > 700 mg; CI in patients with history of nephrolithiasis; may impair renal function	500 mg: $0.98/tablet

Abbreviations: CI=contraindicated; CrCl=creatinine clearance; mL/min=milliliters per minute; UA= uric acid

Pharmacology & Pharmacokinetics

FBX is the newest agent to lower sUA. Like allopurinol, FBX is a xanthine oxidase inhibitor. Unlike allopurinol, FBX does not structurally resemble a purine or pyrimidine. It is more selective because it does not affect other enzymes involved in purine or pyrimidine synthesis. [10] FBX is rapidly absorbed after oral administration, with peak concentrations occurring within 0.5 to 1.3 hours (**Table 5**). About 1-6% of FBX is excreted in the urine as unchanged drug. In the settings of mild to moderate renal impairment, dose adjustment is not required.[25]

Drug Interactions & Contraindications

FBX has no significant interactions with cytochrome P450 enzymes (CYP) including CYP1A2, CYP2C9, CYP2C19 or CYP3A4.[25-27] In vitro, FBX was found to have a weak inhibitory effect on CYP2D6, but this has not been correlated to any clinically meaningful drug interactions.[25,26] Since FBX is commonly used with both colchicine and NSAIDs, it was tested for interactions with both agents; no interactions have been noted. FBX has also been tested with HCTZ, warfarin and desipramine and all were also deemed safe to be used in combination with FBX.[27] Because FBX works by inhibiting xanthine oxidase, concurrent use of any medication that requires xanthine oxidase for metabolism is contraindicated. Examples of drugs metabolized by xanthine oxidase include azathioprine, mercaptopurine, and theophylline.[4,25] Use of these medications along with FBX could result in toxic levels of the corresponding medication and potentially fatal bone marrow suppression.[27]

Special Populations

FBX was studied in mild (CrCl of 60-90 mL/min) and moderate (CrCl of 30-60 mL/min) renal impairment in two phase III clinical trials. Patients with mild and moderate renal impairment had similar adverse event profiles as patients with normal renal function.[28,29] Therefore, no dose adjustments are required for patients with mild to moderate renal impairment.[4] FBX has not been studied in the setting of severe renal impairment (CrCl less than 30 mL/min), and no dosage recommendations are available for these patients.

While not as widely studied, FBX has also been evaluated in the setting of hepatic impairment. No dose reductions are required in the setting of mild to moderate hepatic impairment, defined as Child Pugh Class A or B. However, no dosage recommendations are available in the setting of severe hepatic impair-

Table 5 | Pharmacokinetic Data for Febuxostat [26]

Property	Febuxostat
Dosing Interval	40 mg or 80 mg once daily
Elimination and Metabolism	49% of drug eliminated in urine -3% unchanged drug 45% of drug is eliminated via feces -12% unchanged drug Primary metabolism is via CYP450 enzymes: -IA2,2C8,2C9 and several UGT enzymes
Tmax, Cmax	1.6+/-0.6 mcg/mL for 40 mg dose 2.6+/-1.7 mcg/dL for 80 mg dose
Half-life	5-8 hours
Volume of distribution	0.7 L/kg
Protein binding	99.2%
Tmax	0.5-1.3 hours

Abbreviations: Cmax=maximal concentration; CYP=cytochrome P450 enzyme; kg=kilograms; L=liter; mcg=micrograms; mL=milliliters Tmax=time to maximal plasma concentration; UGT= uridine diphosphate glycosyltransferase

Table 6 | Summary of Febuxostat Clinical Trials Data [4,28-33]

Study (Year)	Design	Outcome	Interventions	Primary endpoint results
FACT (2005)	-RCT, DB, MC, AC -52 wk trial: tx in weeks 9-52 -762 patients received a drug	Primary Efficacy: -sUA <6.0 mg/dL at each of last 3 monthly measurements	-80 mg FBX daily (N=256) -120 mg FBX daily (N=251) -ALL 300 mg daily (N=253)	-80 mg FBX (N=53) -120 mg FBX (N=62) -ALL 300 mg (N=21) -p<0.001 for both 80 mg FBX and 120 mg FBX vs. ALL 300 mg daily
APEX (2008)	-RCT, DB, MC, PC + AC -28 week trial with 2 week initial washout period -1072 patients received drug therapy	Primary Efficacy: -sUA <6.0 mg/dL at each of last 3 monthly measurements:	-80 mg FBX daily (N=161) -120 mg FBX daily (N=188) -240 mg FBX daily (N=83) -ALL daily* (N=208) -PB (N=99)	-80 mg FBX (N=122) -120 mg FBX (N=163) -240 mg FBX (N=78) -ALL daily (N=85) -PB (N=1) -p<0.05 for all AC vs. placebo;
CON-FIRMS (2010)	RCT, DB, MC, AC -6 months of treatment with 30 day washout period -2269 patients received drug therapy	Primary Efficacy: -Proportion of subjects in each treatment group with sUA <6.0 mg/dL at the final visit Primary Safety: - CV-related deaths and adverse events	-40 mg FBX (N=757) -80 mg FBX (N=756) - 200/300 mg ALL (N=755) (Patients with CrCl of 30-59 mL/min received 200 mg ALL)	-40 mg FBX (45.2%) -80 mg FBX (67.1%) -200/300 mg ALL (42.1%) -p<0.001 for FBX 80 mg vs. FBX 40 mg or ALL -FBX 40 mg was non-inferior to ALL but difference in response rates was NS
CON-FIRMS (Subgroup analysis)	-Comparison of safety and efficacy in patients <65 years versus >65 - Also analyzed differences among groups including: BMI, sUA and years with gout at baseline	Same as CONFIRMS trial	-Included 374 patients at least age 65 -1895 patients <65 years	Patients <65 years: - FBX 80 > FBX 40 (p<0.001) - FBX 80 > ALL 300/200 (P<0.001) Patients >65 years: -FBX 40 vs FBX 80 (p=0.104) -FBX 80 vs ALL 300/200 (p=0.004) FBX 40: -Age <65 (42.2%) vs. > 65 (61.7%) (p<0.001) 80 mg FBX: -Age <65 (64%) vs. >65 (82%) (p<0.001)
FOCUS (2009)	-OL, MC, -5 year follow-up study -sUA reduction and maintenance at subsaturating levels -Extension from 28 day phase II study -N=116	Primary Efficacy -Proportion of subjects that achieved and maintained sUA <6.0 mg/dL	-Note: all subjects initially started on FBX 80 mg, but dose could be adjusted: -40 mg FBX (N=8) -80 mg FBX (N=79) 120 mg FBX (N=29)	-40 mg FBX (100%) -80 mg FBX (82%) -120 mg FBX (81%)
EXCEL (2009)	-MC, OL, -Long-term follow up study targeted at extending results of APEX and FACT	Primary Efficacy - Proportion of subjects that had a sUA <6.0 mg/dL - Proportion of subjects that had a sUA <6.0 mg/dL at one year	-80 mg FBX (N=412) -120 mg FBX (N=217) -ALL* (N=35)	Outcome 1: -80 mg FBX (81%) -120 mg FBX (87%) -ALL (46%) Outcome 2: -80 mg FBX: (75-100%) -120 mg FBX (75-100%) -ALL** (75-100%)

AC = active-comparator; Allopurinol= ALL; DB= double blinded; Febuxostat = FBX; MC= multi-center; N=number of patients; OL = open-label; PB = placebo RCT=Randomized controlled trial; *dose adjusted for renal function (subjects with SCr <1.5 received 300 mg ALL, subjects with SCr between 1.5 mg/dL and 2.0 mg/dL received 100 mg daily. Patients with SCr >2.0 were excluded from study **Patients initially started on ALL were able to switch to FBX if sUA lowering was deemed inadequate or gout flares continued; however, these patients were still included in ALL group. 67% of patients in ALL group who switched to FBX group reached target sUA. Note: in all trials prophylaxis against acute flares was used during initiation of uric acid lowering (UA) therapy.

ment.[25]

FBX has been studied in elderly patients. In a subgroup analysis of a major phase III trial conducted by Becker et al., FBX was examined in 374 patients over the age of 65.[30] FBX had a similar adverse effect profile in the elderly as compared to younger patients and was actually found to be more efficacious at lower doses than in younger patients.[30] FBX has not been studied in pediatric patients and is therefore not recommended.[4]

Clinical Trials

In the first phase III clinical trial involving FBX (FACT), Becker et al. compared FBX 80 mg, FBX 120 mg, and allopurinol 300 mg over a period of one year [31] (**Table 6**). In FACT, which involved 762 patients, a majority of whom were white males that admitted to drinking alcohol, both doses of FBX were more efficacious in lowering sUA to < 6.0 mg/dL than allopurinol ($p<0.001$). However, FACT did not allow for dose adjustments of allopurinol based on renal insufficiency and therefore excluded patients with renal insufficiency, a common co-morbidity in patients with gout. FACT also did not allow providers to make adjustments based on efficacy of FBX or allopurinol.[31]

To follow this trial, phase III trials were conducted in patients with renal impairment. In the 28-week APEX trial, Becker et al. compared an additional strength of FBX, 240 mg, to the previously tested dosages (80 and 120 mg) and also tested FBX in patients with mild and moderate renal impairment. All three strengths of FBX were more efficacious than allopurinol in reaching the primary endpoint of lowering sUA to less than 6.0 mg/dL. Additionally, all three doses were more efficacious in patients with renal impairment.[28]

The CONFIRMS trial was the last of the short-term phase III clinical trials involving FBX.[29] CONFIRMS, which lasted 6 months, had three primary goals. First, FBX 40 mg, a dosage that had not previously been tested in phase III trials, was tested for efficacy in comparison to allopurinol. Second, the efficacy of FBX 40 mg and 80 mg was compared with that of allopurinol in patients with renal insufficiency. Finally, CONFIRMS looked at safety, namely cardiovascular events, that had been questioned in previous phase III studies. FBX 40 mg was non-inferior to allopurinol at lowering sUA, but the difference in response rates was non-significant (95% CI: -1.9 to 8.1). However, FBX 80 mg was significantly more efficacious at lowering sUA than FBX 40 mg or allopurinol ($p<0.001$). This was true in patients with normal renal function as well as patients with mild and moderate renal impairment. Adverse event profiles were similar with both FBX doses. There were no increase in CV events in the FBX groups as compared to the allopurinol group, but the study was not powered to investigate differences in CV events. Based on these results it appears that FBX is at least as safe as allopurinol in terms of cardiovascular events,[29] further studies are needed to assess cardiovascular events associated with FBX.

There were two long-term trials conducted to assess the safety and effectiveness of FBX based on previous phase II and III trials. FOCUS, conducted by Schumacher et al. was a five-year follow-up study involving 116 patients initially enrolled in a 28-day phase II study.[32] All patients entered into the study were initially on FBX 80 mg. The primary endpoint was the proportion of subjects who had a final sUA <6.0 mg/dL. By week 260, 93% of patients who completed the trial were at goal. In FOCUS, the dosage of FBX could be titrated among FBX 40, 80 or 120 mg through weeks 4-24 to maintain a sUA of 3-6 mg/dL. It's important to note that FOCUS may have biased results, however, because almost 50% of patients prematurely left the study, a majority of which cited personal reasons.[32] In EXCEL,[33] which consisted of patients from APEX and FACT, patients were followed for up to an additional 40 months for safety and efficacy on either FBX 80 mg or FBX 120 mg. After only one month of treatment greater than 80% of patients on FBX had reached their sUA goal and by the end of the trial, nearly zero required treatment for gout flares.[33]

There are several important points to note about all the major clinical trials involving FBX. First, patients were given prophylaxis against gout flares with either an NSAID or colchicine during the first eight weeks of sUA-lowering therapy in FACT[31] and APEX[28] and throughout the trial in CONFIRMS.[29] Second, though the primary outcome of the trials was to decrease sUA to less than < 6.0 mg/dL, this did not necessarily correlate to a decrease in gout flares.[28,29,31] During the APEX prophylaxis period, more patients in the FBX arms required treatment for gout flares than the allopurinol group.[28] The initial increase in gout flares seen with allopurinol as compared with FBX is believed to be due to FBX's higher potency and increased mobilization of uric acid.[26] As shown in APEX, the number of patients requiring treatment for acute gout flares decreased with increased length of FBX treatment.[25,28] This was also true in FOCUS, where by year five of the study, none of the patients left in the study required acute gout treatment.[32]

Adverse Events and Safety

Overall, FBX is well-tolerated.[26] The most common

adverse effects associated with FBX are acute gout flares during initial sUA-lowering therapy (adding an NSAID or colchicine for six months to help prevent this is recommended in the package insert), flu-like symptoms, arthralgias, myalgias, increases in LFTs, nausea and vomiting. Rashes have been reported rarely in post-marketing studies.[4]

Additionally, the earlier phase III clinical trials revealed a concern for cardiac adverse events associated with FBX.[28,31] Therefore, the safety portion of the CONFIRMS trial was designed to look at cardiac outcomes, more specifically Anti-Platelet Trialist Committee (APTC) associated cardiac outcomes which include cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The number of APTC events in the FBX groups was not higher than the number of events associated with the allopurinol group (none in FBX 40 mg and three events each in FBX 80 mg and allopurinol groups). Furthermore, all patients who did have an APTC event had prior cardiovascular histories.[29] Based on this data, FBX was approved despite the initial concerns for its cardiovascular effects. The package insert warns to monitor for signs and symptoms of myocardial infarction and stroke as a precautionary measure.[25]

Dosing and Cost

FBX is recommended at an initial dosage of 40 mg daily. For patients who do not meet the goal of a sUA of < 6 mg/dL after two weeks of treatment with FBX, an increase in dosage to 80 mg is recommended.[4] Prophylaxis with an NSAID or colchicine during the first six months of FBX therapy is recommended because the most common reason for discontinuation of FBX in clinical trials was an increase in acute gout flares.[25] Based on the average price of three different retailers, the cost of a 30-day supply of febuoxstat 40 mg is $200.99 ($6.69/tablet) and $201.99 ($6.73/tablet) for febuxostat 80 mg.

Summary

Gout is an old disease that is still prevalent in the United States today. Most common medications used in the treatment of gout have been around for years. However, FBX provides an alternative for sUA-lowering. Like allopurinol, FBX is a xanthine oxidase inhibitor. Unlike allopurinol, FBX requires no dose adjustment in mild to moderate renal impairment. Further studies are needed to recommend FBX in the setting of severe renal impairment. FBX is dosed once daily, starting at 40 mg. However, if after two weeks of therapy with FBX, sUA is still not at goal of sUA < 6.0 mg/dL, the dose should be increased to 80 mg once daily. Overall, FBX is well tolerated, even in mild to moderate renal impairment. Most common adverse effects are flu-like symptoms, myalgias, arthralgias, increases in LFTs, and nausea. Overall, FBX represents a well tolerated alternative to allopurinol for sUA-lowering therapy. However, due to cost, FBX will likely only be first line therapy for select patients.

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FDA Updates

Statin Labeling Update [1] — On February 28, 2012 the FDA updated the labeling of all HMG-CoA reductase inhibitors (or statins). Specifically, the labeling has been updated to reflect a potential increased risk for diabetes associated with the use of statins. The new warning is based on clinical trials showing a higher risk for incident diabetes or a worsening of glycemic control in statin users vs. non-users. Notably, the JUPITER trial[2] investigating the use of rosuvatatin for primary prevention of cardiovascular disease (CVD) showed a 27% increase in the rate of physician-reported diabetes in the users of rosuvastatin; the baseline hemoglobin A1c (HbA1c) between groups was not statistically significantly different at the time of premature study discontinuation due to a clear benefit of statin therapy (A1c at 24 months was 5.9% for users of rosuvastatin vs. 5.8% for placebo, p = 0.001). Change in HbA1c was not a primary outcome of the trial, and therefore causality cannot be established.

The mechanism behind the increased risk for diabetes is unknown, but the FDA continues to believe the cardiovascular benefits of statin therapy outweigh these small increased risks. More evidence is needed in order to clearly define the role of statin therapy in contributing to, or causing, the development of diabetes.

The statin label has also been revised to reflect a change in liver enzyme monitoring. Labels now indicate baseline liver enzyme tests should be performed prior to initiation of statin therapy, but periodic routine monitoring is no longer required. The rare and unpredictable incidence of severe liver injury is not sufficiently mitigated with routine monitoring, and therefore is no longer required. Patients exhibiting symptoms potentially suggestive of liver injury (abdominal pain, presence of edema, or flu-like symptoms), further laboratory evaluation may be required to investigate for the presence of liver damage. The decision to test should be based on patient symptoms, comorbidities, current medications, and the results of a thorough history and physical exam. Consistent with previous recommendations, patients with persistently elevated ALT or AST (greater than three-times the upper limit of normal on two consecutive readings) should be evaluated for statin discontinuation or dose adjustment, as appropriate.

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