SUMMARY OF PRODUCT CHARACTERISTICS

Donifoxate 40 mg Film Coated Tablets "Febuxostat 40 mg"

Donifoxate 80 mg Film Coated Tablets "Febuxostat 80 mg"

1 INDICATIONS AND USAGE

DONIFOXATE is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.

Limitations of Use:
DONIFOXATE is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DONIFOXATE dosage is 40 mg or 80 mg once daily.

The recommended starting dosage of DONIFOXATE is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks, the recommended DONIFOXATE dosage is 80 mg once daily.

DONIFOXATE can be taken without regard to food or antacid use *[see Clinical Pharmacology (12.3)].*

Concurrent prophylactic treatment with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended *[see Dosage and Administration (2.4) and Warnings and Precautions (5.2)].*

2.2 Dosage Recommendations in Patients with Renal Impairment and Hepatic Impairment

The recommended dosage of DONIFOXATE is limited to 40 mg once daily in patients with severe renal impairment. No dose modification is necessary when administering DONIFOXATE in patients with mild or moderate renal impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

No dosage modification is necessary in patients with mild to moderate hepatic impairment *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Serum Uric Acid Level Monitoring

Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after initiating DONIFOXATE therapy.

2.4 Recommended Prophylaxis for Gout Flares

Gout flares may occur after initiation of DONIFOXATE due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of DONIFOXATE. Prophylactic therapy may be beneficial for up to six months *[see Clinical Studies (14.1)]*.

If a gout flare occurs during DONIFOXATE treatment, DONIFOXATE need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient *[see Warnings and Precautions (5.2)]*.

DOSAGE FORMS AND STRENGTHS

- 40 mg tablets, Bright green, biconvex round film- coated tablets
- 80 mg tablets, Bright green, biconvex round film- coated tablets

3 CONTRAINDICATIONS

DONIFOXATE is contraindicated in patients being treated with azathioprine or mercaptopurine *[see Drug Interactions (7)]*.

4 WARNINGS AND PRECAUTIONS

4.1 Cardiovascular Death

In a cardiovascular (CV) outcome study, gout patients with established CV disease treated with DONIFOXATE had a higher rate of CV death compared to those treated with allopurinol. Sudden cardiac death was the most common cause of adjudicated CV deaths, 2.7% in the DONIFOXATE group (83 of 3,098) as compared to 1.8% in the allopurinol group (56 of 3,092). DONIFOXATE was similar to allopurinol for nonfatal myocardial infarction (MI), nonfatal stroke and unstable angina with urgent coronary revascularization *[see Clinical Studies (14.2)]*.

Because of the increased risk of CV death, DONIFOXATE should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable *[see Indications and Usage(1)]*.

Consider the risks and benefits of DONIFOXATE when deciding to prescribe or continue patients on DONIFOXATE. Consider use of prophylactic low-dose aspirin therapy in patients with a history of CV disease. Monitor patients for the development of CV events. Inform patients about the symptoms of serious CV events and the steps to take if they occur.

4.2 Gout Flares

After initiation of DONIFOXATE, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when DONIFOXATE is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended *[see Dosage and Administration (2.4)].*

4.3 Hepatic Effects

Cases of fatal and nonfatal hepatic failure in patients taking DONIFOXATE have been reported. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in DONIFOXATE and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted *[see Clinical Pharmacology (12.3)]*.

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating DONIFOXATE.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient presents abnormal liver tests (ALT or AST greater than three times the upper limit of the reference range), interrupt DONIFOXATE treatment while investigating the probable cause.
Permanently discontinue DONIFOXATE if liver injury is confirmed, and no alternate etiology can be found.

Permanently discontinue DONIFOXATE in patients who have serum ALT or AST greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies because they are at risk for severe drug-induced liver injury. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with DONIFOXATE can be used with close monitoring.

4.4 Serious Skin Reactions

Serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported postmarketing in patients taking DONIFOXATE. Discontinue DONIFOXATE if serious skin reactions are suspected *[see Patient Counseling Information (17)].* Many of these patients had reported previous similar skin reactions to allopurinol. DONIFOXATE should be used with close monitoring in these patients.

5 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the prescribing information:

- Cardiovascular Death *[see Warnings and Precautions (5.1)]*
- Hepatic Effects *[see Warnings and Precautions (5.3)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.4)]*

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of DONIFOXATE 40 mg, 1.2% of DONIFOXATE 80 mg, and in 0.9% of patients treated with allopurinol.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of patients treated with DONIFOXATE although not at a rate more than 0.5% greater than placebo.

In the CARES study, liver function abnormalities and diarrhea were reported in more than 1% of patients treated with DONIFOXATE, although not at a rate more than 0.5% greater than allopurinol.

Less Common Adverse Reactions

In clinical studies the following adverse reactions occurred in less than 1% of patients and in more than one subject treated with doses ranging from 40 mg to 240 mg of DONIFOXATE. This list also includes adverse reactions (less than 1% of patients) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, hematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio–edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/altered pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol

increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

6 DRUG INTERACTIONS

6.1 Xanthine Oxidase Substrate Drugs

DONIFOXATE is an XO inhibitor. Based on a drug interaction study in healthy patients, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans *[see Clinical Pharmacology (12.3)]*.
Therefore, use with caution when coadministering DONIFOXATE with theophylline.

A drug interaction study of DONIFOXATE and azathioprine, also metabolized by XO, showed an increase in exposure of 6-mercaptopurine which may lead to toxicity *[see Clinical Pharmacology (12.3)]*. Drug interaction studies of DONIFOXATE with other drugs that are metabolized by XO (e.g., mercaptopurine) have not been conducted. DONIFOXATE is contraindicated in patients being treated with azathioprine or mercaptopurine *[see Contraindications (4)]*.

6.2 Cytotoxic Chemotherapy Drugs

Drug interaction studies of DONIFOXATE with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of DONIFOXATE during cytotoxic chemotherapy.

6.3 *In Vivo* Drug Interaction Studies

Based on drug interaction studies in healthy patients, DONIFOXATE does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine *[see Clinical Pharmacology (12.3)]*. Therefore, DONIFOXATE may be used concomitantly with these medications.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

Limited available data with DONIFOXATE use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. No adverse developmental effects were observed in embryo-fetal development studies with oral administration of febuxostat to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to 40 and 51 times, respectively, the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed in a pre- and postnatal development study with administration of febuxostat to pregnant rats from organogenesis through lactation at an exposure approximately 11 times the MRHD *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7 – 17, febuxostat was not teratogenic and did not affect fetal development or survival at exposures up to approximately 40 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during

the period of organogenesis from gestation Days 6 – 18, febuxostat was not teratogenic and did not affect fetal development at exposures up to approximately 51 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day).

In a pre- and postnatal development study in pregnant female rats dosed orally from gestation Day 7 through lactation Day 20, febuxostat had no effects on delivery or growth and development of offspring at a dose approximately 11 times the MRHD (on an AUC basis at a maternal oral dose of 12 mg/kg/day). However, increased neonatal mortality and a reduction in neonatal body weight gain were observed in the presence of maternal toxicity at a dose approximately 40 times the MRHD (on an AUC basis at a maternal oral dose of 48 mg/kg/day).

Febuxostat crossed the placental barrier following oral administration to pregnant rats and was detected in fetal tissues.

7.2 Lactation

Risk Summary

There are no data on the presence of febuxostat in human milk, the effects on the breastfed infant, or the effects on milk production. Febuxostat is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DONIFOXATE and any potential adverse effects on the breastfed child from DONIFOXATE or from the underlying maternal condition.

Data

Animal Data

Orally administered febuxostat was detected in the milk of lactating rats at up to approximately 7 times the plasma concentration.

8.4 Pediatric Use

Safety and effectiveness of DONIFOXATE in pediatric patients have not been established.

8.5 Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of patients in Studies 1, 2, and 3 (clinical studies of DONIFOXATE in the treatment of gout) *[see Clinical Studies (14.1)]*, 16% were 65 and over, while 4% were 75 and over. Comparing patients in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of DONIFOXATE in geriatric patients (≥65 years) were similar to those in younger patients (18 to 40 years) *[see Clinical Pharmacology (12.3)].*

8.6 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (Cl_{cr} 30 to 89 mL/min). For patients with severe renal impairment (Cl_{cr} 15 to 29 mL/min), the recommended dosage of DONIFOXATE is limited to 40 mg once daily *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].*

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients *[see Clinical Pharmacology (12.3)].*

8.8 Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); DONIFOXATE is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

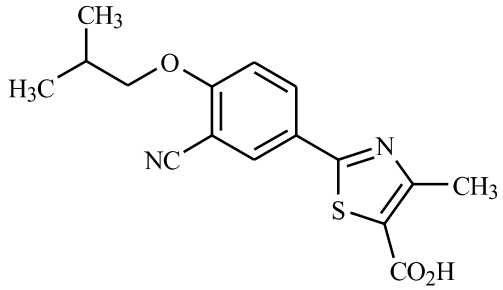
OVERDOSAGE

DONIFOXATE was studied in healthy patients in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of DONIFOXATE was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

DESCRIPTION

DONIFOXATE (febuxostat) is a xanthine oxidase inhibitor. The active ingredient in DONIFOXATE is 2-[3-cyano- 4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$.

The chemical structure is:



Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water. The melting range is 205°C to 208°C.

DONIFOXATE tablets for oral use contain the active ingredient, febuxostat, and are available in two dosage strengths, 40 mg and 80 mg. Inactive ingredients include hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, silicon dioxide, and sodium croscarmellose. DONIFOXATE tablets are coated with Opadry II, green.

9 CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

DONIFOXATE, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. DONIFOXATE is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

9.2 Pharmacodynamics

Effect on Uric Acid and Xanthine Concentrations

In healthy patients, DONIFOXATE resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations and an increase in 24-hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24-hour mean serum uric acid concentrations was between 40% and 55% at the exposure levels of 40 mg and 80 mg daily doses.

Effect on Cardiac Repolarization

The effect of DONIFOXATE on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy patients and in patients with gout. DONIFOXATE in doses up to 300 mg daily (3.75 times the maximum recommended daily dosage), at steady-state, did not demonstrate an effect on the QTc interval.

9.3 Pharmacokinetics

In healthy patients, maximum plasma concentrations (C_{max}) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg (0.25 times the lowest

recommended dosage) to 120 mg (1.5 times the maximum recommended dosage). There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy patients.

Absorption

The absorption of radiolabeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 and 1.5 hours postdose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg/mL (N=30), and 2.6 ± 1.7 mcg/mL (N=227), respectively. Absolute bioavailability of the febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs 51% fasting). Thus, DONIFOXATE may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of DONIFOXATE has been shown to delay absorption of febuxostat (approximately one hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC_{∞}. As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant.
Therefore, DONIFOXATE may be taken without regard to antacid use.

Distribution

The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2% (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism

Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat.

In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1 (~14% of the dose), appeared to be the major metabolites of febuxostat *in vivo*.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

The apparent mean terminal elimination half-life ($t_{1/2}$) of febuxostat was approximately 5 to 8 hours.

Specific Populations

Geriatric Patients

The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of DONIFOXATE in geriatric patients (≥65 years) were similar to those in younger patients (18 to 40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger patients. No dose adjustment is necessary in geriatric patients *[see Use in Specific Populations (8.5)].*

Patients with Renal Impairment

In a dedicated phase I pharmacokinetics study, following multiple 80 mg doses of DONIFOXATE in healthy patients with mild (Cl_{cr} 50 to 80 mL/min), moderate (Cl_{cr} 30 to 49 mL/min) or severe renal impairment (Cl_{cr} 10 to 29 mL/min), the C_{max} of febuxostat did not change relative to patients with normal renal function (Cl_{cr} greater than 80 mL/min). AUC and half-life of febuxostat increased in patients with renal impairment in comparison to patients with normal renal function, but values were similar among three renal impairment groups. Mean febuxostat AUC values were up to 1.8 times higher in patients with renal impairment compared to those with normal renal function. Mean C_{max} and AUC values for three active metabolites increased up to two and four-fold, respectively. However, the percent decrease in serum uric acid concentration for patients with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).

Based on population pharmacokinetic analysis, following multiple 40 mg or 80 mg doses of DONIFOXATE, the mean oral clearance (CL/F) values of febuxostat in patients with gout and mild (n=334), moderate (n=232) or severe (n=34) renal impairment were decreased by 14%, 34%, and 48%, respectively, compared to patients with normal (n=89) renal function. The corresponding median AUC values of febuxostat at steady-state in patients with renal impairment were increased by 18%, 49%, and 96% after 40 mg dose, and 7%, 45% and 98% after 80 mg dose, respectively, compared to patients with normal renal function.

DONIFOXATE has not been studied in end stage renal impairment patients who are on dialysis.

Patients with Hepatic Impairment

Following multiple 80 mg doses of DONIFOXATE in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20% to 30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to patients with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients *[see Use in Specific Populations (8.7)].*

Male and Female Patients

Following multiple oral doses of DONIFOXATE, the C_{max} and AUC_{24} of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.

Racial Groups

No specific pharmacokinetic study was conducted to investigate the effects of race.

Drug Interaction Studies

Effect of DONIFOXATE on Other Drugs

Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline

Febuxostat is an XO inhibitor. A drug-drug interaction study evaluating the effect of DONIFOXATE upon the pharmacokinetics of theophylline (an XO substrate) in healthy patients showed that coadministration of febuxostat with theophylline resulted in an approximately 400-fold increase in the amount of 1-methylxanthine, one of the major metabolites of theophylline, excreted in the urine. Since the long-term safety of exposure to 1-methylxanthine in humans is unknown, use with caution when coadministering febuxostat with theophylline.

A drug interaction study of DONIFOXATE and azathioprine has been conducted *[see Drug Interactions (7)]*. Inhibition of XO by DONIFOXATE caused increased plasma concentrations of 6-mercaptopurine, a metabolite of azathioprine, which may lead to toxicity. Drug interaction studies of DONIFOXATE with other drugs that are metabolized by XO (e.g., mercaptopurine) have not been conducted. DONIFOXATE is contraindicated in patients being treated with azathioprine or mercaptopurine *[see Contraindications (4) and Drug Interactions (7)].*

Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Concomitant administration of allopurinol [a xanthine oxidase inhibitor] with azathioprine or mercaptopurine has been reported to substantially increase plasma concentrations of these drugs. Because DONIFOXATE is a xanthine oxidase inhibitor, it could inhibit the XO-mediated metabolism of mercaptopurine leading to increased plasma concentrations of mercaptopurine that could result in severe toxicity.

P450 Substrate Drugs

In vitro studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between DONIFOXATE and drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on DONIFOXATE

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. Drug interactions between DONIFOXATE and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

In Vivo Drug Interaction Studies

Azathioprine

Concomitant use of DONIFOXATE and azathioprine is contraindicated. Coadministration with febuxostat (40 mg or 120 mg QD) reduced the apparent clearance of mercaptopurine, a XO substrate, by 83.2% to 83.8% following a single oral dose of azathioprine, a prodrug of 6-mercaptopurine. No significant differences were observed in the extent of inhibition of 6-mercaptopurine metabolism by febuxostat 40 mg and 120 mg.

Theophylline

No dose adjustment is necessary for theophylline when coadministered with DONIFOXATE. Administration of DONIFOXATE (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by DONIFOXATE. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to coadminister DONIFOXATE and theophylline.

Colchicine

No dose adjustment is necessary for either DONIFOXATE or colchicine when the two drugs are coadministered. Administration of DONIFOXATE (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in C_{max} and 7% in AUC_{24} of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with DONIFOXATE (120 mg daily) resulted in a less than 11% change in C_{max} or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.

Naproxen

No dose adjustment is necessary for DONIFOXATE or naproxen when the two drugs are coadministered. Administration of DONIFOXATE (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen (less than 2%).

Indomethacin

No dose adjustment is necessary for either DONIFOXATE or indomethacin when these two drugs are coadministered. Administration of DONIFOXATE (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide

No dose adjustment is necessary for DONIFOXATE when coadministered with hydrochlorothiazide. Administration of DONIFOXATE (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in C_{max} or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin

No dose adjustment is necessary for warfarin when coadministered with DONIFOXATE. Administration of DONIFOXATE (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy patients. INR and Factor VII activity were also not affected by the coadministration of DONIFOXATE.

Desipramine

Coadministration of drugs that are CYP2D6 substrates (such as desipramine) with DONIFOXATE are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro* and *in vivo*. Administration of DONIFOXATE (120 mg once daily) with desipramine (25 mg) resulted in an increase in C_{max} (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

10 NONCLINICAL TOXICOLOGY

10.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of the urinary bladder was observed at 24 mg/kg (25 times the MRHD on an AUC basis and 18.75 mg/kg (12.5 times the MRHD on an AUC basis) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

Febuxostat showed a positive clastogenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation *in vitro*. Febuxostat was negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* chromosomal aberration assay in human peripheral lymphocytes, the L5178Y mouse lymphoma cell line assay, the *in vivo* mouse micronucleus assay, and the rat unscheduled DNA synthesis assay.

Fertility and reproductive performance were unaffected in male or female rats that received febuxostat at oral doses up to 48 mg/kg/day (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).

10.2 Animal Toxicology

A 12-month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg/kg (approximately 4 times the MRHD on an AUC basis). A similar effect of calculus formation was noted in rats in a 6-month study due to deposition of xanthine crystals at 48 mg/kg (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).

11. Pharmaceutical particulars

11.1 List of excipients

Tablet core: Lactose monohydrate, microcrystalline cellulose, Croscarmellose Sodium, Hydroxypropylcellulose, Colloidal anhydrous Silica, Magnesium stearate

Tablet coating: Opadry II green 85G21856

11.2 Incompatibilities

Not applicable.

11.3 Special precautions for storage

This medicinal product does not require any special storage conditions.

11.4 Nature and contents of container

Carton Box containing 3 (Al/White Opaque (PVC/PVDC)) strips, each of 10 Film Coated Tablets

12. Marketing authorisation holder

Eva Sciences Nigeria Limited

13. Date of revision of the text

April 2023