Abbreviated prescribing information of Feburic

Abbreviated prescribing information of Feburic® film-coated tablets

Version: 007

Composition:

Febuxostat

Indications:

Feburic is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). Feburic 120 mg is also indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). Feburic is indicated in adults.

Dosage:

Gout 80 mg once daily. **TLS** 120mg once daily; start 2 days before the beginning of cytotoxic therapy and continue for a minimum of 7 days.

Administration:

May be taken by mouth w/o regard to food.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use:

Cardio-vascular disorders

Treatment of chronic hyperuricaemia

In patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina), during the development of the product and in one post registrational study (CARES), a higher number of fatal cardiovascular events were observed with febuxostat when compared to allopurinol.

However, in a subsequent post registrational study (FAST) - in which patients at randomisation had received dose-

optimised allopurinol and 97.3% of whom had already achieved a target serum urate concentration of < 0.357 mmol/L (<6 mg/dL) - febuxostat was not inferior to allopurinol in the incidence of both fatal and non-fatal cardiovascular events.

Treatment of patients with pre-existing major cardiovascular diseases should be exercised cautiously and they should be monitored regularly. In particular, treatment should be exercised cautiously in patients with pre-existing major cardiovascular diseases with evidence of high urate crystal and tophi burden or those initiating urate lowering therapy.

Prescribing clinicians should titrate febuxostat appropriately to minimise gout flares following initiation, thus minimising additional inflammation.

For further details on cardiovascular safety of febuxostat refer to full prescribing information for full description of the CARES and FAST studies.

Prevention and treatment of hyperuricaemia in patients at risk of TLS

Patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome treated with Feburic should be under cardiac monitoring as clinically appropriate.

Medicinal product allergy/hypersensitivity

Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases.

Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions. Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson Syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions including Stevens-Johnson Syndrome and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time.

Acute gouty attacks (gout flare)

Febuxostat treatment should not be started until an acute attack of gout has completely subsided. Gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended.

If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

Xanthine deposition

In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This has not been observed in the pivotal clinical study with Feburic in the Tumor Lysis Syndrome. As there has been no experience with febuxostat, its use in patients with Lesch-Nyhan Syndrome is not recommended.

Mercaptopurine/azathioprine

Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity.

Where the combination cannot be avoided, a reduction of the dose of mercaptopurine/azathioprine to the 20% or less of the previously prescribed dose is recommended in order to avoid possible haematological effects.

The patients should be closely monitored and the dose of mercaptopurine/azathioprine should be subsequently adjusted based on the evaluation of the therapeutic response and the onset of eventual toxic effects.

Organ transplant recipients

As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended.

Theophylline

Co-administration of febuxostat 80 mg and theophylline 400 mg single dose in healthy subjects showed absence of any pharmacokinetic interaction. Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data is available for febuxostat 120 mg.

Liver disorders

During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment.

Thyroid disorders

Increased TSH values (> 5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function.

Lactose

Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Undesirable effects:

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg), post-authorisation safety studies (FAST study: 3001 subjects treated at least with a dose from 80 mg to 120 mg) and post-marketing experience in gout patients are gout flares, liver function abnormalities, diarrhoea, nausea, headache, dizziness, dyspnoea, rash, pruritus, arthralgia, myalgia, pain in extremity, oedema and fatigue. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, and rare events of sudden cardiac death, have occurred in the post-marketing experience.

List of adverse reactions

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below.

The frequencies are based on studies and post-marketing experience in gout patients.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions in combined phase 3, long-term extension studies, post-authorisation safety studies and post-marketing experience in gout patients.

Blood and lymphatic system disorders: Rare: Pancytopenia, thrombocytopenia, agranulocytosis*, eosinophilia*, anaemia[#].

Immune system disorders: Rare: Anaphylactic reaction*, drug hypersensitivity*.

Endocrine disorders: Uncommon: Blood thyroid stimulating hormone increased, hypothyroidism[#].

Eye disorders: Uncommon: Blurred vision. Rare: Retinal artery occlusion[#].

Metabolism and nutrition disorders: Common***: Gout flares. Uncommon: Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase. Rare: Weight decrease, increase appetite, anorexia.

Psychiatric disorders: Uncommon: Libido decreased, insomnia. Rare: Nervousness, depressed mood[#], sleep disorder[#].

Nervous system disorders: Common: Headache, dizziness. Uncommon: Paraesthesia, hemiparesis, somnolence, lethargy[#], altered taste, hypoaesthesia, hyposmia. Rare: Ageusia[#], burning sensation[#].

Ear and labyrinth disorders: Uncommon: Tinnitus. Rare: Vertigo[#].

Cardiac disorders: Uncommon: Atrial fibrillation, palpitations, ECG abnormal, left bundle branch block (see section Tumor Lysis Syndrome), sinus tachycardia (see section Tumor Lysis Syndrome), arrhythmia[#]. Rare: Sudden cardiac death*.

Vascular disorders: Uncommon: Hypertension, flushing, hot flush, haemorrhage (see section Tumor Lysis Syndrome). Rare: Circulatory collapse#.

Respiratory system disorders: Common: Dyspnoea. Uncommon: Bronchitis, upper respiratory tract infection, lower respiratory tract infection#, cough and rhinorrhoea#. Rare: Pneumonia#.

Gastrointestinal disorders: Common: Diarrhoea**, nausea. Uncommon: Abdominal pain, abdominal pain upper#, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort, mouth ulceration, lip swelling#, pancreatitis . Rare: Gastrointestinal perforation#, stomatitis#.

Hepato-biliary disorders: Common: Liver function abnormalities**. Uncommon: Cholelithiasis. Rare: Hepatitis, jaundice*, liver injury*, cholecystitis#.

Skin and subcutaneous tissue disorders: Common: Rash (including various types of rash reported with lower frequencies, see below), pruritus. Uncommon: Dermatitis, urticaria, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular, hyperhidrosis, alopecia, eczema#, erythema, night sweats#, psoriasis#, rash pruritic#. Rare: Toxic epidermal necrolysis*, Stevens-Johnson Syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalized rash (serious)*, erythema multiform*, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash erythematous, rash morbilliform.

Musculoskeletal and connective tissue disorders: Common: Arthralgia, myalgia, pain in extremity#. Uncommon: Arthritis, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis, joint swelling#, back pain#, musculoskeletal stiffness#, joint stiffness. Rare: Rhabdomyolysis*, rotator cuff syndrome#, polymyalgia rheumatica#.

Renal and urinary disorders: Uncommon: Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria, micturition urgency, urinary tract infection#. Rare: Tubulointerstitial nephritis*.

Reproductive system and breast disorder: Uncommon: Erectile dysfunction.

General disorders and administration site conditions: Common: Oedema, fatigue. Uncommon: Chest pain, chest discomfort, pain#, malaise#. Rare: Thirst, feeling hot#.

Investigations: Uncommon: Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase, INR increased#. Rare: Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase*.

Injury, poisoning and procedural complications: Uncommon: Contusion#.

* Adverse reactions coming from post-marketing experience
** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine.
*** See full prescribing information for incidences of gout flares in the individual Phase 3 randomized controlled studies.
# Adverse reactions coming from post-authorisation safety studies.

Description of selected adverse reactions

Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis).

Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended.

Tumor Lysis Syndrome

Summary of the safety profile

In the randomized, double-blind, Phase 3 pivotal FLORENCE (FLO-01) study comparing febuxostat with allopurinol (346 patients undergoing chemotherapy for haematologic malignancies and at intermediate-to-high risk of TLS), only 22 (6.4%) patients overall experienced adverse reactions, namely 11 (6.4%) patients in each treatment group. The majority of adverse reactions were either mild or moderate.

Overall, the FLORENCE trial did not highlight any particular safety concern in addition to the previous experience with Feburicin gout, with the exception of the following three adverse reactions.

Cardiac disorders:

Uncommon: Left bundle branch block, sinus tachycardia.

Vascular disorders:

Uncommon: haemorrhage.

Full prescribing information is available upon request.