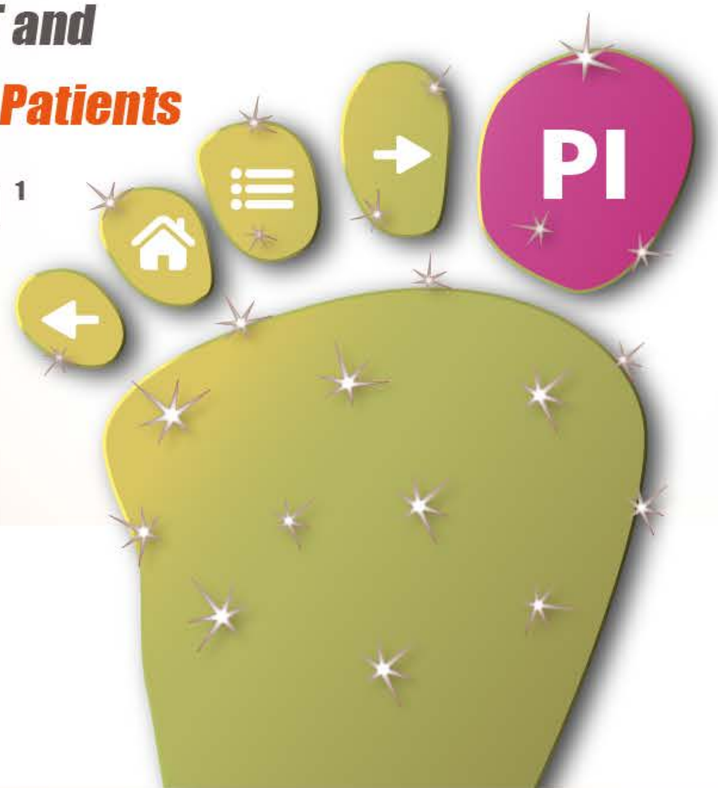
Feburic®
(febuxostat)

Shining Light

on an Overlooked Disease

-GOUT

49% of Gout Patients on ULT and
69% of Gout & CKD Patients
Can't Meet sUA Target Level [1]



astellas
Leading Light for Life

What is Feburic® ?

When gout goes to your kidney

sUA levels were significantly lower for Hyperuricemia Patients with CKD [14]

EULAR Guidelines [11]

Coexistence of HLA-B*5801 and renal impairment increased risk of allopurinol hypersensitivity [16]

Feburic® open-label study proved tophus resolution in long-term [13]

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What is Feburic® ?

Feburic® is a novel non-purine, selective xanthine oxidase inhibitor [2]

Feburic® displayed potent mixed-type inhibition of xanthine oxidase [2]

Gout: Not Only Pain But With Multiple Co-Morbidities [3-7]

Feburic®
(febuxostat)

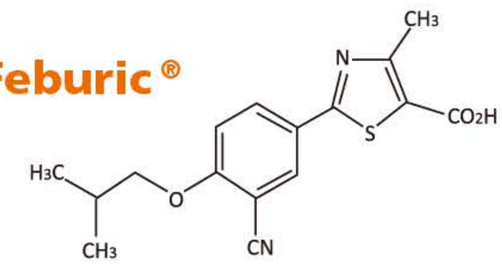
Feburic® is a novel non-purine, selective xanthine oxidase inhibitor[2]

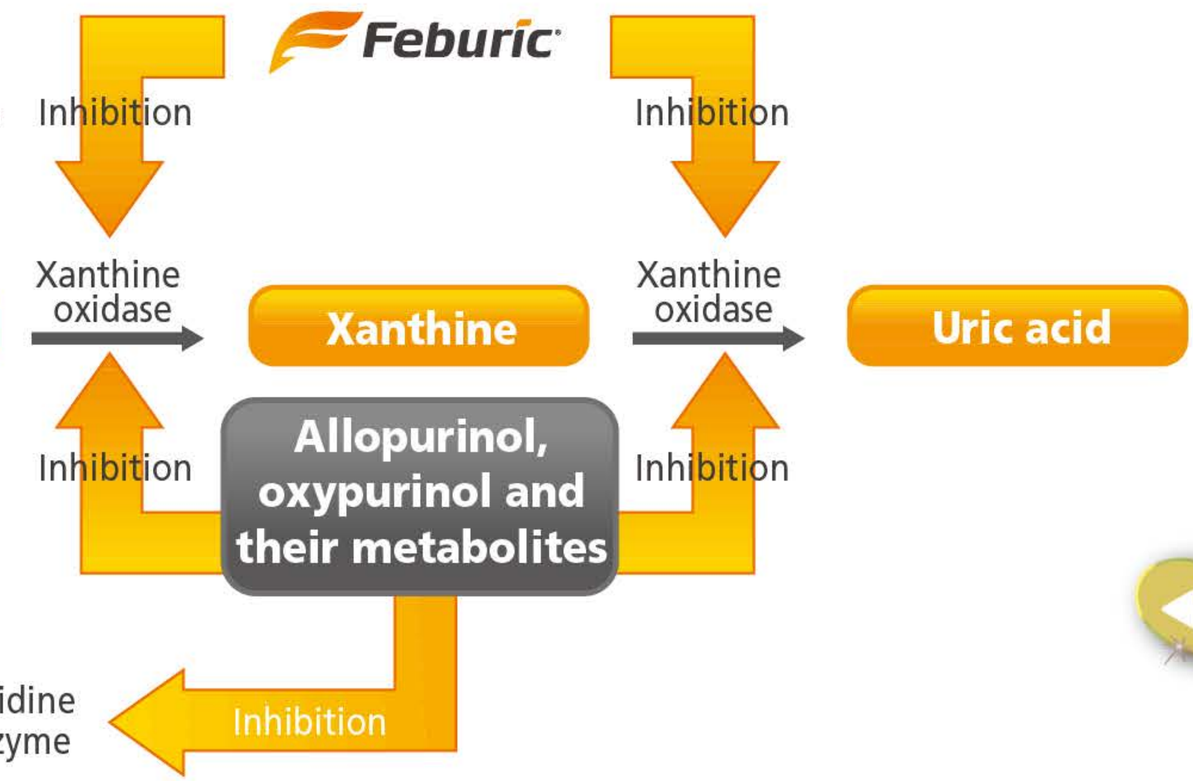
- **Feburic®** (non-purine analogue) selectively inhibits xanthine oxidase and had no significant effects on other purine and pyrimidine metabolizing enzymes.[2]
- Allopurinol (purine analogue), oxypurinol and their metabolites inhibit xanthine oxidase and other purine and pyrimidine metabolizing enzymes, such as PNP and OMPDC. [2]

PNP: Purine nucleoside phosphorylase OMPDC: Orotidine-5'-monophosphate decarboxylase

Mechanism of action

Feburic®





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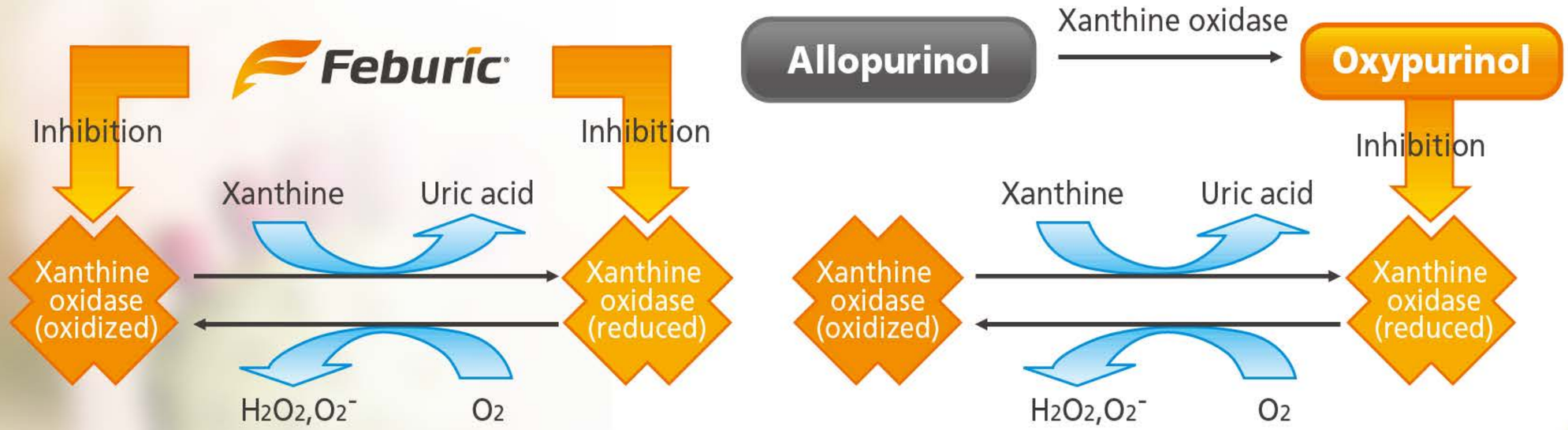
Feburic® displayed potent mixed-type inhibition of xanthine oxidase[2]

- **Feburic®** inhibits both the oxidized and reduced forms of xanthine oxidase.[2]
- Allopurinol is oxidized by xanthine oxidase to oxypurinol which inhibits the reduced form of xanthine oxidase.[2]

Mode of xanthine oxidase inhibition



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Gout: Not Only Pain But With Multiple Co-Morbidities [3-7]

In two American studies, patients with gout were also presented with: [3,4]

We can see:

High prevalence of co-morbidities among gout patients. [3-4]

Gout is linked to increased risk of Renal Failure, Diabetes and Cardiovascular Diseases. [5-7]

Feburic® (febuxostat)

When gout goes to your kidney

CKD Patients Face Therapeutic Dilemma

Feburic® : Preserve Renal Function in Hyperuricemia Patients via Reduction in sUA [9, 10]

Combined pivotal phase III studies showed prompt and persistent efficacy of Feburic® [12]

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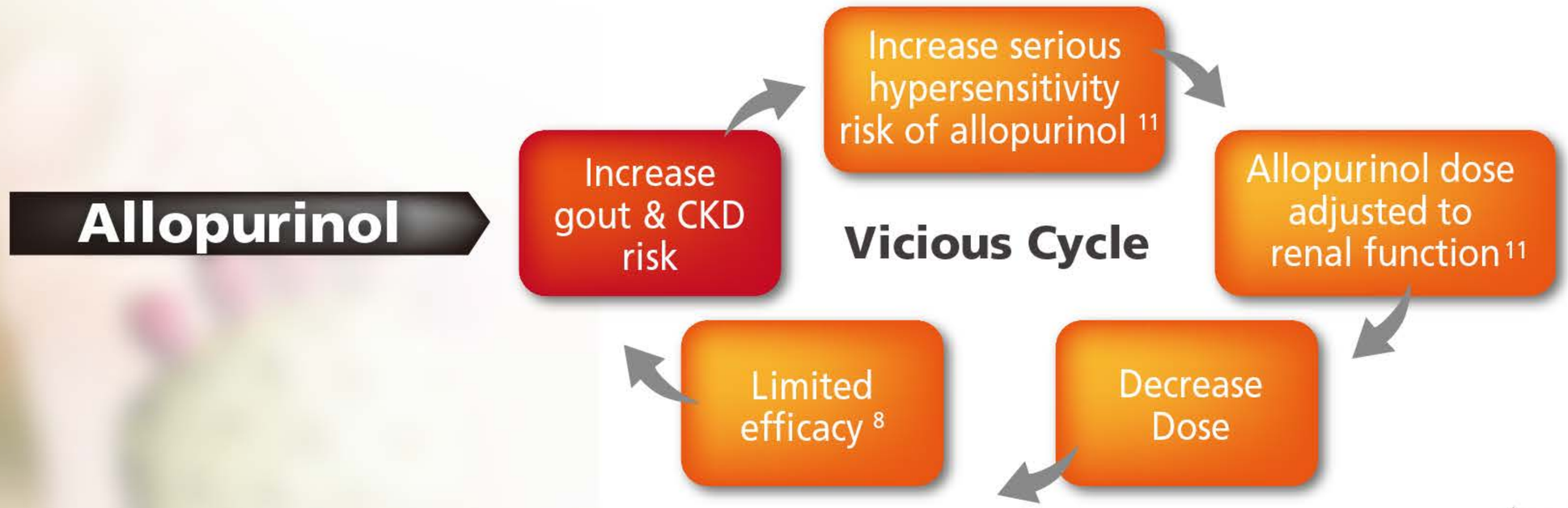
CKD Patients Face Therapeutic Dilemma

Many CKD patients with gout cannot be treated to target because renal impairment limits current gout therapies: [1,8]



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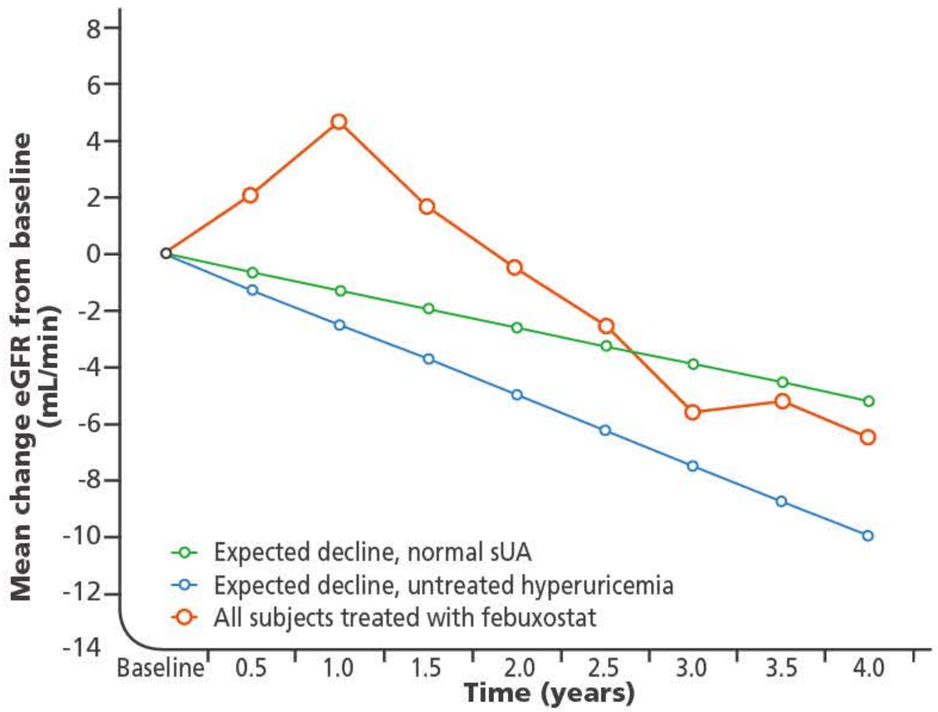
Feburic® : Preserve Renal Function in Hyperuricemia Patients via Reduction in sUA [9,10]



≤ 4-year, open label study, 551 subjects recieved 80/120mg febuxostat daily, Mean baseline sUA=9.8mg/dL

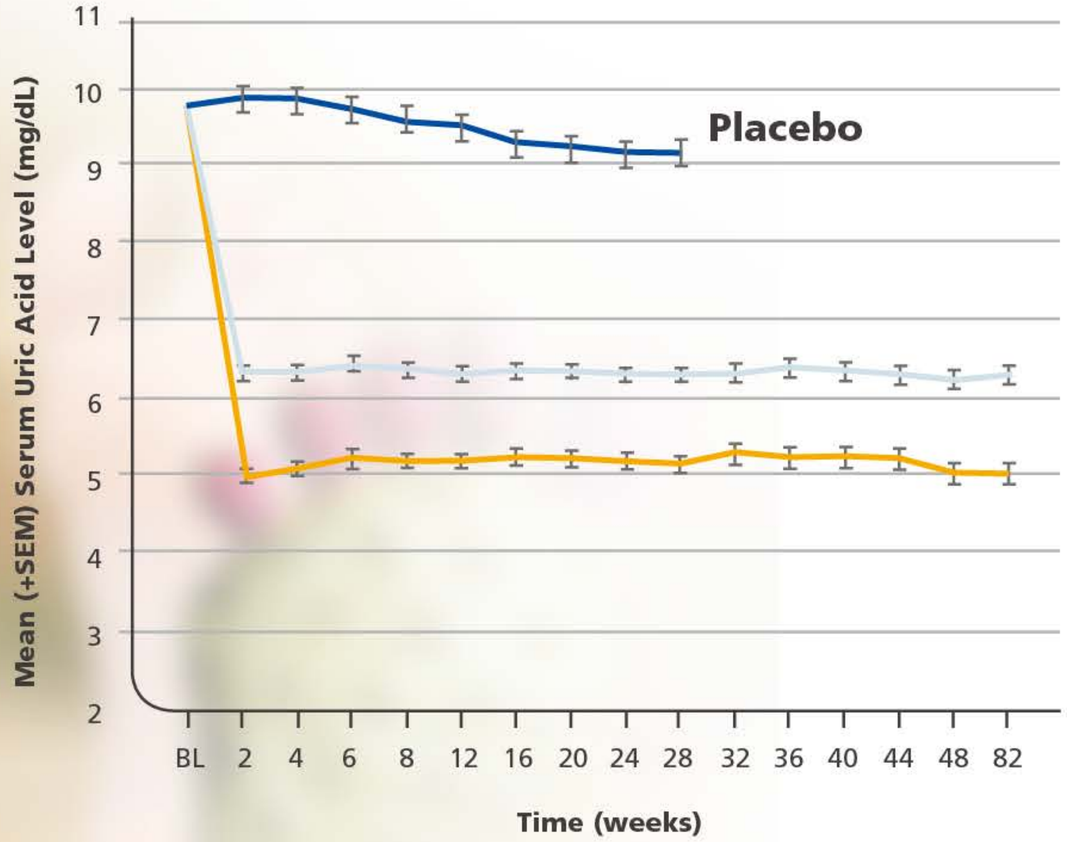
Fig. 1. Overall mean change of eGFR for patients on febuxost compared with expected declines in persons with normal sUA and untreated patients.[9]

- sUA decreases by febuxostat were associated with less renal function decline. [9,10]
- Every 1 mg/dL reduction in sUA would result in a preservation of 1.15 mL/min of eGFR per year as predicted, when compared with no sUA decrease. [9]

Feburic® (febuxostat)

Combined pivotal phase III studies showed prompt and persistent efficacy of Feburic® [12]

- **Feburic®** notably reduced serum uric acid level to <6.0 mg/dL (<360 umol/L) by week 2 and maintained throughout the treatment.[12]



EULAR recommended:
≤ 6 mg/dL (≤ 360 µmol/L)[11]

Allopurinol patients with serum creatinine level >1.5 and≤ 2.0 mg/dL recieved 100 mg (n=10). All other patients recieved Allopurinol 300 mg.

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sUA levels were significantly lower for Hyperuricemia Patients with CKD [14]

Superior Treatment for Hyperuricemia Patients with CKD as shown on NU-FLASH Trial [14]

Better Renal Protective Effect by Feburic® in terms of eGFR [14]

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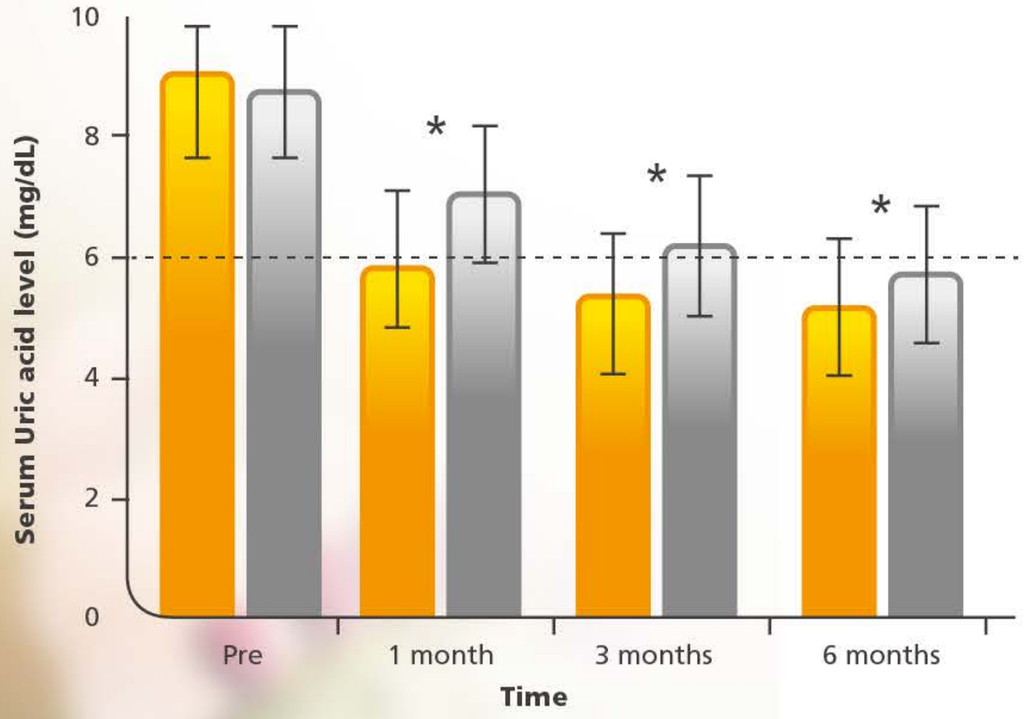
Superior Treatment for Hyperuricemia Patients with CKD as shown on NU-FLASH Trial [14]



Febuxostat

Allopurinol

*p<0.01 Febuxostat vs. Allopurinol

NU-FLASH Trial:
109 Patients
eGFR ≤ 60 mL/min/1.73 m²
sUA ≥ 8 mg/dL

Fig. 3. Changes of sUA level in patients with eGFR≤60 mL/min/1.73m². [14]

For eGFR≤60mL/min/1.73 ², max. dose is 60mg for febuxostat & 300mg for allopurinol. For eGFR≤30mL/min/1.73m ², max. dose is 40mg for febuxostat & 200mg for allopurinol.
The approved dose of febuxostat in Hong Kong is 80mg/day.

- **sUA** levels were **significantly lower** after 1 month of treatment in the febuxostat group than the allopurinol group.
- febuxostat reduced uric acid **more rapidly** than allopurinol.

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Better Renal Protective Effect by Feburic® in terms of eGFR [14]

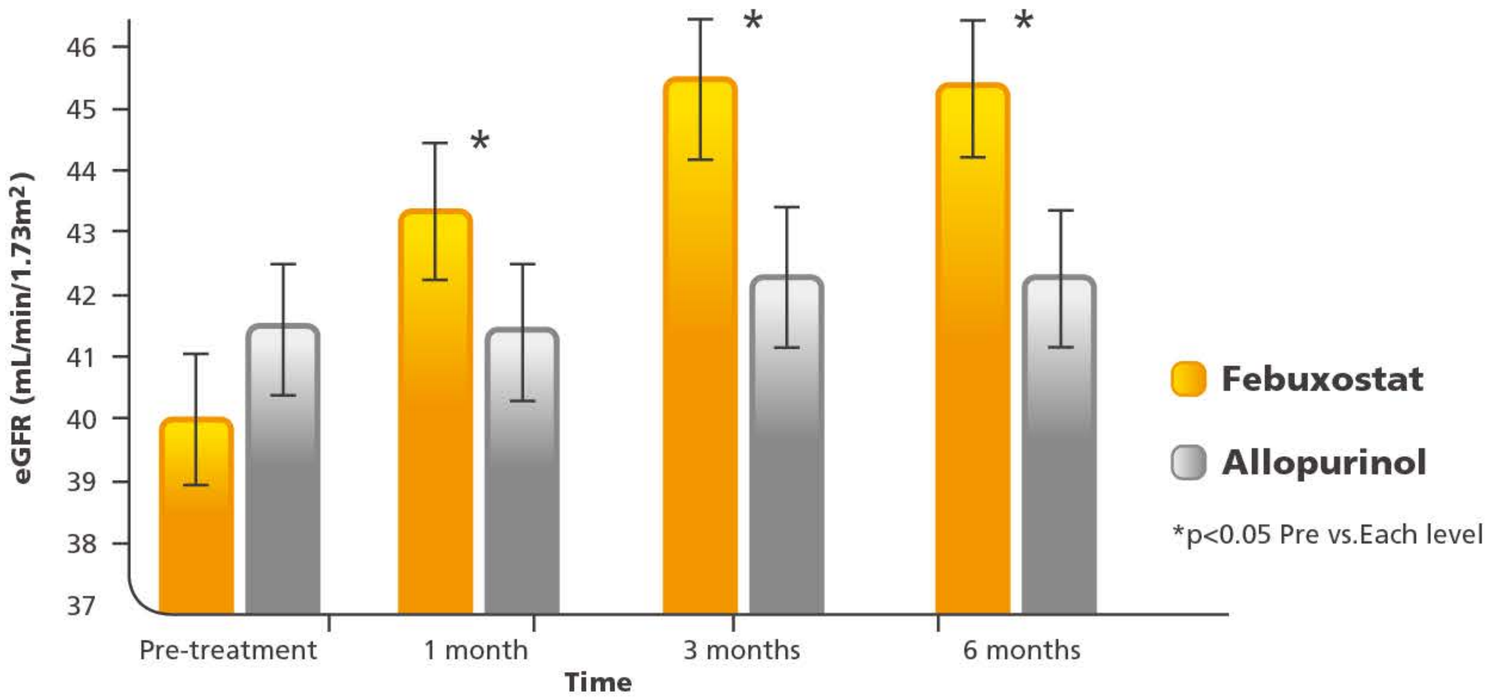

Fig. 4. Changes of eGFR in patients with baseline eGFR ≤60 mL/min/1.73 m². [14] This Figure is drawn from reference 14 table 2.

- eGFR was significantly increased after 1 month in the febuxostat group when compared with baseline. [14]

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EULAR Guidelines[11]

sUA Target and Renal Function Preservation

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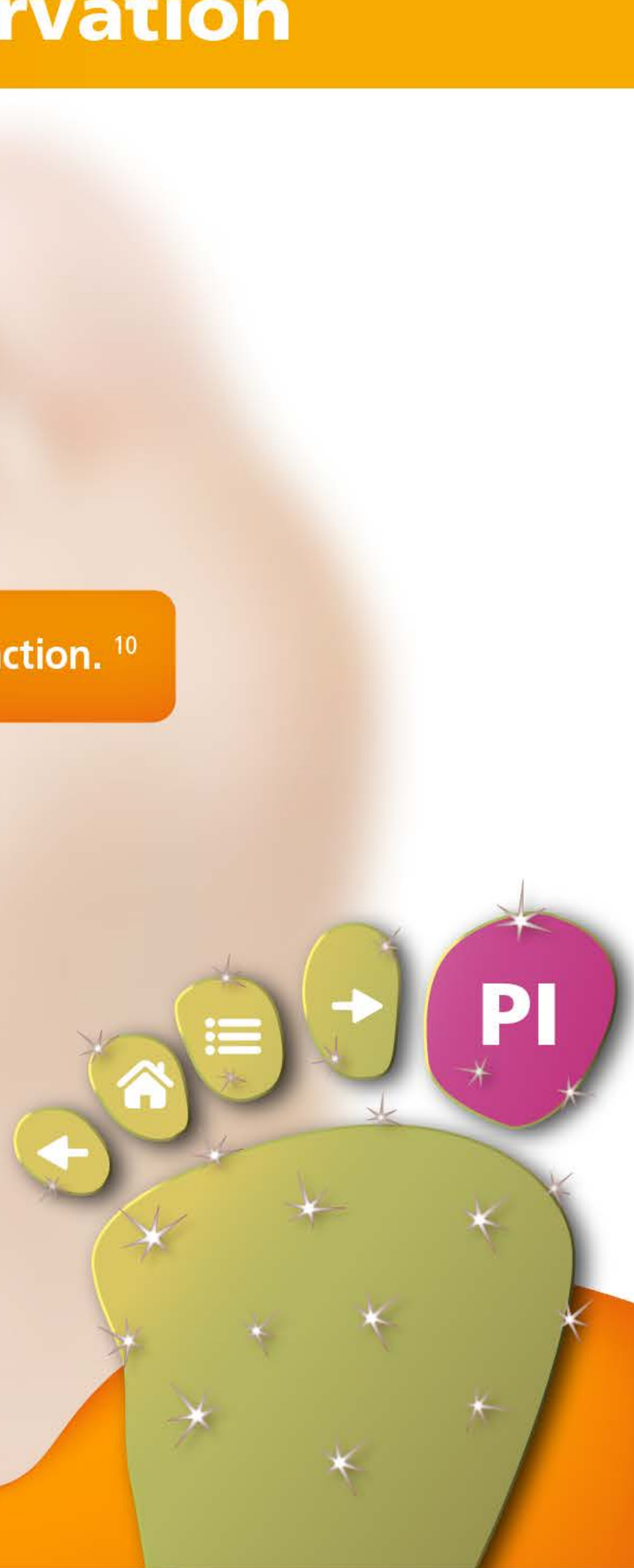
sUA Target and Renal Function Preservation

EULAR Guidelines [11]

- ULT aims to maintain sUA ≤ 6.0 mg/dL or ≤ 360 umol/L

Keep sUA below the saturation point for monosodium urate so as to:
› **Promote crystal dissolution** › **Prevent crystal formation**

- **Maintenance of sUA < 6.0 mg/dL** leads to benefit in **preservation of renal function.** [10]



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Coexistence of HLA-B*5801 and renal impairment increased risk of allopurinol hypersensitivity [16]

Fig.5 Analysis of Risk Factors Associated with Allopurinol Hypersensitivity and Related Mortality. [15,16]

Odds Ratio (95% CI)		
	Allopurinol Hypersensitivity	P value
With chronic renal diseases[§15]	**1.49** (1.38-1.61)	<.001
HLA-B*58:01 Positive[#16] + eGFR:30-60 mL/min/1.73m^2	**300.3** (47.8-3396.1)	<.001
HLA-B*58:01 Positive[#16] + eGFR<30 mL/min/1.73m^2	**1269.45** (192.3-15260.1)	<.001
Age ≥ 80[*15]	**2.27** (1.97-2.60)	<.001

§ consisted of the International Classification of Diseases, 9 th Revision, Clinical Modification (ICD-9-CM) codes 580-586, 589
# homozygous HLA-B*58:01, compared with non-HLA-B*58:01 carriers with eGFR> 60 mL/min/1.73 m2
* compared with age<40

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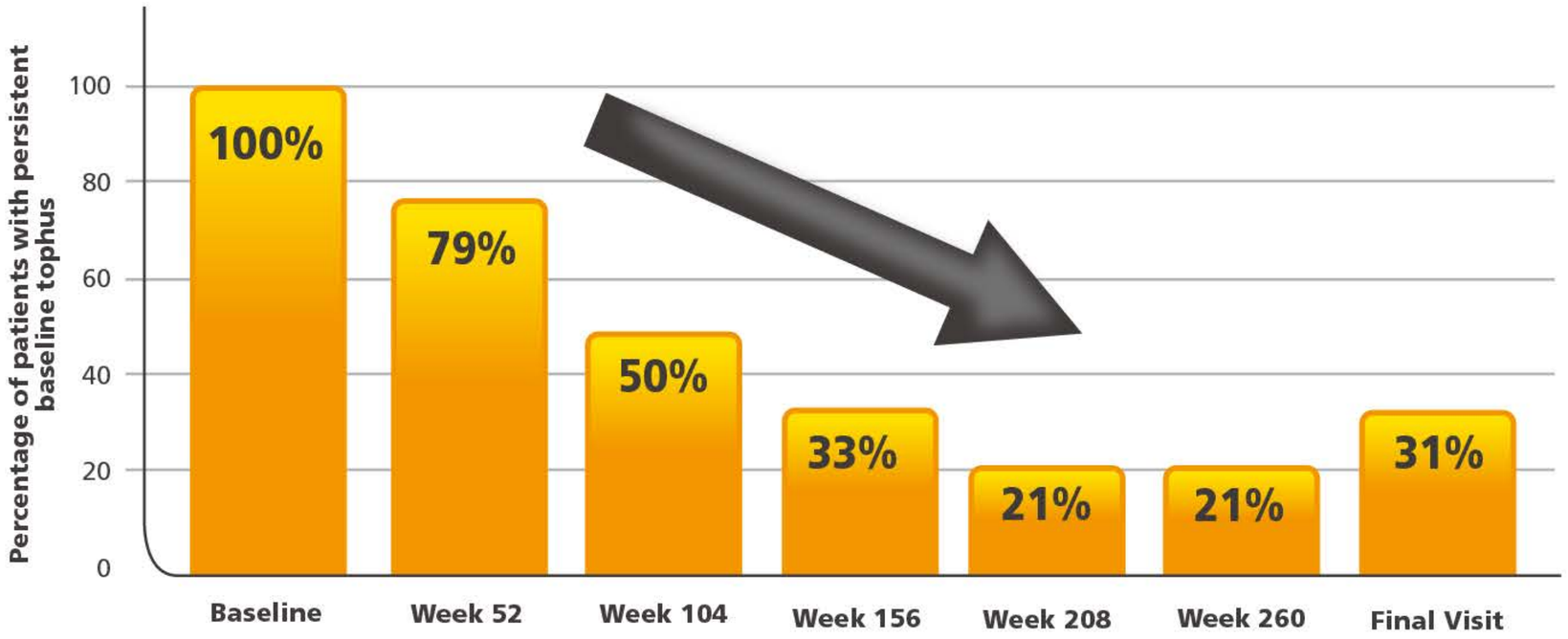
Feburic® open-label study proved tophus resolution in long-term [13]

- In patients with a palpable tophus at baseline, resolution of index tophi was achieved in 69% of patients by final visit. [13]



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References and Abbreviated Prescribing Information

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; ULT, urate-lowering therapy; sUA, serum uric acid.

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1. *Juraschek SP*, et al. *Arthritis Care Res*. 2015;67:588-92. 2. *Takano Y* et al. *Life Sci* 2005;76:1835-47. 3. *Harrold LR*, et al. *Ann Rheum Dis*. 2006;65:1368-72. 4. *Choi HK*, et al. *Arthritis Rheum*. 2007;57:109-15. 5. *Seminog OO & Goldacre MJ. Rheumatology (Oxford)*. 2013;52:2251-9. 6. *Krishnan E*, et al. *QJM*. 2013;106:721-9. 7. *Krishnan E*, et al. *J Rheumatol*, 2013;40:1166-72. 8. *Khanna D*, et al. *Arthritis Care Res (Hoboken)*. 2012;64:1431-46. 9. *Whelton A*, et al. *Postgrad Med*. 2013;125:106-14. 10. *Whelton A*, et al. *J Clin Rheumatol*. 2011;17:7-13. 11. *Richette P* et al. *Ann Rheum Dis*. 2017Jan;76(1):29-42. 12. FEBURIC *Hong Kong package insert*, Nov 2018. 13. *Schumacher HR* et al. *Rheumatology* 2009;48:188-194. 14. *Sezai A*, et al. *J Cardiol*. 2015;66:298-303. 15. *Yang CY*, et al. *JAMA Intern Med*. 2015;175:1550-7. 16. *Ng CY*, et al. *J Invest Dermatol*. 2016;136:1373-1381.

Abbreviated prescribing information of Feburic® film-coated tablets

Version: 005 PI version: Nov 2018 **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 Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended. A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study. The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure. *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. No interaction studies have been performed in humans. Where the combination cannot be avoided, a reduction of the dose of mercaptopurine/azathioprine is recommended. Based on modelling and simulation analysis of data from a pre-clinical study in rats, when coadministered with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to the 20% or less of the previously prescribed dose in order to avoid possible haematological effects. The patients should be closely monitored and the dose of mercaptopurne/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. **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) and post-marketing experience in gout patients are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, 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 and post-marketing experience in gout patients. **Blood and lymphatic system disorders:** Rare: Pancytopenia, thrombocytopenia, agranulocytosis*. **Immune system disorders:** Rare: Anaphylactic reaction*, drug hypersensitivity*. **Endocrine disorders:** Uncommon: Blood thyroid stimulating hormone increased. **Eye disorders:** Rare: Blurred vision. **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. **Nervous system disorders:** Common: Headache. Uncommon: Dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia. **Ear and labyrinth disorders:** Rare: Tinnitus. **Cardiac disorders:** Uncommon: Atrial fibrillation, palpitations, ECG abnormal, left bundle branch block (see section Tumor Lysis Syndrome), sinus tachycardia (see section Tumor Lysis Syndrome). **Vascular disorders:** Uncommon: Hypertension, flushing, hot flush, haemorrhage (see section Tumor Lysis Syndrome). **Respiratory system disorders:** Uncommon: Dyspnoea, bronchitis, upper respiratory tract infection, cough. **Gastrointestinal disorders:** Common: Diarrhoea**, nausea. Uncommon: Abdominal pain, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort. Rare: Pancreatitis, mouth ulceration. **Hepato-biliary disorders:** Common: Liver function abnormalities**. Uncommon: Cholelithiasis. Rare: Hepatitis, jaundice*, liver injury*. **Skin and subcutaneous tissue disorders:** Common: Rash (including various types of rash reported with lower frequencies, see below). Uncommon: Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash popular. Rare: Toxic epidermal necrolysis*, Stevens-Johnson Syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalized rash (serious)*, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*, rash erythematous, rash morbilliform, alopecia, hyperhidrosis. **Musculoskeletal and connective tissue disorders:** Uncommon: Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis. Rare: Rhabdomyolysis*, joint stiffness, musculoskeletal stiffness. **Renal and urinary disorders:** Uncommon: Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria. Rare: Tubulointerstitial nephritis*, micturition urgency. **Reproductive system and breast disorder:** Uncommon: Erectile dysfunction. **General disorders and administration site conditions:** Common: Oedema. Uncommon: Fatigue, chest pain, chest discomfort. Rare: Thirst. **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. Rare: Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase* * 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. *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 charactensed 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 FEBURIC in 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.

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