04.2022

FEBURIC 80 MG film coated tablets **פבאוריק 80 מ"ג טבליות מצופות**

Active ingredient:
febuxostat

חומר פעיל:
פבאוקסוסטאט

רופא/ה, רוקח/ת נכבד/ה,
אנו מתכבדים להודיעך אודות שינויים בעלון לצרכן ובעלון לרופא עבור התכשיר שבנדון.

העדכונים בעלונים מובאים בהודעה זו, **טקסט שנוסף לעלון מופיע מודגש**, ~~טקסט שהוסר מסומן בקו חוצה~~ והחמרות על רקע צהוב

להלן נוסח ההתוויה המאושר לתכשיר:

Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).
Feburic is indicated in adults.

העדכונים העיקריים בעלון לרופא נעשו בסעיפים הבאים:

4.4 Special warnings and precautions for use

Cardio-vascular disorders

~~Treatment with febuxostat in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina) should be avoided, unless no other therapy options are appropriate.~~
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), febuxostat was not inferior to allopurinol in the incidence of both fatal and non-fatal cardiovascular events.
Treatment of this patient group should be exercised cautiously and they should be monitored regularly.
For further details on cardiovascular safety of febuxostat refer to section 4.8 and section 5.1.

~~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 (see section 5.1 for detailed characteristics of the studies). 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.~~
~~In the post registrational CARES trial (see section 5.1 for detailed characteristics of the study) the rate of MACE events was similar in febuxostat versus allopurinol treated patients (HR 1.03; 95% CI 0.87-1.23), but a higher rate of cardiovascular deaths was observed (4.3% vs. 3.2% of patients; HR 1.34; 95% CI 1.03-1.73).~~
(…)

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 is recommended in order to avoid possible haematological effects (see sections 4.5 and 5.3).

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.

(…)

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

4.5 Interaction with other medicinal products and other forms of interaction

Mercaptopurine/azathioprine
On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these drugs leading to myelotoxicity. ~~Drug interaction studies of febuxostat with drugs (except theophylline) that are metabolized by XO have not been performed in humans.~~

~~Modelling and simulation analysis of data from a pre-clinical study in rats indicates that, i~~In case of concomitant administration with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to 20% or less of the previously prescribed dose (see sections 4.4 and 5.3).

The adequacy of the proposed dose adjustment, which was based on a modelling and simulation analysis from preclinical data in rats, was confirmed by the results of a clinical drug-drug interaction study in healthy volunteers, receiving azathioprine 100 mg alone and a reduced dose of azathioprine (25 mg) in combination with febuxostat (40 or 120 mg).

(…)

4.8 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 are gout flares, liver function abnormalities, diarrhoea, nausea, headache, dizziness, dyspnoea, rash ~~and~~ , 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.

(…)

Table 1: Adverse reactions in combined phase 3, long-term extension studies, post-authorisation safety studies and post-marketing experience

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia, agranulocytosis*, anaemia#
Immune system disorders	Rare Anaphylactic reaction*, drug hypersensitivity*
Endocrine disorders	Uncommon Blood thyroid stimulating hormone increased, hypothyroidism#
Eye disorders	~~Rare~~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 ~~Dizziness, p~~Paraesthesia, hemiparesis, somnolence, lethargy# altered taste, hypoaesthesia, hyposmia Rare Ageusia#, burning sensation#
Ear and labyrinth disorders	~~Rare~~Uncommon Tinnitus Rare Vertigo#
Cardiac disorders	Uncommon Atrial fibrillation, palpitations, ECG abnormal, arrhythmia# Rare Sudden cardiac death*
Vascular disorders	Uncommon Hypertension, flushing, hot flush Rare Circulatory collapse#
Respiratory system disorders	Common Dyspnoea Uncommon ~~Dyspnoea, b~~Bronchitis, upper respiratory tract infection, lower respiratory tract infection#, cough, 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 ~~Pancreatitis, ~~Gastrointestinal perforation #, ~~mouth ulceration~~ 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, ~~pruritus,~~ 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,~~ exfoliative rash, rash follicular, rash vesicular, rash pustular, ~~rash pruritic*,~~ rash erythematous, rash morbillifom, ~~alopecia, hyperhidrosis~~
Musculoskeletal and connective tissue disorders	Common Arthralgia, myalgia, pain in extremity# Uncommon ~~Arthralgia, a~~Arthritis, ~~myalgia,~~ musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis, joint swelling #, back pain #, musculoskeletal stiffness#, joint stiffness Rare Rhabdomyolysis*, ~~joint stiffness, musculoskeletal stiffness~~ rotator cuff syndrome #, polymyalgia rheumatica#
Renal and urinary disorders	Uncommon Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria, micturition urgency, urinary tract infection# Rare Tubulointerstitial nephritis*~~, micturition urgency~~
Reproductive system and breast disorder	Uncommon Erectile dysfunction
General disorders and administration site conditions	Common Oedema, Fatigue Uncommon ~~Fatigue, c~~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-authorisation safety studies

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

(…)

FAST study was a prospective, randomised, open-label, blinded-endpoint study comparing the CV safety profile of febuxostat versus allopurinol in patients with chronic hyperuricaemia (in conditions where urate deposition had already occurred) and CV risk factors (i.e. patients 60 years or older and with at least one other CV risk factor). Eligible patients received allopurinol treatment prior to randomization, and dose adjustments were required when needed, according to clinical judgement, EULAR recommendations and the approved posology. At the end of the allopurinol lead-in phase, patients with a sUA level of <0.36 mmol/L (<6 mg/dL) or receiving the maximum tolerated dose or the maximum licensed dose of allopurinol were randomised in a 1:1 ratio to receive either febuxostat or allopurinol treatment. The primary endpoint of the study FAST was the time to the first occurrence of any event included in the Antiplatelet Trialists' Collaborative (APTC) composite endpoint, which included: i) hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome (ACS); ii) non-fatal stroke; iii) death due to a CV event. The primary analysis was based on the on-treatment (OT) approach.

Overall, 6,128 patients were randomized, 3063 to febuxostat and 3065 to allopurinol.

In the primary OT analysis, febuxostat was non-inferior to allopurinol in the incidence of the primary endpoint, which occurred in 172 patients (1.72/100 patient years) on febuxostat compared to 241 patients (2.05/100 patient years) on allopurinol, with an adjusted HR 0.85 (95% CI: 0.70, 1.03), p<0.001. The OT analysis for the primary endpoint in the subgroup of patients with a history of MI, stroke or ACS showed no significant difference between treatment groups: there were 65 (9.5%) patients with events in the febuxostat group and 83 (11.8%) patients with events in the allopurinol group; adjusted HR 1.02 (95% CI: 0.74-1.42); p=0.202.

Treatment with febuxostat was not associated with an increase in CV death or all-cause death, overall or in the subgroup of patients with a baseline history of MI, stroke or ACS. Overall, there were fewer deaths in the febuxostat group (62 CV deaths and 108 all-cause deaths), than in the allopurinol group (82 CV deaths and 174 all-cause deaths).

There was a greater reduction in uric acid levels on febuxostat treatment compared to allopurinol treatment.

העדכונים העיקריים בעלון לצרכן נעשו בסעיפים הבאים:

4. תופעות לוואי

(...)

תופעות לוואי שכיחות (תופעות שיכולות להופיע לכל היותר ב-1 מתוך 10 אנשים)**:**

(...)

- סחרחורת
- קוצר נשימה
- גירוד
- כאבים בגפיים, כאב בשרירים/במפרקים
- עייפות

תופעות לוואי שאינן שכיחות (תופעות שיכולות להופיע לכל היותר ב-1 מתוך 100 אנשים)**:**

(...)

- ~~סחרחורת~~

(...)

- ~~קוצר נשימה~~
  זיהום בדרכי הנשימה התחתונות
- כאבים בבטן העליונה
- גירוד~~פריחה~~ מגרדת
  הזעה מוגברת, הזעת לילה, התקרחות, אדמומיות של העור (אריתמה), פסוריאזיס, אקזמה
- ~~כאב בשרירים/במפרקים~~
  ~~כאבים בגפיים~~
  נוקשות שרירים ו/או מפרקים

- דלקת בדרכי השתן
- ~~עייפות~~
- ירידה בפעילות בלוטת התריס
- טשטוש ראיה, שינויים בראיה
- צלצולים באוזניים
- נזלת
- כיבים בפה
- דלקת של הלבלב: תסמינים נפוצים הינם כאב בטן, בחילה והקאות
- צורך דחוף במתן שתן
- כאב
- חולשה
- עליה ב-INR
- חבלה
- שפתיים נפוחות

תופעות לוואי נדירות (תופעות שיכולות להופיע לכל היותר ב-1 מתוך 1000 אנשים):
(...)

- נפיחות חמורה בשכבות העמוקות של העור, במיוחד סביב ~~השפתיים~~, העיניים, איברי המין, ידיים, כפות הרגליים או הלשון, עם אפשרות לקושי פתאומי בנשימה
- ~~אדמומיות של העור (אריתמה),~~ סוגים שונים של פריחה (כגון: ~~מגרדת,~~ עם נקודות לבנות, עם שלפוחיות, עם שלפוחיות מוגלתיות, עם קילוף העור, פריחה דמוית חצבת), אריתמה נרחבת, נמק, והיפרדות
- ~~צלצולים באוזניים~~
- ~~טשטוש ראיה, שינויים בראיה~~
- ~~נשירת שיער~~
- ~~כיבים בפה~~
- ~~דלקת של הלבלב: תסמינים נפוצים הינם כאב בטן, בחילה והקאות~~
- ~~הזעה מוגברת~~
- ~~נוקשות שרירים ו/או מפרקים~~
- ~~צורך דחוף במתן שתן~~
- זיהום בשלפוחית השתן
- ספירת תאי דם אדומים נמוכה (אנמיה)
- דיכאון
- הפרעות שינה
- אובן חוש טעם
- תחושת בעירה/צריבה
- ורטיגו
- כשל במחזור הדם
- דלקת ריאות
- פצעים בפה; דלקת של הפה
- ניקוב במערכת העיכול
- קרע במסובבי הכתף/ תסמונת השרוול המסובב
- פולימיאלגיה ראומטית
- תחושת חום
- אובדן ראייה פתאומי עקב חסימה של עורק בעין

- העלונים לרופא ולצרכן נשלחו למשרד הבריאות לצורך העלאתם למאגר התרופות שבאתר משרד הבריאות.
- ניתן לקבל עלונים אלה מודפסים על ידי פניה ישירה לבעל הרישום:
ניאופרם בע"מ, רח' השילוח 6, ת.ד. 7063, פתח תקווה 4917001, טלפון: 03-9373737.

בברכה,
אבי ילצינדג,
רוקח ממונה
ניאופרם בע"מ