מרץ 2023

רופא/ה רוקח/ת נכבד/ה,

חברת פאדאגיס מבקשת ליידע אתכם על עדכון בעלונים לרופא ולצרכן של התכשירים:

אימוראן טבליות 25 מ"ג / Imuran Tablets 25mg

אימוראן טבליות 50 מ"ג / Imuran Tablets 50mg

החומר הפעיל בתכשיר וחוזקו: Azathioprine 25mg/Azathioprine 50mg

<u>התוויה הרשומה לתכשיר בישראל :</u>

Immunosuppressive agent used in transplantation surgery for suppression of graft rejection. For special cases of rheumatoid arthritis- not responsive to other agents- and only by rheumatology experts in hospitals or rheumatic clinics.

<u>מהות העדכון</u>:

בהודעה זו מצוינים ומסומנים ברקע צהוב עדכוני בטיחות ועדכוני נוסח מהותיים בלבד. העלונים כוללים גם עדכונים נוספים אשר אינם נחשבים כמהותיים ולכן אינם מצויינים כאן.

העלונים לצרכן ולרופא המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il

בברכה,
פאדאגיס ישראל סוכנויות בע"מ

עלון לרופא

4.4 Special warnings and precautions for use

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Xanthine oxidase inhibitors

If allopurinol, oxipurinol and/or thiopurinol are given concomitantly with azathioprine, the dosage of azathioprine must be reduced to a quarter of the original dose (see section 4.2).

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4.5 Interaction with other medicinal products and other forms of interaction

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Cytostatic/myelosuppressive agents (see Section 4.4)

Where possible, concomitant administration of cytostatic agents, or medicinal products which may have a myelosuppressive effect, such as penicillamine, should be avoided. There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine and ~~co-trimoxazole~~trimethoprim/sulfamethoxazole.

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Neuromuscular ~~blocking~~ agents

There is clinical evidence that azathioprine antagonises the effect of non-depolarising muscle relaxants such as curare, d-tubocurarine and pancuronium. Experimental data confirm that azathioprine reverses the neuromuscular blockade produced by ~~non-depolarising agents (such as d-~~tubocurarine~~)~~, and show that azathioprine potentiates the neuromuscular blockade produced by ~~depolarising agents, such as~~ succinylcholine (see ~~Section~~ section 4.4). There is considerable variation in the potency of this interaction.

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4.6 Fertility, pregnancy and lactation

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Mutagenicity

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There have been reports of intra-uterine growth retardation, premature birth and low birth weight following maternal exposure to azathioprine, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure.

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4.7 Undesirable effects

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Body System	Frequency	Side effects
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Rare	Neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*, acute myeloid leukaemia and myelodysplastic syndrome ~~myelodysplasia~~ (see Section 4.4).

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5.2 Pharmacokinetic properties

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Distribution

The volume of distribution at steady state (Vdss) of azathioprine is unknown. The mean (± SD) apparent Vdss of 6-MP is 0.9 (±0.8) L/kg, although this may be an underestimate because 6-MP is cleared throughout the body (and not just in the liver).

Approximately 30% of azathioprine is protein bound.

Concentrations of 6-MP in cerebrospinal fluid (CSF) are low or negligible after i.v. or oral administration of 6-MP.

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Elimination

After oral administration of 100mg 35S-azathioprine, 50% of the radioactivity was excreted in the urine over 24 hours and 12% in the faeces after 24 hours. In the urine, the major compound was the inactive oxidised metabolite thiouric acid. Less than 2% was excreted in the urine as azathioprine or 6-MP. Azathioprine has a high extraction ratio with a total clearance greater than 3L/min in normal volunteers. There are no data on the renal clearance or half-life of azathioprine. The renal clearance of 6-MP and the half-life of 6-MP are 191 mL/min/m2 and 0.9 hr respectively.

Mercaptopurine, a metabolite of azathioprine, has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.
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5.3 Preclinical safety data

Mutagenicity
Azathioprine was found to be mutagenic in a number of *in vitro* and *in vivo* genotoxicity assays

Carcinogenicity
Long-term carcinogenicity studies of azathioprine showed an increased incidence of lymphosarcomas, as well as epithelial tumours and carcinomas in mice and rats, respectively, at dosages of up to 2-fold the human therapeutic dose and at lower dosages in immunocompromised mice.

עלון לצרכן
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2. לפני השימוש בתרופה

אינטראקציות/תגובות בין תרופתיות
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- ~~קו-טרימוקסאזול (Co-trimoxazole)~~ טרימתופרים/סולפאמתוקסזול (Trimethoprim/sulfamethoxazole) אנטיביוטיקה לטיפול בזיהומים הנגרמים על ידי חיידק.
- אינפליקסימאב (Infliximab) משמש בעיקר לטיפול במחלות מעיים הנקראות קוליטיס כיבית או מחלת קרוהן.
- מרפי שרירים כגון טובוקוררין (Tubocurarine) או סוקסינילכולין (Succinylcholine) משמשים במהלך הניתוח, כיוון שהם עלולים להגיב עם אימוראן טבליות . לפני ניתוח יש לעדכן את הרופא המרדים, על כך שהינך מטופל באזאתיופרין, מאחר ומרפי שרירים הניתנים בהרדמה עלולים להגיב עם אזאתיופרין.

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