יוני 2023

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת נוברטיס ישראל בע"מ מבקשת להודיעכם על עדכון העלון של התכשיר:

METHOTREXAT "EBEWE" 100 MG/ML

Concentrate for solution for infusion

מרכיב פעיל: methotrexate 100 mg/ml

ההתוויות המאושרות לתכשיר:

Antineoplastic Chemotherapy: Treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. Palliation of acute lymphocytic leukemia. In the treatment and prophylaxis of meningeal leukemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem cell) leukemias in children. In combination with other anticancer agents, methotrexate may be used for the induction of remission,but is most commonly used in maintenance of induced remissions. Methotrexate may be used alone or in combination with other antineoplastics in the management of breast cancer, epidermoid cancers of the head and neck, lung cancer (particularly squamous cell and small cell types), bladder cancer and osteogenic cancer.
Methotrexate is effective in the treatment of the advanced stages (III and IV, Peters' Staging System) of lymphosarcoma, particularly in children, and in advanced cases of mycosis fungoides.

בהודעה זו מצויינים רק הסעיפים בהם בוצעו שינויים מהותיים ועדכוני בטיחות בעלון לרופא. החמרות הודגשו בצהוב, עדכונים שאינם החמרות סומנו בצבע שונה, ומידע שהוסר סומן עם קו חוצה.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:

מאגר התרופות(health.gov.il)

לעדכונכם בברכה,

דפנה סנדובסקי

רוקחת ממונה חטיבת סנדוז

נוברטיס ישראל בע"מ

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4.4 Special warnings and precautions for use

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Nervous system

In case of **patients with previous cranial radiotherapy**, there have been reports of **leukoencephalopathy** after intravenous administration of methotrexate**.**

Chronic leukoencephalopathy was also observed in patients who had received a repeated high-dose methotrexate therapy with calcium folinate rescue without previous cranial radiotherapy.

There is evidence that the combined use of cranial irradiation together with intrathecal administration of methotrexate increases the incidence of leukoencephalopathy (see also section 4.8).

Progressive multifocal leukoencephalopathy (PML)
Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, usually in combination with other immunosuppressants. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with newly occurring or worsening neurological symptoms.

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Use ~~Administration~~ in paediatric patients

Particular caution is required if methotrexate is used in the treatment of children and adolescents. Treatment should comply with the therapy protocols that were specifically developed for children.

In **paediatric patients with acute lymphoblastic leukaemia (ALL)**, severe **neurotoxicity** can occur after treatment with moderately high doses (1 g/m^2 BSA) of methotrexate. This is often seen as a generalised or focal epileptic seizure. In symptomatic patients, diagnostic imaging usually shows leukoencephalopathy and/or microangiopathic calcification.

Use ~~Administration~~ in elderly patients

Particular caution is also required in elderly patients. The patients should be examined in short intervals for early signs of toxicity. The clinical pharmacology of methotrexate in the elderly has not yet been fully researched. The methotrexate dose should be adjusted to the hepatic and renal performance, which is reduced due to old age. Partially modified therapy protocols, for example for the treatment of ALL, have been developed for elderly patients (aged 55 and over).

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4.8 Undesirable effects

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Nervous system disorders

Very common:	headaches, dizziness
Common:	drowsiness, paraesthesia
Uncommon:	hemiparesis, confusion, seizures (in parenteral administration), leukoencephalopathy/encephalopathy* (in parenteral administration)
Rare:	paresis, speech disorders including dysarthria and aphasia, myelopathy (after lumbar application)
Very rare:	muscle weakness and pain in the extremities, dysgeusia (metallic taste), acute aseptic meningitis (paralysis, vomiting), cranial nerve syndrome, ~~/~~hypoaesthesia
Not known:	neurotoxicity, arachnoiditis, paraplegia, stupor, ataxia, dementia, increase in cerebrospinal fluid pressure

The intravenous use of methotrexate may lead to acute encephalitis and acute encephalopathy with fatal outcome.

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Skin and subcutaneous tissue disorders*

Very common:	alopecia
Common:	exanthema, erythema, pruritus, photosensitivity, skin ulcerations
Uncommon:	severe toxic manifestations: herpetiform skin eruptions, Stevens-Johnson syndrome*, toxic epidermal necrolysis (Lyell's syndrome)*, urticaria, increased skin pigmentation, nodulosis, painful erosions of psoriatic plaques, impaired wound healing
Rare:	acne, petechiae, ecchymosis, erythema multiforme, erythematous skin rashes, increased pigment changes of the nails, onycholysis
Very rare:	furunculosis, telangiectasia, acute paronychia
Not known:	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), exfoliative dermatitis

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Reproductive system and breast disorders

Uncommon:	vaginal ulcerations and inflammations
Rare:	transient oligospermia, transient irregular menstrual cycles
Very rare:	impaired ~~disturbed~~ oogenesis/spermatogenesis*, infertility*, menstrual disorders ~~irregular menstrual cycles~~, loss of libido, impotence, vaginal discharge, gynecomastia
Not known:	urogenital dysfunction

General disorders and administration site reactions ~~conditions~~

Very common:	exhaustion, malaise
Uncommon:	pyrexia, in **intramuscular administration** of methotrexate, **local adverse reactions** (burning sensation) or damage (sterile abscess formation, destruction of adipose tissue) may appear at the injection site.
~~Very rare:~~	~~chills~~
Not known:	injection site necrosis, chills, oedema

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~~7. MANUFACTURER~~

~~Ebewe Pharma Ges.m.b.H Nfg. KG, Mondseestrasse 11, 4866 Unterach Am Attersee, Austria~~

7.~~8.~~ ~~MARKETING AUTHORISATION~~ LICENSE HOLDER AND IMPORTER'S NAME AND ADDRESS:

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