ספטמבר 2024

רוקח/ת נכבד/ה,רופא/ה נכבד/ה,

חברת פרופארם בע"מ מודיעה על עדכון בהתוויה ובעלון לרופא של התכשיר:

Sodium valproate Wockhardt

סודיום ואלפרואט ווקהרט

חומר פעיל: VALPROIC ACID (AS SODIUM) 100 MG/ML

צורת מינון: SOLUTION FOR INJECTION / INFUSION

צורת המתן:.I.V

עדכונים בעלון לרופא

<u>ההתוויה המעודכנת כפי שאושרה בתעודת הרישום:</u>

Treatment of:
•Generalized seizures in the form of absences, myoclonic and tonic-clonic seizures
•Partial and secondary generalized seizures.
Combination treatment of other forms of seizures.

<u>ברצונינו להודיע שהעלון לרופא עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד(תוספות /שינויים מסומנים באדום והחמרות/מידע חדש באדום על רקע צהוב):</u>

עדכונים עיקריים בעלון לרופא:

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of:

- *Generalized seizures in the form of absence, myoclonic and tonic-clonic seizures*
- *Partial and secondary generalized seizures.*

Combination treatment of other forms of seizures.

4.3 Contraindications

Sodium Valproate Wockhardt is contraindicated in the following situations:

[…]

– In women of childbearing potential, ~~unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.~~

– Patients with uncorrected systemic primary carnitine deficiency (see section 4.4).

4.4 Special warnings and precautions for use

<u>Conditions of occurrence</u>

[…]

disorders including mitochondrial disorders such as carnitine deficiency, urea cycle disorders, POLG mutations (see sections 4.3 and 4.4)

[…]

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Monotherapy is recommended in children under the age of 3 years when prescribing Sodium Valproate Wockhardt, but the potential benefit of Sodium Valproate Wockhardt should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy. (see also section 4.4 Severe liver damage and also section 4.5).

Detection

Liver function should be measured before and then periodically monitored during the first 6 months of therapy, especially in those who seem at risk, and those with a prior history of liver disease**.** Upon changes in concomitant medicinal products (dose increase or additions) that are ~~disease~~ **known to impact the liver, liver monitoring should be restarted as appropriate (see section 4.5).**

Patients at risk of hypocarnitinaemia

Valproate administration may trigger occurrence or worsening of hypocarnitinaemia that can result in hyperammonaemia (that may lead to hyperammonemic encephalopathy). Other symptoms such as liver toxicity, hypoketotic hypoglycaemia, myopathy including cardiomyopathy, rhabdomyolysis, Fanconi syndrome have been observed, mainly in patients with risk factors for hypocarnitinaemia or pre-existing hypocarnitinaemia. Patients at increased risk for symptomatic hypocarnitinaemia when treated with valproate include patients with metabolic disorders including mitochondrial disorders related to carnitine (see also section 4.4 Patients with known or suspected mitochondrial disease and Urea cycle disorders and risk of hyperammonaemia), impairment in carnitine nutritional intake, patients younger than 10 years old, concomitant use of pivalate-conjugated medicines or of other antiepileptics.
Patients should be warned to report immediately any signs of hyperammonaemia such as ataxia, impaired consciousness, vomiting. Carnitine supplementation should be considered when symptoms of hypocarnitinaemia are observed.
Patients with systemic primary carnitine deficiency and corrected for hypocarnitinaemia may only be treated with valproate if the benefits of valproate treatment outweigh the risks in these patients and there is no therapeutic alternative.
In these patients, carnitine monitoring should be implemented.

4.5 Interaction with other medicinal products and other forms of interaction

Metamizole

Metamizole may decrease valproate ~~with Metamizole~~ serum levels when co-administered, which ~~is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction~~ may result in ~~plasma concentrations of~~ potentially decreased valproate clinical efficacy. ~~Therefore caution is advised when Metamizole~~ Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

Methotrexate

Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control) and consider monitoring valproate ~~are administered concurrently; clinical response and/or drug~~ serum levels ~~should be monitored~~ as appropriate.

[…]

Risk of liver damage

The concomitant use of salicylates should be avoided in children under 3 years of age due to the risk of liver toxicity (see section 4.4). Concomitant use of valproate and multiple anticonvulsant therapy increases the risk of liver damage, especially in young children (see section 4.4).

Concomitant use with cannabidiol increases the incidence of transaminases enzyme elevation. In clinical trials in patients of all ages receiving concomitantly cannabidiol at doses 10 to 25 mg/kg and valproate, ALT increases greater than 3 times the upper limit of normal have been reported in 19% of patients. Appropriate liver monitoring should be exercised when valproate is concomitantly used with other anticonvulsants with potential hepatotoxicity, including cannabidiol, and dose reductions or discontinuation should be considered in case of significant anomalies of liver parameters (see section 4.4).

Pivalate-conjugated medicines
Concomitant administration of valproate and pivalate-conjugated medicines (such as cefditoren pivoxil, adefovir, dipivoxil, pivmecillinam and pivampicillin) should be avoided due to increased risk of carnitine depletion (see section 4.4 Patients at risk of hypocarnitinaemia). Patients in whom coadministration cannot be avoided should be carefully monitored for signs and symptoms of hypocarnitinaemia.

4.6 Fertility pregnancy and lactation

[…]
In animals: Teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).
[…]

In utero exposure to valproate may result in eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision

Neurodevelopmental disorders
[…]
When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopmental disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated women with epilepsy.
[…]

Available data ~~suggests~~ from another population-based study show that children exposed to valproate *in utero* ~~may be more likely to develop symptoms of~~ are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study
~~Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).~~
Fertility
[…]
Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited number of case reports suggest that a strong dose reduction may improve fertility function. However, in some other cases, the reversibility of male infertility was unknown.

~~Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.~~

4.8 Undesirable effects

[…]
Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have ~~very rarely~~ uncommonly been observed.
[…]
Not known: hypocarnitinaemia (see section 4.3 and 4.4).

Paediatric population
The safety profile of valproate in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years.
Young children are also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of Post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

4.9 Overdose

Symptoms

[…]

plasma concentration 10 to 20 times the maximum therapeutic levels usually include CNS depression or coma with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome is usual. However some deaths have occurred following massive overdose.

העלון לרופא מצורף להודעה זו וכן נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות.
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בברכה,

מירי חזן
רוקחת ממונה