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Revision of Precautions

Sodium valproate

March 28, 2019

Non-proprietary name

Sodium valproate

Safety measure

Precautions should be revised in the package insert.

In the Contraindications section:
The following language should be revised (revised language is underlined):

<Common indications>
Patients with serious hepatic impairment (severe hepatic impairment may occur, which could become fatal.)
Carbapenem antibiotics (panipenem/betamipron, meropenem hydrate, imipenem hydrate/cilastatin sodium, biapenem, doripenem hydrate, tebipenem pivoxil) should not be administered to patients who are receiving this drug.
Patients with urea cycle disorder (serious hyperammonaemia may occur.)

And the following language should be added (revised language is underlined):

<Prophylaxis of migraine attacks>
Pregnant women or women who may be pregnant

In the Relative Contraindications section:
The following language should be revised (revised language is underlined):

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<Treatment of various types of epilepsy and personality or behaviour disorder associated with epilepsy, treatment of mania or manic state of manic-depressive psychosis>
Pregnant women or women who may be pregnant.

In the Use during Pregnancy, Delivery or Breastfeeding section:
The following language should be revised (revised language is underlined):
<Treatment of various types of epilepsy and personality or behaviour disorder associated with epilepsy, treatment of mania or manic state of manic-depressive psychosis>
Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks.
If administration of this drug during pregnancy is considered absolutely necessary, monotherapy should preferably be chosen whenever possible (an epidemiological study reported an increased number of cases who gave birth to infants with malformation found in the group of women who were taking other antiepileptics, carbamazepine particularly, concomitantly with this drug compared with the group of women who were taking this drug alone.)

Language concerning risks in neonates or born infants, reports on animal studies, and breast-feeding women should be revised as follows (revised language is underlined):

<Common indications>
An epidemiological study reported an increased number of cases who were administered ingredients of this drug in early pregnancy found in women who gave birth to infants with spina bifida compared with the control group. Infants with heart malformation such as ventricular septal defect, external malformation such as polydactyly, cleft palate, or hypospadias, and other types of malformation born to women who were administered ingredients of this drug were also reported. Infants born with distinct faces (frontal protrusion, ocular hypertelorism, depressed nasal ridge, shallow and long philtrum, and thin lips) have been reported.
Administration of this drug during pregnancy may cause respiratory disorder, hepatic impairment, hypofibrinogenemia in infants.

Hypoglycaemia or withdrawal signs (nervousness, hypertonicity, convulsion, vomiting) that administration of this drug during pregnancy may cause in neonates have been reported.
In an observational study conducted overseas that compared intelligence quotient at 6 years of age (age-6 IQ, [mean, 95% CI]) of 244 children among different antiepileptic drugs their mothers were administered during pregnancy, lower age-6 IQs (98, 95-102) in children born to patients with epilepsy who were administered valproate sodium were reported compared with children born to patients with epilepsy who were administered lamotrigine (108, 105-111), phenytoin (108, 104–112), or carbamazepine (106, 103-109). The IQ outcomes associated with daily doses of sodium valprorate lower or higher than 1000 mg/day (the mean of the study) were 104 (99-101) and 94 (90-99), respectively.
In another observational study conducted overseas, an increased risk of autism found in 508 children born to mothers who were administered sodium valprorate during pregnancy was reported compared with 655 107 children born to mothers who were not administered sodium valprorate. Adjusted hazard ratio was 2.9 (1.7-4.9.)
An animal study using mice reported that sodium valprorate may inhibit folic acid metabolism, which could be involved in congenital malformation in newborns.
Women should be counseled to avoid breastfeeding when they are administered sodium valprorate (the drug may be excreted in human breast milk.)

And the following language should be added (revised language is underlined):

<u><Reduction of the risk of migraine attacks></u>
<u>This drug should not be administered to pregnant women or women who may be pregnant.</u>