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HPRA DRUG SAFETY NEWSLETTER

106TH EDITION

Review of latest evidence on risks associated with in-utero exposure to phenytoin, phenobarbital, carbamazepine, pregabalin and valproate

Antiepileptic drugs (AEDs), also known as anti-seizure medications or anticonvulsants, have proven benefits in the treatment of various forms of epilepsy, with some having additional indications in other therapeutic areas*. For some medicines in this class, use during pregnancy has been associated with major congenital malformations (MCMs) and neurodevelopmental disorders in children exposed in-utero. As part of routine safety monitoring activities coordinated at EU level, the risks associated with in-utero exposure to phenytoin, phenobarbital, carbamazepine, pregabalin and valproate were recently reviewed, following which recommended updates to product information** are being implemented.

A summary of the recent reviews in relation to these AEDs, together with recommendations for use in women of childbearing potential and during pregnancy, is provided in this edition.

Key messages for healthcare professionals

- When prescribing AEDs for a woman of childbearing potential, in any indication, healthcare professionals (HCPs) should fully consider and discuss what is known about the potential risks associated with in-utero exposure, as well as any recommendations concerning contraception and pregnancy planning, including actions to take in the event of a suspected or confirmed pregnancy.
- Phenytoin, phenobarbital and carbamazepine have a risk of MCMs approximately 2-3 fold that of the baseline risk seen in the general population. Study findings on the risk of neurodevelopmental disorders are contradictory and a risk cannot be excluded based on available evidence at this time. These findings are also considered relevant for primidone (which is metabolised to phenobarbital) and fos-phenytoin (a pro-drug of phenytoin).
- For pregabalin monotherapy, available data show that if used in the first trimester, it is associated with a slightly higher risk of MCMs as compared to women not using pregabalin, or those using lamotrigine or duloxetine.
- For topiramate, the most recent review of evidence showed the risk of MCMs is approximately 3 fold that of the baseline risk seen in the general population.
- For lamotrigine and levetiracetam, previous reviews of a large amount of post marketing data on pregnant women exposed to lamotrigine or levetiracetam monotherapy during the first trimester did not suggest a substantial increase in the risk for MCMs.
- For valproate, epidemiological data have demonstrated that use of valproate monotherapy during pregnancy is associated with a risk of MCMs of approximately 11% (4-5 fold that of the baseline risk seen in the general population) and up to 30-40% for neurodevelopmental disorders in children exposed in-utero.
- HCPs are reminded that use of valproate is contraindicated in women of childbearing potential unless the specific conditions of a pregnancy prevention program are fulfilled. For further information, refer to the guide for healthcare professionals on the HPRA website.
- In women of childbearing potential treated for epilepsy, sudden discontinuation of an AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

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Phenytoin, phenobarbital, carbamazepine

The recent reviews at EU level for phenytoin, phenobarbital, carbamazepine included the latest data from observational studies, pregnancy registries and meta-analyses on the risks of major congenital malformations (MCMs) and neurodevelopmental disorders in children exposed in-utero. These data are also applicable to primidone (extensively metabolised to phenobarbital) and fos-phenytoin (a pro-drug of phenytoin).

Overall, the increased risk of MCMs in children exposed in-utero was found to be approximately 2 to 3 fold that of the baseline risk seen in general population (which has a frequency of 2-3%). Studies investigating the association between in-utero exposure to these medicines and neurodevelopmental disorders had contradictory findings, and a risk cannot be excluded based on available evidence at this time.

The evidence supports the recommendation that these medicines should only be prescribed for women of childbearing potential or in pregnancy when the potential benefit is judged to outweigh the risks, and following consideration of other suitable treatment options.

A summary of the key findings for each of these AEDs is provided in the table below.

Phenytoin **Fos-phenytoin**	• The prevalence of MCM in children exposed in-utero to phenytoin as monotherapy was found to be 6.26% (95% CI: 4.37% – 8.47%) in a meta-analysis[1] based on data from 25 studies including 1279 exposed pregnancies, and 6.4% (95% CI: 2.8%–12.2%) in a prospective cohort study based on data from a pregnancy registry, including 125 exposed pregnancies[2]. • Malformations such as orofacial clefts, cardiac defects, craniofacial defects, nail and digit hypoplasia, and growth abnormalities (including microcephaly and prenatal growth deficiency), have been reported either individually or as part of a Foetal Hydantoin Syndrome among children born to women with epilepsy who used phenytoin during pregnancy. • Available evidence was insufficient to conclude on a dose-dependent risk of MCM. • Neurodevelopmental disorders have been reported among children born to women with epilepsy who used phenytoin alone or in combination with other AEDs during pregnancy. Study findings on the risk of neurodevelopmental disorders in children exposed to phenytoin in-utero are contradictory and a risk cannot be excluded. • The magnitude of the risk to the unborn child is unknown when phenytoin use is of short duration in emergency situations, for example, parenteral phenytoin administration in a hospital setting. • Study findings are also relevant for fos-phenytoin which is a pro-drug of phenytoin and is rapidly converted into phenytoin.
Phenobarbital **Primidone**	• The prevalence of MCM in children exposed in-utero to phenobarbital monotherapy was found in the meta-analysis to be 7.10% (95% CI: 5.36 - 9.08) based on 23 studies including 709 exposures[1] and 7.10% (95% CI: 5.36 - 9.08) in the prospective cohort study and 6·5% (95% CI 4·2–9·9) based on 294 exposures[2]. • Available evidence suggests the risk is dose-dependent; however, no dose has been found to be without risk. • Associations between exposure in-utero and specific birth defects of cleft lip and palate and cardiac malformations have been demonstrated[1,3] while data from a registry study suggests an increased risk of children born small for gestational age or with reduced body length, compared to lamotrigine monotherapy[4]. • Neurodevelopmental disorders have been reported among children exposed to phenobarbital in-utero. However studies related to the risk of neurodevelopmental disorders in children exposed are inconclusive and contradictory, but a risk cannot be excluded. Pre-clinical studies have also reported adverse neurodevelopment effects. • The magnitude of the risk to the unborn child is unknown when phenobarbital use is of short duration, for example, parenteral administration in emergency situations. • As primidone is extensively metabolised into phenobarbital, the results of these studies were considered to be relevant also for primidone.

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Carbamazepine	• The prevalence of MCM in children exposed in-utero to carbamazepine monotherapy was found to be 4.93% (95% CI: 3.84 to 6.16) in the meta-analysis, based on data from 30 studies including 4666 pregnancy exposures[1], and 5·5% (95% CI: 4·5–6·6) in the prospective cohort study, based on 1957 exposed pregnancies[2]. • Available evidence suggests that the risk is dose-dependent. • The types of malformations which have been reported in exposed children include neural tube defects (spina bifida), craniofacial defects such as cleft lip/palate, cardiovascular malformations, hypospadias, hypoplasia of the fingers, and other anomalies involving various body systems. • Study findings on the risk of neurodevelopmental disorders in children exposed to carbamazepine in-utero are contradictory; however, a risk cannot be excluded.

Advice to healthcare professionals

Key recommendations in relation to use of these medicines in women of childbearing potential and during pregnancy are summarised below. For recommendations specifically related to the use of parenteral products in the context of emergency situations, please refer to the SmPC for the individual products.

- The latest evidence supports the recommendation that these medicines should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options.
- When necessary to prescribe for a woman of childbearing potential, the patient should be informed of the potential risks to an unborn child, and treatment regularly reviewed.
- The patient should be counselled on the need to use effective contraception during treatment and for an appropriate length of time following discontinuation, should treatment be stopped.
- A pregnancy test should be considered before initiation of treatment.
- Due to enzyme induction, phenytoin, fos-phenytoin, phenobarbital, primidone and carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives. Therefore, counselling regarding the use of other effective contraceptive methods should be given.
- The patient should be informed to consult a doctor if pregnancy is being planned to allow for review of alternative treatments before contraception is discontinued and prior to conception.
- The patient should be informed to contact her doctor immediately if pregnancy is suspected or confirmed.
- In the event of pregnancy, treatment should be reassessed and alternative suitable treatment options should be considered.
- When prescribed as part of AED therapy, specialist medical advice should be given regarding the potential risks to an unborn child caused by both seizures and antiepileptic treatment, especially when pregnancy is planned or a woman is pregnant. Sudden discontinuation of any AED therapy should be avoided as this may lead to seizures that could have serious consequences for the woman, and if pregnant, the unborn child.
- Pregnant women should be prescribed the lowest effective dose if, following a careful evaluation of the risks and benefits, no alternative treatment option is suitable.
- Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

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Pregabalin

A population-based cohort study examined outcomes following exposure during pregnancy, using data from national administrative registries from four Nordic countries (Denmark, Finland, Norway, and Sweden) and included more than 2700 pregnancies exposed to pregabalin in the first trimester[5]. Results indicate a higher prevalence of major congenital malformations (MCMs) among the paediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%) within the study.

The risk of MCMs among the paediatric population exposed to pregabalin monotherapy in the first trimester was slightly higher compared to the unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)), and compared to the population exposed to lamotrigine (1.29 (1.01–1.65)) or to duloxetine (1.39 (1.07–1.82)). Analyses of specific malformations showed higher risks for orofacial clefts and for nervous system, eye, urinary and genital malformations; however, the numbers of events were low and estimates are imprecise.

The results of this study reinforce the existing recommendations that it is appropriate for women of childbearing potential to use effective contraception during treatment and that pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the unborn child).

Advice to healthcare professionals

- Observational data suggest that first trimester pregabalin monotherapy may be associated with a slightly higher risk of MCMs compared to women not using pregabalin, or those using lamotrigine or duloxetine.
- Results reinforce current advice that women of childbearing potential must use effective contraception during treatment and that pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the unborn child.

Valproate (Epilim®)

Healthcare professionals (HCPs) are reminded that for valproate, epidemiological data have demonstrated that use of valproate monotherapy during pregnancy is associated with a risk of approximately 11% for major congenital malformations (MCMs) and up to 30-40% for neurodevelopmental disorders in children exposed in-utero. Emerging data continue to be evaluated at EU level, based on which the risk of in-utero exposure to valproate continues to be characterised, including the impact of valproate in polytherapy on the risk of MCMs or neurodevelopmental disorders compared to valproate monotherapy. Epidemiological studies and other cumulative data suggest that the risk of MCMs in children following in-utero exposure to AED polytherapy including valproate is higher than AED polytherapy not including valproate. This risk is dose-dependent in valproate monotherapy, with no threshold dose below which there is no risk, and available data suggest it is dose-dependent in valproate polytherapy. Additionally, although already recognised that the risk of neurodevelopmental disorders (including that of autism) seems to be dose-dependent when valproate is used as monotherapy, the risks of neurodevelopmental disorders is also significantly increased when valproate is administered as part of a polytherapy AED regimen, compared to the unexposed population.

In April 2018, a special edition of the HPRA Drug Safety Newsletter (Editions 87) was published to communicate increased restrictions around the use of valproate in female children and women of childbearing potential to prevent valproate exposure during pregnancy. Due to the known teratogenic potential, valproate should not be used in female children and women of childbearing potential[1] unless other treatments are ineffective or not tolerated. Treatment must be initiated and supervised by a suitably experienced specialist. In addition, use in women of childbearing potential in any indication (epilepsy, bipolar disorder) is contraindicated unless the conditions of a pregnancy prevention programme (known as 'prevent') are fulfilled. Valproate is contraindicated as treatment for bipolar disorder during pregnancy and as a treatment for epilepsy during pregnancy unless there is no suitable alternative.

A cross-sectional study was conducted in June 2019 using anonymous online surveys among general practitioners (GPs), pharmacists, and specialist consultants in Ireland to examine their awareness, knowledge, and practice in the year following implementation of the 'prevent' pregnancy prevention program for valproate[6]. The survey was sent to a random sample of HCPs, 3820 in total. Response rates were 5.8% for GPs (90/1544), 10.7% for pharmacists (219/2052), and 7.6% for specialists (17/224). Across HCP groups, in those that responded, there was high awareness (>90%) for specialist referral when female valproate patients are planning pregnancy, or become pregnant, but less awareness to refer annually for specialist review. While awareness of a possible teratogenic effect at any stage of pregnancy was high (>80%), most GPs (62.2%, 95% CI: 51.3, 71.9%) and

community pharmacists (53.1%, 95% CI: 43.2, 62.8%) were unsure of the magnitude of risk for developmental disorders, while most specialists underestimated this risk (46.7%, 95% CI: 24.8, 69.9%). Although >70% of the respondents identified valproate to be contraindicated in any woman of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled, experience implementing key elements in practice varied. Whilst acknowledging the limitations of the study, including a low response rate, the findings highlight the importance of continued effort to support full implementation of 'prevent' in clinical practice. The HPRA published a special edition Drug Safety Newsletter (Edition 97) to remind HCPs of the conditions of the pregnancy prevention program, which includes a summary of the necessary actions for HCPs to take. A guide for healthcare professionals regarding 'prevent' is also available on the HPRA website.

Advice to healthcare professionals

- HCPs are reminded that valproate has a high teratogenic potential, with children exposed in-utero having an approximate 11% risk of MCMs and up to 30-40% risk of neurodevelopmental disorders.
- Recent reviews of epidemiological studies and other cumulative data suggest that the risk of MCMs in children following in-utero exposure to AED polytherapy including valproate is higher than AED polytherapy not including valproate. This risk is dose-dependent in valproate monotherapy and available data suggest it is dose-dependent in valproate polytherapy.
- A threshold dose of valproate below which no risk exists cannot be established based on current evidence.
- The HPRA published a special edition Drug Safety Newsletter (Edition 97) to remind HCPs of the conditions of the pregnancy prevention program (called 'prevent'), which includes a summary of the necessary actions for HCPs to take. Further background information is available from the HPRA website, including a guide for healthcare professionals.

References

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2. *Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol. 2018 Jun;17(6):530-538.*
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4. *Hernández-Díaz S, McElrath TF, Pennell PB, et al. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. Ann Neurol. 2017 Sep;82(3):457-465.*
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6. *Hughes JE, Buckley N, Looney Y, Kirwan G, Curran S, Doherty CP, Mullooly M & Bennett KE (2021) Awareness, knowledge and practice of healthcare professionals following implementation of a pregnancy prevention program for sodium valproate in Ireland: a multi-stakeholder cross-sectional study, Expert Opinion on Drug Safety, 20:8, 965-977*

* *These medicines are indicated (as per their approved product information) in the treatment of various forms of epilepsy, with some having additional indications in other therapeutic areas such as psychiatry (for example treatment of generalised anxiety disorder and mania, prophylaxis of manic depressive illness and management of alcohol withdrawal symptoms) and neuropathic pain (for example treatment of peripheral and central neuropathic pain and trigeminal neuralgia).*

** *Product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is accessible from the HPRA website.*

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Champix (varenicline)	Batches to be recalled due to presence of impurity N-nitroso-varenicline above acceptable limit
Vaxzevria (COVID-19 Vaccine AstraZeneca)	Risk of thrombocytopenia (including immune thrombocytopenia) with or without associated bleeding
COVID-19 Vaccine Janssen	Risk of immune thrombocytopenia (ITP) and venous thromboembolism (VTE)
Forxiga (dapagliflozin)	Forxiga 5mg should no longer be used for the treatment of Type 1 Diabetes Mellitus
Beovu (brolucizumab)	Updated recommendations to minimise the knowns risk of intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion

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