Valproic acid (sodium valproate)

Essential medicine status ✓

Section: 24. Medicines for mental and behavioural disorders > 24.2. Medicines for mood disorders > 24.2.2. Medicines for bipolar disorders

ATC codes: N03AG01

Indication	Bipolar or related disorders ICD11 code: 6A8Z
INN	Valproic acid
Medicine type	Chemical agent
List type	Core
Additional notes	Avoid use in pregnancy and in women and girls of child-bearing potential, unless alternative treatments are ineffective or not tolerated because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.
Formulations	Oral > Solid: 200 mg tablet (enteric-coated) ; 500 mg tablet (enteric-coated)
EML status history	First added in 1997 (TRS 882) Changed in 2007 (TRS 950) Changed in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Valproic acid (sodium valproate)
DrugBank	Valproic acid

Expert Committee recommendation

The Expert Committee recognized the serious risks associated with the use of valproic acid in pregnant women and in females of child-bearing potential. While most of the evidence and regulatory measures described in the application are from Europe, the risks with valproate when prescribed to women and girls of child-bearing potential are equally relevant globally. Sodium valproate is currently listed as an essential medicine for use in the treatment of epilepsy and bipolar disorder, indications for which it has regulatory approval. Furthermore, valproic acid is recommended for the management of epilepsy and bipolar disorder in the WHO mhGAP intervention guide. These guidelines also include a strong recommendation to avoid the use of valproic acid in women of child-bearing age. The Committee considered that inclusion of a cautionary note with the listings of valproic acid to indicate that use should be avoided in pregnant women and females of child-bearing potential was appropriate, although it is aware the EML does not replace prescribing information issued by national medicine regulatory authorities. The Committee did not recommend transferring the listing of valproic acid from the core to the complementary list. The Committee considered doing so may have negative implications for access to valproic acid and undermine its important role in the management of epilepsy and bipolar disorder, particularly in resource-constrained settings, where access to valproate and alternative treatments is limited. The Committee supported the need for patient and prescriber education on the risks and appropriate use of valproic acid, including its use for off-label indications, but considered this to be a responsibility of the relevant national decision-makers. The Committee recommended the following note be included with the listings for valproic acid on the EML and EMLc: “Avoid use in pregnancy and in women and girls of child-bearing potential unless alternative treatments are ineffective or not tolerated, because of the high risk of birth defects and developmental disorders in children exposed to valproate in the womb.”

Background

Valproic acid has been included on the EML as a medicine for epilepsy since 1979. It was included on the first EMLc for this indication in 2007. Since 1997, valproic acid has also been included on the EML for the treatment of bipolar disorder in adults.

Public health relevance

Valproic acid is used in the treatment of labelled indications of epilepsy and bipolar disorder, as well as off-label indications such as migraine prophylaxis, neuropathic pain and behavioural disturbances in dementia. Valproic acid is a known human teratogen, and its use during pregnancy is associated with an increased risk of birth defects and neurodevelopmental disorders in children exposed to the drug in utero (1–7). To address these risks, regulatory agencies in many parts of the world, including Europe, the United Kingdom and the USA have issued guidance and/or restrictions on the use of valproic acid in pregnancy and in women and girls of child-bearing potential (8–11).

Harms

The application reproduced the warnings, precautions and contraindications for the use of valproic acid in female children, adolescents and women of child-bearing potential and in pregnancy from past and current summaries of product characteristics. The application also briefly described two studies that evaluated the effects of antiepileptic medicines, including valproic acid, on cognitive and neurodevelopmental outcomes in children exposed to the drugs in utero. The NEAD study was a prospective, observational multicentre study conducted in the United Kingdom and USA that evaluated the effects of commonly prescribed antiepileptic medicines (carbamazepine, lamotrigine, phenytoin or valproic acid) on cognitive outcomes in children up to 6 years of age born to mothers receiving these medicines during pregnancy (12). The primary outcome of the study was intelligence quotient (IQ) of children at age 6. A total of 244 children were included in the age 6 analysis. The study found that the age 6 IQ was lower in children exposed to valproic acid compared with children exposed to other antiepileptic drugs. Children exposed to valproate also did poorly on measures of verbal and memory abilities compared with children exposed to other antiepileptic drugs. These effects of valproic acid were dose-dependent. Another prospective, observational study of children born to women with epilepsy compared with a control group of children born to women without epilepsy was conducted in the United Kingdom (1). This study reported an increased risk of neurodevelopmental disorders in children exposed to valproic acid as monotherapy (adjusted odds ratio (aOR) 6.05, 95%CI 1.65 to 24.53) and as polytherapy (aOR 9.97, 95% CI 1.82 to 49.40) compared with controls. Autistic spectrum disorder was the most frequent diagnosis. No significant increase in neurodevelopmental disorders was found among children exposed to carbamazepine or lamotrigine as monotherapy.

WHO guidelines

The WHO mhGAP intervention guide, version 2.0 for mental, neurological and substance use disorders in non-specialized health settings (13) includes recommendations for the use of valproic acid in the treatment of epilepsy and manic episodes in bipolar disorder. The guide also includes warnings to avoid the use of valproic acid in women of child-bearing age and during pregnancy and breastfeeding due to the known risks to the child. The WHO Pharmaceuticals Newsletter (14) states the following in relation to the use of valproic acid in pregnancy or in females of child-bearing potential. “Medicines containing valproate (e.g. sodium valproate, valproic acid, divalproex) should be avoided in pregnant women or in females of child-bearing potential, unless alternative treatments are ineffective or not tolerated, because of the high risk of birth defects (such as spina bifida, facial, skull, limb and heart malformations) and developmental disorders in infants who are exposed to valproate in the womb. When alternative treatments are not available or appropriate, female patients prescribed valproate medicines should be made aware of the risk and use effective contraception methods.”

1. Bromley RL, Mawer GE, Briggs M, Cheyne C, Clayton-Smith J, García-Fiñana M, et al. The prevalence of neurodevelopmental disor ders in children prenatally exposed to antiepileptic drugs. J Neurol Neurosurg Psychiatry. 2013;84(6):637–43.
2. Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014;2014(10):Cd010236.
3. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children of women with epilepsy, unexposed or e xposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. Drug Saf. 2010;33(1):73–9.
4. Kaneko S, Battino D, Andermann E, Wada K, Kan R, Takeda A, et al. Congenital malformations due to antiepileptic drugs. Epilepsy R es. 1999;33(2–3):145–58.
5. Diav-Citrin O, Shechtman S, Bar-Oz B, Cantrell D, Arnon J, Ornoy A. Pregnancy outcome after in utero exposure to valproate: evid ence of dose relationship in teratogenic effect. CNS drugs. 2008;22(4):325–34.

6. Dravet C, Julian C, Legras C, Magaudda A, Guerrini R, Genton P, et al. Epilepsy, antiepileptic drugs, and malformations in children of women with epilepsy: a French prospective cohort study. Neurology. 1992;42(4 Suppl 5):75–82.
7. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016;11(11):Cd010224.
8. Casassus B. France bans sodium valproate use in case of pregnancy. Lancet. 2017;390(10091):217.
9. PRAC recommends new measures to avoid valproate exposure in pregnancy [internet]. Amsterdam: European Medicines Agency; 9 February 2018 (https://www.ema.europa.eu/en/news/prac-recommends-new-measures-avoid-valproate-exposure-pregnancy, accessed 5 May 2021).
10. Iacobucci G. MHRA bans valproate prescribing for women not in pregnancy prevention programme. BMJ. 2018;361:k1823.
11. FDA drug safety communication: valproate anti-seizure products contraindicated for migraine prevention in pregnant women due to decreased IQ scores in exposed children [internet]. Washington, DC: US Food and Drug Administration; 2016 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-valproate-anti-seizure-products-contraindicated-migraine-prevention, accessed 5 May 2021).
12. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244–52.
13. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP) – version 2.0. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250239, accessed 12 August 2021).
14. WHO Pharmaceuticals Newsletter No. 5, 2020. Geneva: World Health Organization; 2020. (https://apps.who.int/iris/handle/10665/336439, accessed 5 May 2021).