Justification

- Evidence was extracted from one systematic review and NMA: Veroniki et al., 2017 (96 studies; 92 cohort studies, 3 case–control studies and 1 RCT) *(184)*.
- Most ASMs are associated with higher risks of major congenital malformations in offspring of women taking these medicines during pregnancy compared with controls who were not taking an ASM.
- The highest risks of major (OR = 2.93; 95% CI: 2.36 to 3.69) and minor (OR = 17.76; 95% CI: 1.60 to 633.30) congenital malformation were reported in infants of women taking sodium valproate.
- Phenobarbital, phenytoin and carbamazepine were also associated with higher risks of major and minor congenital malformations.
- Topiramate was associated with higher risks of major congenital malformations with no information on minor congenital malformations available.
- The risk of major congenital malformation was not significantly higher in infants of women taking lamotrigine (OR = 0.96; 95% CI: 0.72 to 1.25) or levetiracetam (OR = 0.72; 95% CI: 0.43 to 1.16). No information on minor congenital malformations is available.
- There were no data on the teratogenic effect of lacosamide.
- There were no high-quality studies identified on the side-effects related to ASM exposure exclusively through breast-milk and the 2015 recommendation has been validated by the GDG.
- Due to the high risk of teratogenic effect with valproic acid, the GDG believed it was important to provide clear directions on the use of ASM in women and girls with epilepsy who are of childbearing potential and therefore made a strong recommendation despite the low certainty of evidence.

Remarks

- Major congenital malformations include malformations present from birth with surgical, medical, functional or cosmetic importance (cardiac malformations, cleft lip/palate, club foot, hypospadias, inguinal hernia, and undescended testes in boys). Minor congenital malformations include any congenital malformation that did not qualify as major congenital malformation.

Research gaps

- Most of the research is from HICs. Further research is needed in LMICs.
- There were no data on the side-effects related to ASM exposure exclusively through breast-milk. It is, though, noted that the amount of ASM in breast-milk is extremely low and that the baby will likely have been exposed to the same ASM(s) in higher concentration while in utero.

Implementation considerations

- The choice of medicine is affected by a number of factors, including seizure semiology, comorbidities, availability, cost and side-effects.
- Women and girls of childbearing potential who are prescribed sodium valproate should be advised to use effective contraception without interruption, for the entire duration of treatment. Further information on contraception is available in the WHO fact sheet on family planning and contraceptive methods *(185)*. They must be provided with information on pregnancy prevention and risks associated with use of sodium valproate during pregnancy, and referred for contraceptive advice if they are not using effective contraception. When choosing the contraception method, individual circumstances should be evaluated in each case, involving the woman in the discussion to guarantee her engagement and compliance with the chosen measures.
- If a woman taking sodium valproate is planning to become pregnant, a person trained in the management of epilepsy in pregnant women should consider alternative treatment options. Women should be informed of the need to consult their physician as soon as they are planning pregnancy and to urgently consult their physician in case of pregnancy.
- Every effort should be made to switch from sodium valproate to appropriate alternative treatment prior to conception. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making.