C.5	Sodium valproate – complementary list/cautionary note
Does the application adequately address the issue of the public health need for the medicine?	☐ Yes ☐ No ☒ Not applicable Comments: Sodium valproate is already listed in both EMLs (adults and children), the application is to move the medicine to complementary list and adding a cautionary note (see summary)
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Though several Anti-epileptic medicines (AEMs) namely carbamazepine, diazepam, lorazepam, phenytoin, lamotrigine, magnesium sulphate, phenobarbital, midazolam, Valproic acid and ethosuximide (E- only complementary) are listed in both EMLa and EMLc, only carbamazepine, Valproic acid and lamotrigine are suitable for maintenance therapy for epilepsy With lamotrigine not included in many national EMLs of resource limited countries, the option is limited to carbamazepine and sodium valproate for these countries. Hence, sodium valproate is an important medicine to remain in EMLs
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☒ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: 1. Application is to move sodium valproate from core to complementary list 2. Evidence supporting this request is mainly limited to UK and has considered only one aspect of sodium valproate, its teratogenic potential
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☐ No ☒ Not applicable Issue is about the teratogenicity risk of Valproic acid. Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☐ Yes ☐ No ☒ Not applicable- Application is focussing only on one aspect of sodium valproate, it's teratogenic risk Comments: 1. Teratogenicity of Valproic acid is well known 2. The application has meticulously compiled a. Changes in the SPC and PIL of main brands of sodium valproate available in UK and USA with regard to safety of its product during pregnancy b. Studies and audits done in the UK with regard to safety of sodium valproate during pregnancy
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Not only Teratogenicity, sodium valproate also causes hepatic toxicity, pancreatitis, obesity and metabolic abnormalities It is known to cause idiosyncratic hepatotoxicity 1 in 37,000 people taking the drug and the risk increases to 1 in 500 in children on combination of multiple drugs
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Overall benefit is favourable compared to the risks associated with the use of Valproic acid Benefits: Epilepsy is a debilitating disease which affect all ages. Uncontrolled epilepsy in children has serious long term medical, psychological and social long term consequences. In addition, uncontrolled epilepsy has economic implications for individuals and for society. Sodium valproate is effective in seizure control for many types of epilepsy (BNF indications: All forms of epilepsy, migraine prophylaxis, mania) Risks: Teratogenicity, hepatotoxicity, metabolic abnormalities, obesity, drug interactions Comparison: In my assessment, overall benefits is favourable. HOWEVER What is required is: Prevention of teratogenicity (completely avoidable if all stakeholders play their role) and prevention of hepatotoxicity (not completely preventable, but with proper precautions, frequency and severity can be minimised)
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Sodium valproate is already listed in WHO Model EML, Application is to move it to complementary list and add a cautionary note
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: See my summary

Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	See below
Any additional comments	See below
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	1. Epilepsy is an important non communicable disease of all ages, both in recourse limited and resource rich countries 2. Sodium valproate is indicated for all forms of epilepsy 3. Serious risks associated with sodium valproate is teratogenicity (FVS) and valproate induced liver disease (VILD) 4. BNF (2018)*: Risk of serious developmental disorders (up to 30-40%) and congenital malformations (approximately 11% risk) 5. Key features of FVS include neural tube disorders 6. VILD: 1 in 37,000 people taking the drug and the risk increases to 1 in 500 in children on combination of multiple drugs 7. FVS is completely preventable if all stakeholders strictly adhere to the guidance and information 8. BNF 2018: Sodium valproate should not be used in female children, females of child bearing potential and during pregnancy unless alternative treatments are ineffective or not tolerated 9. BNF 2018 also lists the precautions the pregnant women had to take if they are using sodium valproate 10. Points 8 and 9 shows that use of sodium valproate is permitted during pregnancy in UK (this may have been changed in recent volumes of BNF, in that case, I withdraw my points 8,9 and 10) 11. In WHO model EML, valproate is listed under epilepsy and mania 12. Under Epilepsy, even though several AEMs are listed in the WHO Model EML, only carbamazepine, sodium valproate and lamotrigine are suitable for maintenance therapy for epilepsy. 13. WHO EML is a Model. Many national EMLs of resource limited countries list only carbamazepine and sodium valproate 14. Carbamazepine is effective for only few types of epilepsy and not to be given for few types of epilepsy such as myoclonic epilepsy and absence seizures (Sodium valproate is effective for both these epilepsies) 15. Essential Medicine Lists are used for procurement and supply of essential medicines in resource limited countries. 16. Definition of complementary list in WHO EML: The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt medicines may also be listed as complementary

	on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings. 17. Hence, moving sodium valproate to complementary list will give mixed signals: It will undermines its role in the management of epilepsy and affect large number of patients especially in RLCs 18. Studies have reported poor access to AEMs in developing countries. Removing sodium valproate from core list of EML will further reduce the access to AEMs 19. In addition, purpose of EMLs is "Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts" – Hence, individual countries can plan the levels of hospitals where sodium valproate should be made available 20. Risk of FVS is limited to females of child bearing potential – However, epilepsy occurs from infancy to elderly and in both genders – FVS will not be an issue for males, female children before puberty and females after menopause 21. I totally agree with the concerns raised in the application regarding the risk of foetal valproate syndrome when female of child bearing potential are exposed to valproate, but moving sodium valproate to complementary list is not an answer for this problem 22. Moving sodium valproate to complementary list will compromise its access to many patients with epilepsy in resource limited countries. The impact will be beyond estimation 23. Nearly 80% of people with epilepsy live in low- and middle-income countries (WHO) 24. Hence, for the proposals given in the application **A.** Should have an additional Cautionary Note attached to its listing in the EML and EMLc (**recommended)** **B.** Valproate should be transferred to the Complementary Listing **(not recommended)** **C.** Valproate should receive additional monitoring with a view to the De-prescribing in the UK (**should leave to countries to decide as alternatives are more expensive and may not be listed in National EML, WHO can provide the technical guidance)** D. Extra guidance given to Valproate and off label prescribing (recommended) *25.* Suggest using a symbol in the core-list to caution the use of sodium valproate in female of chid bearing age indicating what the symbol denotes (e.*g.; Where the [c] symbol is placed next to an individual medicine or strength of medicine on the core list it signifies that there is a specific indication for restricting its use to children)* 26. 23 C and 23 D- There will be other medicines in the EMLs which also need this guidance and
	https://www.who.int/medicines/services/essmedicines_def/en/

***** *Recent volumes are not accessible to people in RLCs*

Note: The incidence of epilepsy is higher in the youngest and oldest age-groups [11], with estimates of 86 per 100,000 per year in a well-defined population in the first year of age, a trend to decrease to about 23–31 per 100,000 in people aged 30–59 years, and a subsequent increase up to 180 per 100,000 in the over 85 age-group [16]. In children, the incidence of epilepsy is highest in the first year of life and declines to adult levels by the end of 10 years of age [17]. In LMIC, epilepsy peaks in children; this may be a result of under-ascertainment of the condition in older individuals as well as the demographic structure of the country.

Beghi E: The Epidemiology of Epilepsy. Neuroepidemiology 2020;54:185-191. doi: 10.1159/000503831