| C.5 | Sodium Valproate – move to complementary list with cautionary note |
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| Does the application adequately address the issue of the public health need for the medicine? | ☐ Yes<br>☐ No<br>☒ Not applicable<br>Comments:<br>This application is requesting that that Sodium Valproate should have an additional cautionary note attached to its listing in the EML and EMLc for pregnant women and women of child bearing age, and should be transferred to the complementary listing. Valproic acid (sodium valproate) is currently included on the core list of the EML and EMLc in the following dose forms: Oral liquid: 200 mg/5 mL; Tablet (crushable): 100 mg; Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate). Valproic acid (sodium valproate) is currently included on the complementary list of the EML and EMLc in the following dose forms: Injection: 100 mg/mL in 4 mL ampoule; 100 mg/mL in 10 mL ampoule. |
| 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. | Currently, valproic acid (sodium valproate) is listed in the WHO Model List of Essential Medicines (EML) in two different sections: section 5 anticonvulsants/antiepileptics (oral formulations in the core list in 1979 for epilepsy/seizure, injectable formulations in complementary list in 2015 for status epilepticus) and section 24.2.2 medicines used in bipolar disorders (since 1997). |
| Have all important studies and all relevant evidence been included in the application? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>If no, please provide brief comments on any relevant studies or evidence that have not been included: |
| Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication? | ☒ Yes<br>☐ No<br>☐ Not applicable<br><br>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).<br>n/a<br>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?<br>Yes |

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| Does the application provide adequate evidence of the safety and adverse effects associated with the medicine? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>Pregnancy exposure risk related to valproate: Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.<br>Data Sheet from company: "Uses: In women of child bearing age, the product should only be used in severe cases or in those resistant to other treatment."<br>"CONTRA-INDICATIONS, WARNINGS, ETC<br>Precautions - women of childbearing age This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings." The current SmPC (revised 23 March 2020) is available at https://www.medicines.org.uk/emc/product/1446/smpc#gref. |
| Are there any adverse effects of concern, or that may require special monitoring? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>Pregnancy related congenital abnormalities are possible |
| Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.) | Risks greater than benefit and should be avoided in pregnancy |
| Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.) | Moderate |
| Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?**<br>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>Pregnant women would need to seek specialist neurological advice, and be monitored regularly through their pregnancy if this medication is continued. Children born to mothers on this medication would need to seek special care post birth as well. |

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| Are you aware of any issues regarding the registration of the medicine by national regulatory authorities?<br>(e.g. accelerated approval, lack of regulatory approval, off-label indication) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>Comments:<br>The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and the European Medicines Agency (EMA) introduces updated warnings to the women prescribed Sodium Valproate in their children bearing years. In April 2018, in the UK this was upgraded to a mandatory action and a Pregnancy Prevention Programme was introduced to avoid prescribing to those who were of child bearing potential and could use other anticonvulsant drugs. |
| Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee?<br>(refer to: https://www.who.int/publications/who-guidelines) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>The WHO mhGAP Intervention Guide (Version 2.0, 2016) includes recommendations for the use of valproate for the treatment of manic episodes in bipolar disorder and epilepsy. These are the indications for which valproate is currently included on the WHO Model Lists. |
| Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings. | Available and affordable across settings. |
| Any additional comments | Family planning facilities may not be available to women in all settings and an alternative to sodium valproate should be offered to all women of childbearing age in all settings. Some alternatives to sodium valproate, are not widely available, especially in low-and middle-income countries (LMICs), availability and affordability of these medicines should be facilitated through partnership with the Medicines Patent Pool or through the WHO Pre-qualification mechanisms, to allow therapeutic options for the treatment of epileptic women of childbearing age. |
| 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. | A cautionary note could be included for pregnant women and women of child bearing ages in the EML and EMLc, regarding congenital defects in babies with use of this product. However, the move to the complementary list should only be approved if sufficient alternatives are available. |
| References<br>(if required) | |