Peer Review Report
Valproic Acid (Sodium Valproate)

(1) Does the application adequately address the issue of the public health need for the medicine?
   Yes ☑ No ☐

Please provide brief details:

The application provides data supporting the need for alternative medications other than those traditionally used (phenytoin and phenobarbitone) for status epilepticus (SE) following failure to respond to benzodiazepines. SE carries a high morbidity and mortality in both adults and children worldwide and some 30 – 40% do not respond to benzodiazepines. Evidence is provided to support a better safety profile for IV Valproic acid compared with parenteral formulations of the traditional alternatives to benzodiazepines, with the additional advantage of less monitoring which could be especially useful in resource poor settings.

(2) Have all important studies that you are aware of been included in the application?
   Yes ☑ No ☐

Please provide brief comments on any relevant studies that have not been included:

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
   Yes ☑ No ☐

Briefly summarise the reported outcomes (e.g. clinical, surrogate, other) and comment, where possible, on the magnitude of clinical benefit associated with use of the medicine:

The systematic evaluation by Yasiry Z, et al. (Seizure. 2014) in benzodiazepine-resistant seizures in both adults and children showed similar efficacy of sodium valproate (75.7%; 95% CI: 63.7–84.8%) compared with phenobarbital (73.6%; 95% CI: 58.3–84.8%) but a superior effect of valproate compared with phenytoin (50.2%; 95% CI: 34.266.1%)
Other studies in adults and/or children with status epilepticus which did not respond to first-line intravenous diazepam showed no difference in efficacy in terms of seizure cessation or seizure recurrence (Agarwal P et al. Seizure 2007; 16: 527–532) and seizure cessation with sodium valproate group versus phenytoin, and versus Phenobarbital similar efficacy with seizure cessation but superiority for phenobarbitone with seizure recurrence in children (Malamiri RA et al. Eur J Paediatr Neurol 2012;16(5):536–41.)

(4) Is there evidence of efficacy in diverse settings and/or populations?
Yes ☒ No ☐

Please provide brief details:

A few smaller studies from less resourced settings and populations add to the information appended by the application to suggest that Intravenous sodium valproate is non-inferior, and often superior and safer compared, to intravenous phenytoin in SE with no significant cardiovascular compromises.

- Puneet Agarwal et al. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure. Volume 16, Issue 6, September 2007, 527–532

(5) Has the application adequately considered the safety and adverse effects of the medicine?
Yes ☒ No ☐

Please provide brief details:

Are there any adverse effects of concern, or that may require special monitoring? Yes ☐ No ☒

Several studies show a better safety profile and fewer adverse events with IV valproate versus other comparators in status epilepticus.


ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☐ No ☒

Please provide brief details:
Apart from the avoidance in acute liver disease and porphyria

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☒

Please provide brief details:
It is already available in many markets (available as IV formulation since 1993) for use in individuals on oral valproate who for one reason or other cannot take it orally

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☐ No ☒

Please provide brief details:
Not as yet approved by WHO-GRC. However, it was considered and subsequently recommended by the U.S. Department of Health & Human Services (Brophy GM, et al. Neurocritical Care Society Status Epilepticus Guideline Writing Committee.
(9) Please comment briefly on issues regarding cost and affordability of this medicine.

No reference is made to the parenteral formulation in the International Drug Price Indicator Guide 2013 edition. BNF 61 quotes 100 mg/ml vial = UK Sterling 7.00, Injection Phenobarbital sodium 200 mg/ml = 2.00; phenytoin 50 mg/ml =3.40

(10) Any additional comments?

(11) Please summarise the action you propose the Expert Committee takes.

Approve IV sodium valproate for use in adults and children with status epilepticus as second line agent when first line treatment, IV diazepam, is ineffective in aborting seizures within 15 minutes or seizure recurrence evident after benzodiazepine treatment.