Application for Inclusion of IV sodium valproate in the WHO List of Essential Medicines

Submitted by
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To:
Expert Committee on the Selection and Use of Essential Medicines
1. **Summary statement of the proposal for inclusion, change or deletion**

Intravenous sodium valproate is proposed for inclusion in the complementary WHO Model Essential Medicine List for the treatment of established status epilepticus in adults and children.

2. **Name of the focal point in WHO supporting the application**

Dr Tarun Dua, Department of Mental Health and Substance Abuse  
Dr Wilson Were, Department of Maternal, Newborn, Child and Adolescent Health

3. **Name of the organizations consulted and supporting the application**

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, Department of Public Health and Community Medicine, Section of Psychiatry, University of Verona, Verona, Italy  
WHO Collaborating Centre for Research and Training in Child and Neonatal Health, Centre for International Child Health, University of Melbourne, Australia

4. **International non-proprietary name of the medicine**

Sodium valproate

5. **Formulation proposed for inclusion**

The EML already contains preparations of oral sodium valproate. This application is for the additional inclusion of an intravenous (IV) preparation of sodium valproate.

6. **Information supporting the public health relevance**

6.1 **Definition and epidemiology of status epilepticus**

Status epilepticus (SE) is defined as a continuous seizure lasting more than 30 min, or two or more seizures without full recovery of consciousness between any of them. Based on recent understanding of the pathophysiology, it is now considered that any seizure that lasts more than 5 min needs to be treated as SE. The first line treatment for SE is a benzodiazepine (lorazepam, diazepam) given rectally, intramuscularly (IM) or IV depending on the situation and the drug type. However, approximately 30–40% of patients fail to respond to initial treatment with benzodiazepines (established status epilepticus) and need further treatment with intravenous antiseizure medications.1
The annual incidence of status epilepticus in Europe is estimated as between 10^2 and 17^1 per 100,000 people, and in America as between 18^3 and 41^4 per 100,000 people. The incidence is thought to be higher in resource-poor countries, although evidence for this is limited.5 A study conducted between 2001 and 2004 in a hospital in Queensland, Australia, which provides the only specialist neurological services for the region, looked at the patterns of epilepsy in Indigenous and non-Indigenous people presenting to hospital.6 The health status of the Indigenous population is thought to be typical of that in resource-poor countries. Of those admitted in status epilepticus 44% were Indigenous, compared with 13% non-Indigenous. The difference was more pronounced in the adults presenting with status epilepticus of whom 53% were Indigenous. A prospective study conducted in Richmond, USA, in around 1990, found the annual incident rate to be 20/100,000 in whites, and 57/100,000 in non-whites4, but it is difficult to extrapolate this to the rates which would be expected in different countries. There seem to be no studies of the incidence of status epilepticus in resource-poor countries.

The incidence of status epilepticus varies with age, having a bimodal distribution with peaks in early childhood and in the elderly.

Not all people presenting in status epilepticus have a history of epilepsy. Indeed, studies of people in status have shown a previous history of epilepsy in 68% (children 0 to 12 years in Saudi Arabia7), 57% (patients 12 years and over in Hong Kong8), 50% (German adults5), 47% (children up to ten years in India9), 42% (USA, all ages4) and 27% (children in Finland – almost one third had an episode of either febrile or acute symptomatic status epilepticus prior to the onset of epilepsy10).

People with status epilepticus have a high risk of death, particularly if this is not adequately and urgently treated. One study showed the mortality rate to be 31% in white people with status epilepticus but only 17% in non-white people.4 Other studies have shown the mortality to be lowest in children (short-term mortality approximately three to nine percent, long-term mortality in short-term survivors seven percent) and highest in the elderly (short-term mortality 22 to 38%, long-term mortality 82%).11 A study conducted in the 1980s set out to find predictors of mortality in adults with status epilepticus.12 Overall mortality was 23%, although only two percent died during the status. Those with prolonged status (an hour or more) had a one-month mortality rate of 32% whereas those with status lasting 30 to 59 minutes had one-month mortality of three percent. Mortality increased with increasing age, and non-black people had a higher mortality rate (31%) than black people (19%). Those with status probably alcohol related, or due to AED discontinuation had low mortality rates, while those with anoxia or haemorrhage had high mortality rates. The Saudi Arabian study, looking at 47 children with status epilepticus (59 episodes) found that in only 18 (31%) episodes was appropriate AED treatment initiated. In many cases there was delay in administration of second- or third-line drugs, or delayed treatment of underlying metabolic disturbances.7 The Hong Kong study found delay in treatment in 29%, and found that poor outcome (defined as death or functional deterioration) was predicted by increased age, status due to cerebrovascular disease, CNS infection and delay in treatment.8 In a retrospective study from India nine of 30 children admitted to the paediatric intensive care unit with status epilepticus died either during seizure activity or before discharge from hospital. The risk of death was increased in those with seizure activity for more than 45 minutes and septic shock.9 A study of status epilepticus in 184 subjects with a first non febrile episode of status in Rochester, Minnesota, found case-fatality at 30 days to be 21%.13 Most deaths occurred in
the group with acute symptomatic aetiology, in whom the case fatality rate was 34% (mostly due to cerebrovascular disease or hypoxic insults). Most deaths occurred in those aged over 65 years. In this study neither seizure type nor duration of status affected the short-term mortality rate. A retrospective study of children in Pakistan found the mortality to be 25%.¹⁴ In this small study mortality was higher in those under one year, those with abnormal imaging and those with longer duration of status.

6.2 Current Treatments

Traditionally, intravenous phenytoin or phenobarbital have been used in management of status epilepticus resistant to initial treatment with benzodiazepines. Both phenobarbital and phenytoin are associated with a range of side-effects such as cardiac arrhythmias, hypotension, and respiratory depression (although the latter may be exacerbated due to the prior administration of benzodiazepines).³ Phenytoin in addition can cause serious skin reactions at the injection site. It should be administered slowly through a large vein, and cardiac monitoring is required (which is frequently not available in resource-poor countries).

There has been use of intravenous formulations of other anti-epileptic drugs such as sodium valproate in status epilepticus resistant to initial treatment with benzodiazepines. These drugs may offer advantages in terms of safety and improved tolerability.

6.3 Target population

Intravenous sodium valproate is indicated as second line treatment for status epilepticus resistant to initial treatment with benzodiazepines in both children and adults.

7. Treatment details

7.1 Indications
Sodium valproate IV is an option in the treatment of status epilepticus resistant to initial treatment with benzodiazepines in children and adults as a second-line agent.

7.2 Dose
Sodium valproate: Loading dose – 20-30mg/kg IV over 5 min

Maintenance dose – 10mg/kg twice daily oral

7.3 Duration
Continue oral treatment with sodium valproate or another anti-convulsant as appropriate to the clinical circumstances. In some situations an ongoing anticonvulsant will not be needed. In others it will be appropriate to use sodium valproate or carbamazepine or phenytoin.
7.4 Monitoring
Patients with status epilepticus who receive intravenous sodium valproate will need monitoring of vital signs, oxygenation and respiratory efforts. Liver function tests and complete blood counts also need to be monitored.


The Department of Mental Health and Substance Abuse (MSD) and the Maternal, Newborn, Child and Adolescent Health Department (MCA) recently commissioned a review of evidence on management of status epilepticus in adults and children as part of the update of Mental Health Gap Action Programme (mhGAP) Guidelines for management of mental, neurological and substance use disorders including epilepsy (http://www.who.int/mental_health/mhgap/evidence/en/) and Paediatric Emergency Triage Assessment and Treatment (ETAT) Guidelines on Fluids, Oxygen therapy and Seizures http://www.who.int/maternal_child_adolescent/documents/9241546875/en/.

These evidence profiles included the evidence on comparative effectiveness of IV sodium valproate. Both the guidelines are currently in the process of finalisation to be approved by WHO Guideline Review Committee. The recommendations for the management of status epilepticus in adults and children have been ratified by the respective Guideline Development Groups.

8.1 Systematic search strategy

In order to identify relevant systematic reviews the following databases were searched: Medline, Embase, The Cochrane Library, BMJ Clinical Evidence and Psychinfo up to September 2014. The following search strategy, developed by the McMaster University for systematic reviews was used to identify existing meta analyses:

(meta analysis [Publication Type] OR meta analysis [Title/Abstract] OR meta analysis [MeSH Terms] OR review [Publication Type] OR search*[Title/Abstract]).
The following additional terms were used: (status epilepticus OR acute seizures) AND (phenytoin OR valproate OR phenobarbital).

In order to identify additional primary studies, the search strategy developed by the McMaster University for Randomised controlled trials was used: (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract]). The following additional terms were used: (status epilepticus OR acute seizures) AND (phenytoin OR valproate OR phenobarbital).

8.2 Inclusion and exclusion criteria

Study type and design: Systematic reviews, Randomized controlled trials, quasi-randomized controlled trials (blinded or un-blinded) comparing one treatment with another.
Population: Children and adults presenting with an acute seizure (hospital or community setting) and who continued to have seizures after the administration of intravenous benzodiazepines (lorazepam, diazepam or midazolam). This included those presenting de novo with a first convulsion and those with an established diagnosis of epilepsy. Any and all causes of the convulsion (including convulsive status epilepticus) were included in the review.

Interventions: Subsequent treatment with intravenous phenytoin, phenobarbital, or sodium valproate.

Outcome measures (primary or surrogate):
- Cessation of seizures
- Death
- Adverse effects
- Recurrence of seizures within 24 hours

8.3 Data collection and analysis methodology

Two members of the research team independently assessed trials for inclusion. The research team extracted the outcome data according to the inclusion and exclusion criteria specified above and a preliminary assessment of the quality of the evidence. Data were independently extracted by two review authors and cross-checked. Any disagreements were resolved by team discussion.

The preliminary methodological quality assessment of each trial was carried out using the following criteria: randomisation method; baseline comparability of the trial arms; blinding; and whether the published data permitted an intention-to-treat analysis. Data on the number of participants with each outcome event, by allocated treatment group, were sought to allow an intention-to-treat analysis. If the evidence was deemed of satisfactory quality, it was included.

8.4 Details of included studies in GRADE tables and footnotes


This was a systematic evaluation of the published evidence-base for the efficacy of five antiepileptic drugs (lacosamide, levetiracetam, sodium valproate, phenytoin and phenobarbital) in benzodiazepine resistant convulsive status epilepticus. Eight studies describing treatment with intravenous sodium valproate in 250 benzodiazepine-resistant episodes were included in the meta-analysis. The meta-analysis was performed on a combination of different study designs, randomized with different comparators (phenytoin in Agarwal 200717, phenobarbital in Malamiri 201218), as well as observational studies. Three of the eight studies were in adults and Chen 2009 was in children and adults with status epilepticus resistant to IV Diazepam and intramuscular phenobarbital. The meta-analysis yielded a mean effect size for the efficacy of sodium valproate of 75.7% (95% CI: 63.7–84.8%). In this review, the efficacy of
phenytoin was 50.2% (95% CI: 34.2–66.1%) and that of phenobarbital was 73.6% (95% CI: 58.3–84.8%).


This was a randomized open-label trial of sodium valproate versus phenytoin in patients (adults and children) with status epilepticus which did not respond to first-line intravenous diazepam. Outcomes included seizure cessation, death, adverse effects and seizure recurrence within 24 hours. There was no difference in efficacy in terms of seizure cessation (44/50 in the sodium valproate group versus 42/50 in the phenytoin group) or seizure recurrence within 24 hours in both the groups (no patient in either group).


This was a randomized double blind study comparing the efficacy and safety of intravenous sodium valproate versus intravenous phenytoin in children with status epilepticus not responding to intravenous diazepam. There was no difference in efficacy in terms of seizure cessation efficacy in terms of seizure cessation (27/30 in the sodium valproate group versus 23/30 in the phenobarbital group). Seizure recurrence within 24 hours was more in the phenobarbital (12/23) group as compared to the sodium valproate group (4/27).

8.5 Other relevant studies but excluded from GRADE tables and footnotes


The Cochrane Review did not evaluate the specified population of our scoping question i.e. established status epilepticus (i.e. seizures persisting after the first line agent or Benzodiazepine-resistant status epilepticus). Although the authors included studies on premonitory, early, established, and refractory status epilepticus; ultimately the studies were not analysed based on the type of status epilepticus.

This review included one study comparing intravenous phenytoin to intravenous valproate (Agarwal 2007). The outcome showed uncertainty as to whether Intravenous valproate was more effective than intravenous phenytoin in reducing risk of non-cessation of seizures (RR 0.75, 95% CI 0.28 to 2.00).


This review included studies on the use of intravenous sodium valproate as first line or second line treatment. For the comparison of intravenous sodium valproate versus intravenous phenytoin, three studies with 256 participants were analysed. There was no statistically significant difference in the control of status epilepticus between the two groups (110/134 vs. 78/108 participants; RR 1.07, 95% CI 0.91, 1.24). There was a statistically non-significant trend favouring sodium valproate for reducing the requirement for
ventilatory support (2/64 vs. 3/73 participants; RR 0.96, 95% CI 0.06, 15.26) and liver dysfunction (6/64 vs. 3/73 participants; RR 2.30, 95% CI 0.29, 18.51).

Brigo F, Storti M, Del Felice A, Fiaschi A, Bongiovanni LG. IV Valproate in generalized convulsive status epilepticus: a systematic review. Eur J Neurol. 2012 Sep;19(9):1180-91.21 This review included studies on the use of intravenous sodium valproate as first line or second line treatment for generalized convulsive status epilepticus. For the comparison of intravenous sodium valproate versus intravenous phenytoin, three studies were analysed. Compared with intravenous phenytoin, intravenous valproate had statistically lower risk of adverse effects (RR 0.31, 95% CI 0.12–0.85), with no differences in cessation of status epilepticus (RR 1.31, 95% CI 0.93–1.84). The authors of this review suggest that intravenous valproate has a better tolerability than intravenous phenytoin in the treatment of generalized convulsive status epilepticus, with no statistically significant differences in terms of efficacy.

Trinka E, Höfler J, Zerbs A, Brigo F. Efficacy and safety of intravenous valproate for status epilepticus: a systematic review. CNS Drugs. 2014 Jul;28(7):623-39.22 This was a systematic review of data from randomized and non-randomized controlled trials to evaluate the efficacy and safety of intravenous valproate for the treatment of status epilepticus. The pooled evidence included a total of 860 patients with various forms of status epilepticus treated with intravenous valproate. The overall response rate (control of status epilepticus) was 70.9 % (601/848; 95 % confidence interval [CI] 67.8–73.9).

8.6 GRADE tables

Table 1

Author(s): Suvasini Sharma
Date: 2014-08-26
Question: Should sodium valproate vs phenytoin be used for children with benzodiazepine resistant status epilepticus?

<table>
<thead>
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<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
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<td>Seizure cessation (assessed with: percentage of patients with seizure cessation)</td>
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<td>serious4</td>
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<tr>
<td>Death (assessed with: proportion)</td>
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<tr>
<td>1 randomised trials</td>
<td>serious1</td>
<td>no serious inconsistency</td>
<td>no serious indirectness3</td>
<td>very serious6</td>
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<td>Adverse effects (assessed with: proportions)</td>
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<tr>
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<td>no serious</td>
<td>no serious</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Trials</th>
<th>Inconsistency</th>
<th>Indirectness</th>
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<th>RR (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
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<tr>
<td>Seizure recurrence within 24 hours (assessed with: proportion of patients)</td>
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<tr>
<td>1</td>
<td>randomised trials</td>
<td>serious¹</td>
<td>no serious inconsistency²</td>
<td>no serious indirectness³</td>
<td>very serious⁷</td>
<td>none</td>
<td>0/50 (0%)</td>
</tr>
</tbody>
</table>

¹ Method of randomization not clear, no allocation concealment, no blinding
² single study
³ study enrolled both adults and children
⁴ Wide confidence intervals
⁵ RR and CI calculated by us
⁶ Very few events, Wide CI crossing 1
⁷ No events

Table 2

Author(s): Suvasini Sharma
Date: 2014-08-26
Question: Should valproate vs phenobarbital be used for children with benzodiazepine resistant status epilepticus?

The meta-analysis by Yasiry et al\textsuperscript{16} found the mean efficacy of sodium valproate to be 75.7%. The fact all the comparative, prospective and randomized studies include valproate as one of their two or three arms gives more power to the statistical analysis. In addition to its high efficacy in acute situations, follow-up seizure freedom rates were also higher, and the drug was well-tolerated, even with large doses (up to 100 mg/kg) and high rates of infusion (up to 6 mg/kg/min). It is free of cardio-respiratory side effects which is an important advantage. However, high doses of IV valproate are likely to cause hyperammonaemia and, in susceptible patients, it is likely that ammonia concentrations could rise to very high and potentially dangerous levels, although data on this is lacking. There is a risk of hepatic and pancreatic toxicity, and valproate encephalopathy. There is also a theoretical risk that the use of high dose valproate will exacerbate a bleeding tendency due to its effects on platelets and platelet function, which might carry risks in some situations in status epilepticus (for instance in acute stroke), but to the best of author’s knowledge no such side-effects have been reported in practice in status epilepticus\textsuperscript{16}.

Intravenous valproate may be preferred over intravenous phenobarbital or intravenous phenytoin because of its superior risk-benefit profile. The choice of these drugs depends on local resource settings, including availability and facilities for monitoring.

9. Summary of comparative evidence on safety

The systematic review by Trinka et al\textsuperscript{22} provides key evidence as to the safety of sodium valproate. In this study, evidence for the safety of intravenous sodium valproate was obtained from dedicated safety studies, adverse event reporting in the efficacy studies, individual case reports, and pharmacovigilance reporting. The incidence of adverse events was low overall (<10 %), mainly dizziness, thrombocytopenia, and mild hypotension, which was independent of infusion rates, and a good cardiovascular and respiratory tolerability even in high doses and fast infusion rates up to 30 mg/kg at 10 mg/kg/min. The most frequent reported side effects in uncontrolled studies and case series include nausea/vomiting, dizziness and sedation. No effect on respiratory function was noted. Mild hyperammonemia and mild thrombocytopenia have been reported in few patients.

Brigo et al\textsuperscript{21} conducted a systematic review assessing the role of sodium valproate in generalized convulsive SE included the studies comparing intravenous sodium valproate with intravenous phenytoin in a meta-analysis. Compared with phenytoin, intravenous sodium valproate had a statistically lower risk of adverse effects (considered as a whole) (RR 0.31, 95 % CI 0.12–0.85).

In the Malamiri study\textsuperscript{18}, which is a randomized controlled trial comparing the use of intravenous sodium valproate versus intravenous phenobarbital in children with benzodiazepine-resistant status epilepticus, sodium valproate was associated with significantly lesser adverse effects as compared to phenobarbital (7/30 in sodium valproate group versus 23/30 in the phenobarbital group).
In a study comparing the risk of local injection-site reactions with intravenous sodium valproate versus intravenous phenytoin\textsuperscript{23}, injection-site reactions occurred in 18\% of patients receiving sodium valproate and 25\% of those receiving phenytoin, for the most part during administration of the initial loading dose. Rarely reported side effects include encephalopathy secondary to hyperammonemia, pancreatitis and fulminant hepatic failure.

As on 31\textsuperscript{st} January 2006, a total of 517 medically confirmed adverse drug reactions in 224 patients receiving intravenous sodium valproate had been reported in the worldwide Sanofi-Aventis post-marketing pharmacovigilance database since 1994.\textsuperscript{24} Given the estimated exposure to intravenous sodium valproate over the period (1 million units prescribed per year worldwide), the reporting rate for adverse events was less than one case per 100,000 administrations.

10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

There are no data on cost effectiveness, and no systematic cost comparison data are available. The cost of IV sodium valproate differs from country to country. E.g. in Australia sodium valproate IV is around $60 per vial, phenobarbital $4 per vial and phenytoin $3 per vial. Whereas in India, the cost of injection sodium valproate is around Rs 6 per 100 mg (Rs 24 or 0.4 USD for 400 mg), that of IV phenytoin is Rs 5 per 100 mg, and that of IV phenobarbitone is Rs 12 per 100 mg (1 US $ is around is Rs 60). For a 10 kg child, at the standard 20 mg/kg dose, the cost will work out to be Rs 12 for IV sodium valproate, Rs 10 for IV phenytoin and Rs 24 for IV phenobarbital.

The cost of second line agents for the treatment of established status epilepticus must be balanced against the costs and complications of the need for mechanical ventilation in children who develop prolonged apnoea because of the respiratory depressant effect of alternative agents, or hypotension because of the negative effect on cardiac function. These costs are difficult to quantify, but the morbidity is substantial, and where mechanical ventilation cannot be given, the risk of death from otherwise treatable status epilepticus is substantial.

11. Summary of regulatory status of medicine.

Intravenous sodium valproate: the intravenous formulation is available in most countries, and the approved indication is treatment of a patient on oral sodium valproate who is not able to take it orally.

- US FDA\textsuperscript{25}: Sodium valproate is indicated as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions: Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures. (Status epilepticus is not mentioned as an indication).

- European MA\textsuperscript{26, 27}: Authorized indications: Generalised Epilepsy, partial and focal seizures, absence seizures, myoclonic and atonic seizures (Finland) Prevention of febrile
seizures (France). Low priority for identified need for efficacy/safety in status Epilepticus. If to be tested would need to be compared to phenytoin.

- Australia: Sodium valproate is approved for treatment of patients with epilepsy or mania, who would normally be maintained on oral sodium valproate, and for whom oral therapy is temporarily not possible. (Prescribing information for IV epilim: http://www.tga.gov.au)

- Canada- Not mentioned. (Site searched: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index-eng.php)

- Japan- not mentioned (Site searched: http://www.pmda.go.jp/english/index.html)

12. Availability of pharmacopoieal standard
United States Pharmacopoeia - standard available.

13. Proposed text for the WHO Model Formulary
Sodium valproate

Injection, (solution for injection) 100 mg/ml

Uses:
Treatment of established status epilepticus, i.e. benzodiazepine-resistant status epilepticus in adults and children.

Dosage:

Sodium valproate: Loading dose – 20-30 mg/kg IV over 5 min

Maintenance dose – 10mg/kg twice daily oral

The most common adverse effects of valproic acid are digestive complaints like diarrhoea, nausea, vomiting and indigestion; vision problems like seeing double or lazy eye; hormonal disturbances (increased testosterone production in females and menstrual irregularities), hair loss, memory problems, weight gain, infections, low platelet count (which can make one bleed more easily), dizziness, drowsiness, tremor and headache. Less common, yet serious side effects include liver damage, brittle bones (becomes far more common with long-term use), polycystic ovaries, movement disorders (which may be irreversible like tardive dyskinesia), psychiatric/neurologic disturbances like hallucinations, anxiety and confusion; swollen pancreas, low body temperature and potentially life-threatening blood abnormalities.

Contraindications

- Pregnancy
- Pre-existing acute or chronic hepatic dysfunction or family history of severe hepatitis, particularly medicine related
- Known hypersensitivity to valproate or any of the excipients used in the preparation
- Urea cycle disorders
- Hepatic porphyria
- Mitochondrial disease
- Pancreatitis

**Interactions**

Valproate inhibits CYP2C9, glucuronyl transferase, and epoxide hydrolase and is highly protein bound and hence may interact with drugs that are substrates for any of these enzymes or are highly protein bound themselves. It may also potentiate the CNS depressant effects of alcohol. It should not be given in conjunction with other antiepileptics due to the potential for reduced clearance of other antiepileptics (including carbamazepine, lamotrigine, phenytoin and phenobarbitone) and itself. It may also interact with:

- Anticoagulants, due to its ability to prolong the bleeding time.
- Psychotropic agents; potential pharmacokinetic interactions.
- Benzodiazepines; may potentiate CNS depression and there are possible pharmacokinetic interactions.
- Ethosuximide; potential for ethosuximide toxicity.
- Primidone; may reduce pyrimidone's clearance leading to toxicity.
- Zidovudine; may raise its (zidovudine's) serum concentration and lead to toxicity.
- Aspirin; may displace valproate from plasma proteins, leading to increased plasma concentrations. Also interferes with valproate's metabolism.
- Felbalmate; may increase plasma concentrations of valproate.
- Mefloquine; potential for increased valproate metabolism combined with the direct epileptogenic effects of mefloquine.
- Cimetidine; inhibits valproate's metabolism in the liver, hence leading to reduced plasma concentrations of valproate.
- Erythromycin; inhibits valproate's metabolism in the liver, hence leading to increased plasma concentrations of valproate.
- Carbapenem antibiotics; reduces valproate levels, potentially leading to seizures.
References