RXADVANCE
2 Park Central Drive
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Clinical Policy Title: **Valproate Sodium for Intravenous Injection (Depacon)**
Policy Number: **RxA.95**
Drug(s) Applied: **Valproate sodium (Depacon®)**
Last Review Date: **05/01/2020**
Line of Business: **Commercial**

Background

Valproate sodium (Depacon®) for intravenous injection is an anticonvulsant agent and antiepileptic drug (AED).

Epilepsy:
Depacon is indicated as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions:

- As monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures.
- As sole and adjunctive therapy in the treatment of patients with simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.*
  **Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.*

Limitation(s) of use:

- Because of the risk to the fetus of decreased IQ, neurodevelopmental disorders, neural tube defects, and other major congenital malformations, which may occur very early in pregnancy, valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.
- Valproate should not be administered to a woman of childbearing potential unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.
- For prophylaxis of migraine headaches, valproate is contraindicated in women who are pregnant and in women of childbearing potential who are not using effective contraception.

Indication	Dosing Regimen	Maximum Dose
Epilepsy	Initial dose: 10 to 15 mg/kg/day IV, increasing at 1 week intervals by 5 to 10 mg/kg/day IV to achieve optimal clinical response. * _____ *Depacon has not been systematically studied for use in epilepsy; accordingly, the dosing information provided was obtained from studies utilizing oral divalproex sodium products for complex partial seizures in adults and children 10 years of age or older, and for simple and complex absence seizures (Depacon Package Insert).	60 mg/kg/day
Migraine - acute treatment (off-label)	Peer reviewed literature cites single doses, per IV infusion, from 300 mg to 1,200 mg.	1,200 mg/infusion

Single-dose vials: 100 mg/mL (5 mL)

Clinical Policy
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Epilepsy (must meet all)**:**

1. Diagnosis of epilepsy;
2. Age ≥ 2 years;
3. Prescribed by or in consultation with a neurologist;
4. Oral valproate* administration *(Appendix B)* is temporarily not feasible (e.g., status epilepticus, reliance on gastrostomy tube, recent oral or neck surgery, esophageal condition or intraoral infection, myasthenia gravis or other neuromuscular condition);
   **May require prior authorization.*
5. At the time of request, member does not have any of the following contraindications:
   a. Mitochondrial disorder (e.g., Alpers Huttenlocher syndrome) caused by a mutation in mitochondrial DNA polymerase gamma (POLG);
   b. Urea cycle disorder (UCD) *(see Appendix D)*; 6. Dose does not exceed 60 mg/kg per day.

Approval duration: 1 month

B. Acute Migraine (off-label) (must meet all)**:**

1. Diagnosis of migraine;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Oral administration of migraine medication is not feasible (e.g., due to migraine associated nausea);
5. Failure of at least 2 non-oral medications* from 2 different therapeutic classes unless contraindicated or clinically adverse effects are experienced *(see Appendix B)*;
   *May require prior authorization.
6. At the time of request, member does not have any of the following contraindications:
   a. Mitochondrial disorder (e.g., Alpers Huttenlocher syndrome) caused by a mutation in mitochondrial DNA POLG;
   b. UCD *(see Appendix D)*;
7. Dose does not exceed 1,200 mg per infusion.

Approval duration: 1 infusion

II. Continued Therapy

A. Epilepsy (must meet all)**:**

1. Currently receiving medication that has been authorized by RxAdvance, or documentation supports that member is currently receiving Depacon for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Dose does not exceed 60 mg/kg per day.

Approval duration: 1 month

B. Acute Migraine (must meet all)**:**

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

III. Appendices

Appendix A: Abbreviation/Acronym Key

AED: antiepileptic drug
FDA: Food and Drug Administration
POLG: polymerase gamma
UCD: urea cycle disorder

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Epilepsy: Oral Valproate Formulations valproic acid (Depakene®): capsule divalproex sodium (Depakote® Sprinkles): capsule DR sprinkle valproate sodium (Depakene®): oral solution divalproex sodium (Depakote®): tablet DR divalproex sodium (Depakote® ER): tablet 24 hr ER	Varies	Varies

Acute Migraine: Non-Oral Medications *(evidence levels A and B - American Headache Society, 2019, 2015)*
Nonsteroidal anti-inflammatory drugs (NSAIDs)
• IM, IV: ketorolac
• Intranasal: Sprix(tromethamine)
Triptans
• Intranasal:
  • sumatriptan nasal spray (Imitrex®)
  • Zomig® nasal spray (zolmitriptan)
• Exhaler powder
  • sumatriptan nasal powder (Onzetra®, Xsail®)
• SC
  • sumatriptan succinate injection (Imitrex®) sumatriptan needle-free delivery system (Sumavel® DosePro)
  • sumatriptan auto-injector (Zembrace®, SymTouch®)
Ergotamine derivatives
• SC, IM, IV:
  • dihydroergotamine (D.H.E. 45®)
• Intranasal:
  • dihydroergotamine (Migranal®)
Antiemetics
• IV: metoclopramide
• IM, IV:
  • chlorpromazine
  • promethazine (Phenergan®)
  • droperidol
  • prochlorperazine
• Rectal suppository
  • prochlorperazine (Compro®)
	Varies	Varies

• promethazine (Phenadoz®, Promethegan®)		

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

• Contraindication(s):
  - Hepatic disease or significant hepatic dysfunction
  - Known mitochondrial disorders caused by mutations in mitochondrial DNA POLG
  - Suspected POLG-related disorder in children under two years of age
  - Known hypersensitivity to the drug
  - UCDs
  - Prophylaxis of migraine headaches: Pregnant women, women of childbearing potential not using effective contraception

• Boxed warning(s):
  o Hepatotoxicity, including fatalities, usually during the first 6 months of treatment
  o Fetal Risk, particularly neural tube defects, other major malformations, and decreased IQ
  o Pancreatitis, including fatal hemorrhagic cases

Appendix D: Examples of Urea Cycle Disorders

- N-acetyl glutamate synthetase deficiency
- Carbamoylphosphate synthetase I deficiency
- Ornithine transcarbamylase deficiency
- Argininosuccinate synthetase deficiency
- Argininosuccinate lyase deficiency
- Arginase deficiency
- Ornithin translocase deficiency
- Citrin deficiency

References

1. Depacon Prescribing Information. February 2019. North Chicago, IL: AbbVie Inc.; February 2019. Available at Accessed May 1, 2020.
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Epilepsy

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Acute Migraine

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy was established	01/2020	02/07/2020
Updated References	05/01/2020	05/21/2020