



Canadian League Against Epilepsy Ligue canadienne contre l'épilepsie

2014-2016
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Divalproex Shortage – Suggestions for Management of Patients with Epilepsy

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All brand name and generic formulations of divalproex sodium (brand name Epival) enteric coated tablets (125 mg, 250 mg, and 500 mg) are currently on backorder across Canadaⁱ. Divalproex sodium is a derivative of valproic acid (sodium valproate) which the World Health Organization includes on the list of essential medicines for children and adultsⁱⁱ.

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Health Canada is aware of this serious situation and is working diligently with all manufacturers to restore supply as quickly as possibleⁱⁱⁱ. The divalproex sodium shortage is now classified as the highest level of urgency, a Tier 3 drug shortage^{iv}.

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Currently there is a limited supply being allocated to pharmacies across the country. The availability of divalproex sodium products may vary from pharmacy to pharmacy or from one region to another. Patients may receive partial refills during the shortage, this mitigation strategy helps distribute the limited supply to the greatest number of patients possible.

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Antiseizure drug therapy cannot be interrupted. Divalproex sodium is a Level 1 Critical Drug for patients with epilepsy, according to the Canadian Pharmacists Association classification^v.

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In the treatment of seizures, abrupt withdrawal of any chronic seizure medication may result in breakthrough seizures and status epilepticus, both of which can be dangerous to the patient. It is therefore recommended that patients stabilized on divalproex sodium not have this medication abruptly withdrawn without finding an alternative.

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In the absence of other alternatives, prescribers should consider switching their patients with epilepsy from divalproex sodium to an equivalent dose of valproic acid until divalproex sodium can be resupplied to the patient.

Conversion from divalproex sodium to valproic acid: equivalent dose and schedule

Patient monitoring: Patient response should be monitored for any changes in seizure control or toxicity. See below for suggestions regarding serum valproate levels and liver enzyme monitoring.

Valproic acid (brand name Depakene) is an older formulation, containing a single salt form of the biologically active valproate ion.

Valproic acid is available as a 50 mg/mL oral syrup (for pediatric use) and as 250 mg and 500 mg capsules.

One of the alternative valproic acid formulations, 500 mg enteric coated capsules, is also reported as a current shortage^{vi}, presumably due to increased demand. The level of supply of the 500 mg capsules across the drug supply chain is not known.

Currently, there are no reported shortages of the other valproic acid (Depakene) formulations, 250 mg capsules and the 50 mg/ml syrup, on the Canadian drug shortage notification website^{vii}. Although this could change, due to increased demand, if the divalproex sodium shortage is not quickly resolved.

Divalproex sodium is an enteric coated formulation that consists of a 1:1 mix of valproic acid and another valproate salt, sodium valproate. The divalproex mixture slowly dissociates in the intestines, and was developed to minimize gastrointestinal upset associated with valproic acid.

The Epival and Depakene Product Monographs^{viii} provide information about the reverse conversion, from valproic acid to divalproex sodium.

Although the active ingredient is the valproate ion for both formulations, divalproex sodium and valproic acid have different absorption and side effect profiles. Patients switched from one formulation may therefore experience changes in seizure control and adverse effects (especially GI side effects) upon switching. To minimize G.I. irritation, valproic acid can be taken with food.

If feasible, serum valproate levels and liver enzymes should be monitored prior to and after the switch to ensure consistent concentrations of valproate ion are being achieved. These points should be discussed with the patient and caregiver(s) when initiating the switch. Should practitioners have reservations or concerns about the clinical management of their patients with epilepsy during this shortage, they should consult their nearest neurologist with epilepsy expertise or comprehensive epilepsy centre.

The Canadian League Against Epilepsy is working closely with regional epilepsy programs, the Canadian Epilepsy Alliance, Health Canada, pharmaceutical manufacturers and other stakeholders to advocate for an expeditious resolution.

ⁱ Canadian Drug Shortage Database drugshortages.ca (accessed March 20, 2016)

ⁱⁱ WHO Model Lists of Essential Medicines
www.who.int/medicines/publications/essentialmedicines/en/ (accessed March 20, 2016)

ⁱⁱⁱ Canadian Epilepsy Alliance Update on Divalproex Sodium Shortage – March 19, 2016
<http://epilepsymatters.com/news/update-on-divalproex-sodium-shortage/> (accessed March 20, 2016)

^{iv} “Tier 3 captures those shortages with the greatest potential impact on the Canadian drug supply and health care systems by virtue of availability of alternative supplies, ingredients or therapies. The response time required for action at Tier 3 is immediate.”

From: The Multi-Stakeholder Steering Committee on Drug Shortages in Canada (2013), Protocol for the Notification and Communication of Drug Shortages.

www.drugshortages.ca/CMFiles/MSSC_Notification_Communication_Protocol_EN.pdf (accessed March 20, 2016)

^v “Level 1 Critical Drug: Drug therapy for disease is essential and cannot be interrupted for even one dose or one day.”

From: Canadian Pharmacists Association (2010), Drug Shortages: A Guide for Assessment and Patient Management
www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/DrugShortagesGuide.pdf (accessed March 20, 2016)

^{vi} Canadian Drug Shortage Database drugshortages.ca (accessed March 20, 2016)

^{vii} Canadian Drug Shortage Database drugshortages.ca (accessed March 20, 2016)

^{viii} Epival Product Monograph (2015); Depakene Product Monograph (2015)

Product monographs are available for download from the Health Canada Drug Product Database:
www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php