



Canadian League Against Epilepsy | Ligue canadienne contre l'épilepsie

Clobazam Shortage

Suggestions for Management of Pediatric & Adult Patients with Epilepsy

June 20, 2016

There is a widespread shortage of generic clobazam and Frisium in Canada. The shortage has impacted availability of this medication at community and hospital pharmacies.

It is recommended that **clobazam be restricted to patients currently on therapy**, unless absolutely necessary, to preserve the limited supplies until there is improved availability of this drug.

Clobazam is a **Level 1 Critical Drug** for patients with epilepsy, according to the Canadian Pharmacists Association classification.ⁱ

Prescribers asked to switch a patient from clobazam to an alternate drug, due to the shortage, should first request that the patient's pharmacist double check all supply avenues to obtain either the same formulation or an interchangeable form (generic or brand) of clobazam. In addition to regular wholesalers, pharmacists can explore if supply is available from other wholesalers, other pharmacies or directly from one of the manufacturers.

All supply avenues should be exhausted before a patient who has been stabilized on clobazam is switched to an alternate drug. A decision must be made more quickly if the patient has minimal supply remaining to prevent interruption in therapy.

Efforts underway to address the clobazam shortage

As per the *Protocol for the Notification and Communication of Drug Shortages*ⁱⁱ, Health Canada and the Provinces and Territories Drug Shortages Task Team have classified this situation as a Tier 3 shortage, which indicates a national shortage with the greatest potential impact.

Health Canada is working with pharmaceutical manufacturers and other stakeholders to address this serious shortage. The Canadian League Against Epilepsy and the Canadian Epilepsy Alliance have been participating in multi-stakeholder meetings this month, organized by Health Canada, along with other groups representing provincial health authorities, clinicians, pharmacists and pharmacy distributors.

There is still residual supply of clobazam remaining at some pharmacies and distributors. Patients with epilepsy and their caregivers may need advocacy assistance to help them locate and obtain supply if their pharmacy is out-of-stock and if the pharmacist has exhausted all avenues to obtain generic clobazam and Frisium. Contact the CLAE office for further information or call the Canadian Epilepsy Alliance at 1-866-EPILEPSY (1-866-374-5377).

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In an update provided by Apotex Inc. on June 17, 2016 to Health Canada and other stakeholders the pharmaceutical company indicated that a batch of Apo-clobazam was released to wholesalers on June 16, 2016. **This replenishment of generic clobazam is expected to arrive at pharmacies before the end of June.** The transit time for a controlled substance to move from the manufacturer to distributors and then to pharmacies is approximately 1 – 1.5 weeks. This process is being expedited with some shipments being sent by air to help move supply across the county.

A second batch of Apo-clobazam is expected to be released to wholesalers during the week of June 20, 2016.

The other manufacturer of generic clobazam, Teva Canada Ltd., is currently on back-order of their product Teva-clobazam/Novo-clobazam.

Frisium, brand name clobazam, is available but is currently on allocation. Lundbeck LLC has indicated that there have been periodic releases of Frisium from the Canadian distributor. This allocation plan is expected to continue for the coming weeks until the next resupply of Frisium is available in August.

Health Canada, with assistance and input from other stakeholders, will be continuing to monitor the supply status.

Suggestions for Patient Management During the Clobazam Shortage

Clobazam is a 1,5-benzodiazepine with a long duration of action and has been marketed as an antiseizure drug in Canada for over 20 years. This medication is commonly used to treat epilepsy.

Interruption or sudden discontinuation of antiseizure drug therapy can cause a loss of seizure control, or worsening of a patient's condition, with significant short- and long-term implications for patient safety, independence and quality of life. Breakthrough seizures can have potentially fatal consequences.ⁱⁱⁱ

There are additional concerns related to this particular drug shortage. Sudden discontinuation of clobazam can cause benzodiazepine withdrawal syndrome.^{iv} Abrupt discontinuation of clobazam may exacerbate seizures and cause other benzodiazepine withdrawal symptoms.^v Abrupt withdrawal of clobazam can also put patients at risk of life-threatening status epilepticus.^{vi}

Patients who require de novo treatment

In patients who require de novo treatment with an antiseizure medication during the clobazam shortage, physicians should consider whether an alternative medication could be used at least initially.

Patients currently taking clobazam

If all supply avenues have been exhausted and there is no clobazam available, an alternate medication should be substituted until clobazam can be resupplied to the patient.



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The following rationale for the selection of clonazepam as an alternative medication to clobazam during a drug shortage is from a document written by J.C. Martin del Campo, MD, FRCP and Jorge G. Burneo, MD, MSPH in 2013^{vii}:

From the benzodiazepine group, only two other drugs have been found useful for the chronic management of seizure disorders: nitrazepam and clonazepam.

While there is no published evidence of efficacy under the circumstances, the most reasonable substitute for clobazam is clonazepam.

It is not known if this will be efficacious in all patients or if the recommended equivalent will result in a decompensation of the seizure disorder, but it is reasonable to surmise that it may prevent the development of a withdrawal state resulting in status epilepticus. Any given dosage will need to be carefully monitored by the prescribing physician and adjustments made where necessary.

While making these recommendations, it is hoped that the health authorities and pharmaceutical companies will protect the public by urgently implementing a strategic plan that will prevent such shortages from occurring. It is imperative to be reminded of the potentially fatal consequences of breakthrough seizures.^{viii}

Reproduced with permission from del Campo and Burneo.

Recommendations for Therapeutic Substitution of Clonazepam for Clobazam

Clonazepam (brand name Rivotril) is a 1,4-benzodiazepine. This medication is available as an oral tablet in 0.25 mg, 0.5 mg, 1 mg and 2 mg formulations.

Clonazepam and clobazam have similar lipophilicity and protein binding therefore likely very similar CNS penetration.

Clonazepam is more potent than clobazam. It is *at least* 10X more potent than clobazam if not $\leq 20X$, therefore, 1 mg of clonazepam may be similar in potency to 10 mg of clobazam but could be as potent as 20 mg of clobazam.^{ix}

Following conversion to clonazepam, some dose titration may be required to achieve the desired therapeutic effect. Clinical judgement is necessary to determine the optimum dose for each patient.

Patients should be carefully monitored for changes in seizure frequency, as well as the emergence of any adverse effects (excessive sedation, ataxia, increased difficulty handling secretions, worsening liver function) following the switch. Clonazepam causes more sedation than equipotent doses of clobazam and tolerance may be more likely to develop to its antiseizure activity.



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The excipients and non-medicinal ingredients between formulations may be different so caution should be exercised in patients with known hypersensitivity to excipient. These, along with any differences in adverse event profiles, can be verified in the appropriate Product Monographs and labels. The Product Monographs are available from the Health Canada Drug Product Database.^x

ADULTS

Initiate at 0.5 mg clonazepam for every 10 mg clobazam (1:20)^{xi}; in 3-5 days, in the absence of adverse effects, increase to 1 mg clonazepam for every 10 mg clobazam if required, to a maximum of 3 mg clonazepam/day.

Consider initiating clonazepam with a simultaneous gradual tapering of clobazam by 5-10 mg/week if supply allows.

PEDIATRICS

Initiate at 0.5 mg clonazepam for every 10 mg clobazam (1:20); direct substitution can be made, tapering of clobazam is not mandatory. Dose titration, up or down, should be based on patient response.

Dose increases in pediatric patients, if required, are typically 0.25-0.5 mg/day every 5-7 days to a maximum of 0.1 mg/kg/day (or 0.2mg/kg/day for patients on enzyme-inducing drugs)^{xii}

SENIORS, PATIENTS WITH LIVER DISEASE OR PATIENTS ON MEDICATIONS THAT INHIBIT P450-3A4

Initiate clonazepam at lower dosages in the elderly, in patients with liver disease, or in patients who are currently on medications which inhibit cytochrome P450-3A4.

Drug Metabolism and Pharmacokinetics

Clobazam and clonazepam are primarily metabolized by CYP 3A4. Clobazam's active metabolite, N-desmethyloclobazam, is primarily metabolized by CYP 2C19. When substituting clonazepam for clobazam, a thorough drug interaction assessment should be done taking these metabolic paths into consideration.

Drug	Benzodiazepine Group	Active Metabolite	Half-life of parent (hrs)	Half life of active metabolite (hrs)
clobazam	1,5-benzodiazepine	N-desmethyloclobazam	30 ^{xiii}	80 ^{xiv}
clonazepam	1,4-benzodiazepine		18-39 ^{xv}	---

Information and Support for Practitioners and Patients

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.

Patients and caregivers can contact their local Canadian Epilepsy Alliance agency for information and support by calling 1-866-EPILEPSY (1-866-374-5377).



ⁱ “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

ⁱⁱ “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

ⁱⁱⁱ Steinhoff, B.J., et al. (2009) Substitution of anticonvulsant drugs. *Ther Clin Risk Manag.*, 5, 449–457.

www.ncbi.nlm.nih.gov/pmc/articles/PMC2701486/pdf/tcrm-5-449.pdf

^{iv} Frisium Product Monograph (2015)

^v *ibid*

^{vi} Engel, J. (2013). *Seizures and Epilepsy*, 2nd Edition. Oxford University Press, New York, page 557.

^{vii} Del Campo, M. and Burneo, J. (2013). Therapeutic alternative to clobazam: Medical recommendation for adults with epilepsy. Retrieved from Epilepsy Ontario website: epilepsyontario.org/wp-content/uploads/2014/01/Clobazam_Therapeutic-alternative-for-adults_Jan2013.pdf

^{viii} Steinhoff, B.J., et al. (2009) Substitution of anticonvulsant drugs. *Ther Clin Risk Manag.*, 5, 449–457.

^{ix} Sankar, R. et al. (2014) Clinical considerations in transitioning patients with epilepsy from clonazepam to clobazam: a case series. *J. Med. Case Rep.*, 8: 429.

www.ncbi.nlm.nih.gov/pmc/articles/PMC4302143/pdf/13256_2014_Article_3028.pdf

^x 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

^{xi} Benzodiazepine equivalence table <http://www.benzo.org.uk/bzequiv.htm> (accessed May 16, 2016)

^{xii} Farrell, K. and Michoulas, A. (2008) Benzodiazepines. In J.M. Pellock et al. (Ed), *Pediatric Epilepsy: Diagnosis and therapy*, 3rd Edition. Demos Medical Publishing, New York, page 559.

^{xiii} Brodie, M.J., et al. (2016) Clobazam and clonazepam use in epilepsy: Results from a UK database incident user cohort study. *Epilepsy Research* 123, 68-74.

^{xiv} *ibid*

^{xv} Comparison of benzodiazepines <http://www.vhpharmsci.com/vhformulary/tools/benzodiazepines-comparison.htm> (accessed May 18, 2016)