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Clobazam Shortage

Suggestions for Management of Pediatric & Adult Patients with Epilepsy

May 19, 2016

There are shortages of clobazam, generic and brand name (Frisium) 10 mg tablets.

Manufacturers of generic clobazam, Teva Canada Ltd. and Apotex Inc., have reported that their estimated datesⁱ to resupply this drug are September 30, 2016 and November 30, 2016 for Teva-clobazam and Apo-clobazam, respectively. Lundbeck, the manufacturer of Frisium, has not posted a shortage notification on drugshortages.ca but pharmacists are reporting difficulty obtaining the brand name drug as well.

Clobazam is a 1,5-benzodiazepine with a long duration of action and has been marketed as an antiseizure drug in Canada for nearly 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.ⁱⁱ

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

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

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.



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Suggestions for Patient Management During the Clobazam Shortage

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. The clobazam shortage could last many months, based on currently available information, and a widespread shortage is anticipated.

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.

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.

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-desmethylclobazam, 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 Canadian Drug Shortage Database drugshortages.ca (accessed May 16, 2016)

ⁱⁱ 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

ⁱⁱⁱ Frisium Product Monograph (2015)

^{iv} *ibid*

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

^{vi} "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

^{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)