



Metformin Shortage

Background

In late 2019, the impurity n-nitrosodimethylamine (NDMA) was identified in some metformin products available outside of Canada.¹ Health Canada began working with Canadian manufacturers of metformin as well as international agencies. **As of February 2020, metformin is still available on the market;** however, the possibility of a future shortage looms as Health Canada continues to test products.

On February 5, 2020, Health Canada issued an [advisory](#) that certain lots of APO-Metformin ER 500 mg tablets have been recalled as they were found to contain NDMA. It is important to note all lots of APO-Metformin ER 500 mg were tested and only some found to contain the impurity. This advisory was updated 26 Feb 2020 to include six lots of Ranbaxy brand metformin. It is possible NDMA may be identified in other Canadian products, which could create a shortage situation. Refer to Health Canada's [advisory](#), which will be updated with any further recalls.

NDMA is the same impurity that was most recently discovered in ranitidine, as well as, in various angiotensin receptor blockers in the past.² While classified as a probable human carcinogen, low levels are of no concern. NDMA is likely unavoidable in our environment as it is found in some foods and drinking water. Health Canada continues to investigate to ensure the amounts found in metformin products do not exceed levels that could be harmful with long-term use. This is a global issue and Health Canada is working with other international regulators to try to determine and address the root causes.²

Health Canada approved indications of metformin³:

- Control of hyperglycemia in patients with type 2 diabetes that cannot be controlled by proper dietary management, exercise and weight reduction or when insulin therapy is not appropriate.
- Treatment of obese patients with diabetes.

Off-label uses of metformin (not comprehensive)³:

- Improvement of fertility and menstrual pattern in women with polycystic ovary syndrome.

Management Options

Compounding

- Should all commercially available metformin products be recalled/unavailable, bulk metformin may be available for compounding. As of 10 Feb 2020, Medisca has some bulk metformin HCl in stock.⁴ However, bulk powder is also subject to NDMA contamination and may also be recalled.

Therapeutic Alternatives

Type 2 Diabetes Mellitus

- Refer to [RxFiles](#), [Diabetes Canada 2018 Guidelines](#), and/or [RxTx](#) for alternatives and algorithms
- As per RxFiles⁵:
 - Attempt to individualize treatment by considering:
 - adverse effect profile
 - age/frailty
 - cardiovascular risk
 - convenience
 - cost/formulary inclusion of drugs
 - current control (e.g. A1C)
 - goals of therapy
 - hypoglycemia risk

- patient priorities
 - pregnancy/lactation
 - presence of neuropathy
 - renal function
 - weight concerns
- Optimize other modifiable cardiovascular risk factors⁶:
 - blood pressure
 - dyslipidemia
 - cardiovascular protection (e.g. statins, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, antiplatelets where appropriate)
 - exercise/diet
 - smoking cessation

Polycystic Ovarian Syndrome (PCOS)

- Metformin is used off-label for PCOS-related menstrual irregularities and anovulation; for the most part, it is recommended 2nd line but may be used earlier on account of price and prescriber familiarity. Metformin is not effective for PCOS-associated hirsutism.⁷
- Options for menstrual irregularities⁸⁻¹⁰:
 - combined hormonal contraception considered first line
 - continuous or cyclic progestins including oral and levonorgestrel intrauterine system
- Options for women wishing to conceive (treatment of infertility)⁸⁻¹¹:
(Note: metformin alone not as effective as other agents with respect to live birth rates⁹ and is considered adjunctive¹¹)
 - weight loss
 - aromatase inhibitors
 - most recommended agent is letrozole
 - some evidence for anastrozole¹²
 - clomiphene citrate (less effective than letrozole for live birth rates^{13,14})
 - not commercially available since 2017¹⁵ but powder is available for compounding¹⁶
 - recombinant follicle-stimulating hormone (rFSH) (more effective than clomiphene citrate but costly¹⁷)
 - follitropin alfa (Gonal-f[®])
 - follitropin beta (Puregon[®])
 - follitropin delta (Rekoverle[®])

Prepared by Carmen Bell BSP, medSask | 29 Oct 2019 | Updated 27 Feb 2020
Reviewed by Kirsten Bazylak BSP, medSask

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