Société canadienne de la MASTOCYTOSE MASTOCYTOSIS Society Canada

Briefing Note:
Compounding Medication in Canadian Pharmacare & Rare Diseases
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1) What is compounding medication?

The US Food and Drug Administration (FDA) defines compounding medication as the preparation of a custom formulation of a drug composed of individual ingredients (usually a single pure drug and a filler) to make a medication suitable for a specific patient.[1] In 2009, Health Canada released its "Policy on Manufacturing and Compounding Drug Products in Canada" that provides background information on the compounding of drugs in Canada and a policy framework to assist in distinguishing between compounding and manufacturing activities of drug products in Canada.[2]

2) Why is compounding needed in different scenarios (general public)?

Compounding of a medication is pursued when a strength, concentration or dosage form is inadequate for a patient. Compounding of a medication is also used when the ingredients of a generic form of medication pose a health risk to a patient, as such they have an allergy, intolerance or sensitivity to other ingredients beyond the active ingredient.

For example, many people who suffer from hypothyroidism and are prescribed the generic drug Synthroid. However, generic Synthroid may not be suitable for all patients with lactose intolerance as lactose is a listed ingredient. As a result, working with their health practitioner and a special compounding pharmacy they can have a synthroid medication made that includes the drug without the ingredient they have an intolerance to.

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[1] Food and Drug Administration. 'Compounding and the FDA: Questions and Answers'. 2021, retrieved from: https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers#:~:text=Drug%20compounding%20is%20often%20regarded,of%20two%20or%20more%20drugs.

[2] Health Canada. 'Policy on Manufacturing and Compounding Drug Products in Canada (POL-0051)'. 6 February 2009, retrieved from: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/policy-manufacturing-compounding-drug-products.html#a51.

3) Filling a Gap in Canada's Proposed Pharmacare System

Within the Final Report of the Advisory Council on the Implementation of National Pharmacare, titled: "A Prescription for Canada: Achieving Pharmacare for All", there is a clear gap as it relates to Canadians who require medications that are compounded.[3] There is no mention of Canadians who may have more complex treatment needs and the creation of processes to ensure that patients who require compounded medications also have processes to have the costs covered under the pharmacare regime that the government intends to create.

It is also important to note that the "A Prescription for Canada: Achieving Pharmacare for All" report, recommends the creation of "mandatory generic substitution policies to encourage patients and prescribers to choose the most cost-effective therapies and help keep national pharmacare affordable".[4] This recommendation includes no mention in the report of a need to recognise that not all Canadians will be able tolerate the generic medications, particularly those who have intolerances or allergies to the excipients in the generic medication. Although it is understandable that this may be the general policy that is created to ensure the affordability of the pharmacare system, it is apparent there is a need to create alternative processes to ensure that those that require compounded medications are not excluded from the pharmacare for all policy. This is particularly important to ensure that rare disease patients, such as ours, are able to equitably access their medication through the pharmacare regime being set up.

4) What is Mastocytosis and Other Related Mast Cell Activation Diseases?

MCAD (Mast Cell Activation Disease) includes all forms of disease in which your body makes too many mast cells or mast cells are not functioning appropriately creating symptoms in multiple organ systems.[5] Mast cells are an important part of a normal immune system and live in the bone marrow and body tissue. Mast cell diseases can cause tremendous suffering and disability due to symptomatology from daily mast cell mediator release, and/or symptoms arising from infiltration and accumulation of mast cells in major organ systems.[6] Mast cell disease is rare, affecting less than 200,000

[3] Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. N Engl J Med. 2015 Jul 9;373(2):163-72. doi: 10.1056/NEJMra1409760. PMID: 26154789.
[4] Horny HP, Sotlar K, Valent P, Hartmann K. Mastocytosis: a disease of the hematopoietic stem cell. Dtsch Arztebl Int. 2008 Oct;105(40):686-92. doi: 10.3238/arztebl.2008.0686. Epub 2008 Oct 3. PMID: 19623287; PMCID: PMC2696962.
[5] Gilfillan AM, Austin SJ, Metcalfe DD. Mast cell biology: introduction and overview. Adv Exp Med Biol. 2011;716:2-12. doi: 10.1007/978-1-4419-9533-9_1. PMID: 21713648; PMCID: PMC3398748.
[6] Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. N Engl J Med. 2015 Jul 9;373(2):163-72. doi: 10.1056/NEJMra1409760. PMID: 26154789.

people in the US and is most likely underdiagnosed.[7] There are different types of mast cell disease ranging from non-clonal mast cell activation syndrome (MCAS), monoclonal mast cell activation, clonal mastocytosis, hereditary alpha tryptasemia (HAT), and more aggressive forms such as mast cell leukemia, mast cell sarcomas and smoldering mastocytosis.

One of the most concerning complications of MCAD is anaphylaxis, which can occur regularly and can happen idiopathically (with no known trigger). MCAD symptoms include skin/cutaneous symptoms (hives, flushing, itching, angioedema and dermographism), GI symptoms (abdominal pain, nausea, vomiting, diarrhea, constipation, bloating, malabsorption), respiratory symptoms (cough, asthma-like symptoms, dyspnea, rhinitis, sinusitis), cardiovascular symptoms (pre-synoscopy, synoscopy, high or low blood pressure, high or low heart rate, chest pain, irregular heart beat, palpitations, hot flush), neurologic symptoms (headache, migraine, neuropathy, tingling, numbness, tremors, feeling faint), neuropsychiatric symptoms (headache, neuropathic pain, decreased attention span, anxiety, depression, sleeplessness etc.), and constitutional symptoms (fatigue, asthenia, fever, environmental sensitivities).[8]

There is no known cure for MCAD, and treatments are sometimes difficult to access. Treatment includes many medications and lifestyle adjustments to cut out any known triggers such as specific foods, exercise, environmental triggers (such as diet modifications and perfume scents). Typical drug treatment includes daily H1 and H2 antihistamines (e.g. Allegra and pepcid), mast cell stabilizers (e.g ketotifen and Cromolyn sodium), leukotriene inhibitors (e.g. Singulair), Aspirin therapy (if tolerated), epinephrine (epipens), chemotherapy for more advanced cases; and drugs to manage any other comorbidities (e.g. POTS, EDS, thyroid issues, other autoimmune diseases).[9]

5) What is the Mastocytosis Society of Canada?

Mastocytosis Society Canada (MSC) is a national organisation for individuals living with mastocytosis and other mast cell diseases (including MCAS, HATS & idiopathic anaphylaxis) in Canada. It is a registered Canadian charity whose primary goals are to represent the needs and provide support to patients and caregivers who manage mast cell disease. As an extension of this goal, MSC seeks to raise awareness, provide education

[7] Horny HP, Sotlar K, Valent P, Hartmann K. Mastocytosis: a disease of the hematopoietic stem cell. Dtsch Arztebl Int. 2008 Oct;105(40):686-92. doi: 10.3238/arztebl.2008.0686. Epub 2008 Oct 3. PMID: 19623287; PMCID: PMC2696962.
[8] Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Journal of hematology & oncology. 2011 Dec;4(1):1-8.
[9] Molderings, G.J., Haenisch, B., Brettner, S., Homann, J., Menzen, M., Dumoulin, F.L., Panse, J., Butterfield, J. and Afrin, L.B., 2016. Pharmacological treatment options for mast cell activation disease. Naunyn-Schmiedeberg's Archives of Pharmacology, 389(7), pp.671-694.

and partner with healthcare professionals to improve the quality of life of Canadians living with mast cell diseases.

6) Why is compounding important for MCAD?

Medications often contain dyes and inactive ingredients such as lactose and alcohol that can trigger symptoms in MCAD patients. Many patients take compounded medications to avoid these adverse effects. Prominent mast cell researchers have documented the need to compound mast cell patient medications, such as in:

- Molderings et al. (2016): "Any drug can induce intolerance symptoms in the individual MCAD patient. In some MCAD patients, the disease creates such remarkable states of not only constitutive MC activation but also aberrant MC reactivity that such patients unfortunately experience a great propensity to react adversely to a wide variety of medication triggers. Those MCAD patients begin demonstrating (either acutely or subacutely) odd/unusual/weird/strange/ bizarre/unexpected symptoms soon after beginning new medications. It is very important to note that such patients often demonstrate even a greater propensity to react to medication excipients (i.e., fillers, binders, dyes, preservatives) than to the active ingredients.".[10]
- Furthermore, in Schofield & Afrin (2019): "MCAS patients are more sensitive than the average person to chemicals in the environment, including the nondrug ("inactive") ingredients (excipients) in medications and supplements. Excipient reactivity may explain unusual side effects to medications health professionals often find puzzling, such as the patient who appears intolerant of prednisone, acetaminophen, levothyroxine, or a vitamin".[11]

7) Other diseases that could benefit from compounding?

MCAD is not the only disease that requires patients to seek out compounded medication due to reactions or intolerances to the ingredients in the generic or marketed drug product. Some examples include: celiac disease; individuals living with food allergies, including anaphylactic reactions and lactose intolerance and allergy. Further research into the importance of compounded medications to patients living with rare diseases has been developed by Dooms and Carvalho (2018).[12]

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[10] Molderings, G.J., Haenisch, B., Brettner, S., Homann, J., Menzen, M., Dumoulin, F.L., Panse, J., Butterfield, J. and Afrin, L.B., 2016. Pharmacological treatment options for mast cell activation disease. Naunyn-Schmiedeberg's Archives of Pharmacology, 389(7), pp.671-694.
[11] Schofield JR, Afrin LB. Recognition and management of medication excipient reactivity in patients with mast cell activation syndrome. The American journal of the medical sciences. 2019 Jun 1;357(6):507-11.
[12] Dooms, M., Carvalho, M. Compounded medication for patients with rare diseases. *Orphanet J Rare Dis* 13, 1 (2018). https://doi.org/10.1186/s13023-017-0741-y.

8) Case Study: Ontario

I was diagnosed with a mast cell disorder in 2019 at the age of 24 years old (female). After working with a team of hematologists to screen out systemic mastocytosis, I was diagnosed with Mast Cell Activation Syndrome and began working with a gastroenterologist and immunologist to manage my condition. By 2019, I had been living with increasingly difficult symptoms that included allergic (hives, flushing, iching), gastroenterological (GERD, abdominal pain, weight loss, IBS), and cognitive (brain fog and memory issues) symptoms.

In 2019 I worked with my immunologist and gastroenterologist to iteratively add on medications to manage my condition. My treatment has ultimately resulted in a treatment regime of H1 antihistamines (fexofenadine), H2 blockers (famotidine), low dose gastro-specific budesonide, Nalcrom (oral cromolyn sodium) and ketotifen (Zatiden). I take a total of 18 pills a day and all of my symptoms prior to treatment have become fully controlled through this medication combination.

As one can imagine these medications are expensive. In the year that I was being screened for diagnosis and developing my treatment plan, I paused my academic studies (between masters and PhD studies). In doing so, I lost access to the medical insurance under my parents plan, which extended to children up to twenty-five years old but only if they were enrolled as students. My annual costs to cover my medication are over $12,000 out of pocket a year.

Seeking to help offset my costs, I turned to the Ontario Drug Benefit program for support. As an individual under the age of 25 years old I was eligible for the OHIP+. Unfortunately, I faced significant challenges within the Ontario Drug Benefit (ODB), particularly in gaining access to medication that requires compounding.

The best example is my experience seeking access to ketotifen through OHIP+. Ketotifen (Zatiden) is listed on the Ontario Drug Formulary as only being through the Exceptional Access Program (EAP). My immunologist was prepared to submit the forms on my behalf. I reached out the EAP access program to inquire about the coverage of ketotifen if it is compounded. Due to my condition I have had allergic reactions in the past to lactose and alcohol excipients that are in the brand name ketotifen offered through ODB. Thus, I required my ketotifen to be compounded without those excipients. When I reached out to the EAP representatives, I was referred to the Ontario Drug Programs Reference Manual and told that under this policy compounding would only be covered if it was altering the generic medication, not if compounding was used to prepare a custom formulation of the drug due to allergies.[13] I subsequently inquired about the Compassionate Review Policy[14] and was told it was unlikely I met the criteria for this policy as it requires "Life, limb, or organ-threatening (threat must be immediate)". I was also informed by the EAP representative that regardless, this policy would not cover the compounded ketotifen because it is not designed to be applied to medications already on the ODB. I inquired one final time about the Rare Disease Drug Review Process (referenced section of the Compassionate Review Policy" and was informed that this process had been discontinued and no longer existed. I was incredibly disappointed with my experience with the ODB, Ketotifen is a medication that is covered under the Ontario drug program, I was disappointed that there were no processes to accomodate my unique needs based on my rare disease. To this day, I pay for compounded Ketotifen out-of-pocket, despite my status as a low-income student.

[13] Ontario Drug Programs Reference Manual, November 27, 2019, access at: http://www.health.gov.on.ca/en/pro/programs/drugs/resources/odp_reference_manual.pdf
[14] Ontario, Compassionate Review Policy, access at: http://health.gov.on.ca/en/pro/programs/drugs/pdf/compassionate_review_policy.pdf.