

# Off-Label Use of Drugs

## Questions and answers about the off-label use of drugs for health care providers

### What does off-label mean?

The term “off-label” refers to any use of a drug beyond what Health Canada has reviewed and authorized to be marketed in Canada and as indicated on the product label. Usually, this means using a drug for an illness or disease other than the authorized reasons for use — in other words, an “off-label indication.” However, drug doses, when and how often to take a drug, and the type of patient (e.g., children, pregnant women, and elderly) uses may be considered “off-label,” as well. Off-label use is also sometimes called expanded use.

### What is an indication?

An indication for a drug is the reason the drug is used, usually to treat an illness or disease.

For example, insulin is indicated for the treatment of diabetes. This does not mean that every person with diabetes should be treated with insulin. It means that insulin *can* be used for this purpose, and that diabetes is an acceptable reason for using insulin.

Many drugs have more than one indication. In other words, they can be used for several reasons. When Health Canada authorizes a drug for sale in Canada, this authorization is for a specific indication or indications. These specific uses of the drug are known as Health Canada indications or authorized indications.

### What is a label?

When a drug is authorized for sale in Canada, Health Canada authorizes specific indications, doses, safety profiles, and directions for use. This information is then included in the labels affixed to the container or packaging (i.e., inner/outer labels) of the drug and in any separate Health Canada-authorized documents, such as the official prescribing information, product monographs, package inserts, etc., that are collectively referred to as the “label” for that drug.<sup>1</sup>

### What are off-label drugs used for?

The off-label uses for a drug include (but are not limited to) using the drug to treat an illness other than the authorized indication (e.g., using a beta blocker to prevent migraines), using the drug in

a different population than authorized (e.g., use in children when authorized only for patients 12 years of age or older), prescribing a drug with different dose and administration instructions (e.g., taking the drug twice daily instead of the authorized three times a day), and using the drug in a different authorized route of administration (e.g., taking as an oral solution instead of the authorized capsule format).

### How does a drug get authorized for an indication?

In Canada, the authorization of an indication for a drug can only be obtained if a manufacturer files an application that is reviewed and granted authorization by Health Canada to market that drug. A manufacturer cannot promote any off-label uses of their products, as Health Canada has only verified and authorized the drug for the indication applied for.

### Why are common uses of drugs sometimes still considered off-label?

A drug may be useful for other indications as well as the approved ones, but a manufacturer may choose not to apply for an indication if there is unlikely to be a good return on investment, as seeking approval for a medication can be costly and time-consuming. One example of this is an older drug that no longer has patent protection that could be used for another treatment in a very small population of patients. In this case, there is little financial incentive for the manufacturer to apply to Health Canada for new marketable indications.

### How do authorized indications affect marketing and prescribing?

Drug manufacturers are only allowed to market their drugs in Canada for indications authorized by Health Canada. Drug manufacturers can be fined heavily if they are found to be promoting off-label uses for a product.

Clinicians, however, may prescribe for off-label indications. An authorized indication provides the safety net of a Health Canada

review. However, other indications may have just as much scientific evidence behind them, yet their manufacturers have not submitted this to Health Canada. Of course, off-label use may not be well-supported by scientific evidence, as well.

## How common is off-label prescribing?

A Canadian study found that 11% of drugs are not prescribed for their listed indication.<sup>2</sup> In the pediatric population, 75% of drugs are used off-label.<sup>3</sup> Children are rarely included in clinical trials, so the indications, doses, and regimens commonly used in children rarely appear on the product label.

## Why prescribe something off-label?

If a drug has not been authorized for a certain indication, this does not mean it is not an effective therapy. Possibly, the manufacturer may have simply chosen not to apply for this indication. However, there are many reasons for prescribing a drug off-label:

- Clinical trials are not commonly done in the elderly, children, and pregnant or nursing women. As a result, prescribing in these groups is often off-label by necessity.
- The condition being treated may be similar in symptoms or physiology to the authorized indication. For example, a drug may be authorized for a certain stage of breast cancer but used off-label for bone cancer or a different stage of breast cancer.
- A clinician may have exhausted all on-label (authorized by Health Canada) options to treat a patient.
- In the treatment of rare diseases, there may be few or no other treatment options.
- New uses may be discovered for drugs that are already on the market but Health Canada has not yet authorized the new use (e.g., no manufacturers have submitted an application to Health Canada for authorization of the “new uses”).

## Is off-label prescribing safe?

Yes, provided there is strong scientific evidence to support it, including the balancing of risks and benefits.

It has been estimated that 79% of off-label prescriptions lack strong scientific evidence (defined as at least one randomized controlled clinical trial).<sup>2</sup> One Canadian study showed that when strong scientific evidence for off-label uses was lacking, the rates of adverse events were higher with off-label use as compared with on-label use. However, for off-label use with strong scientific evidence, adverse events were the same as for on-label use.<sup>4</sup>

## Examples of off-label prescribing without strong evidence

Health Canada issued a warning regarding the off-label use of quinine, an antimalarial drug, in 2011. It is prescribed off-label 99.5% of the time for nocturnal leg pain but lacks strong evidence to support this. Quinine is also associated with serious adverse events.<sup>5</sup> So why is it prescribed? There are currently no effective drugs to treat nocturnal leg pain, but quinine has a long history of being prescribed for this. Therefore, many physicians feel comfortable prescribing it. However, considering that the risks outweigh the benefits around this treatment, such use is not advisable.

## Example of off-label prescribing with strong evidence

Metoprolol is indicated for the treatment of mild or moderate hypertension. Although it is not indicated for atrial fibrillation in Canada,<sup>6</sup> it is often considered a first-line treatment option, supported by evidence-based Canadian clinical practice guidelines,<sup>7</sup> for controlling heart rate in patients with atrial fibrillation.

## Where can I find a list of Health Canada-authorized drugs and indications?

The *Drug and Health Product Register*<sup>8</sup> includes all marketed drugs for human use, with their related side effect reports.

### Bottom Line:

- “Off-label” use means that a drug is being used in a way that has not been reviewed and authorized by Health Canada.
- A Health Canada review occurs when a manufacturer submits an application to Health Canada. Authorization allows the manufacturer to market the product for the authorized use.
- Marketing of off-label uses is prohibited for drug products sold in Canada. Off-label prescribing is allowed, and necessary in some cases.
- Off-label use may or may not be supported by strong scientific evidence.

## References

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