

## » What you need to know about off-label drug use

As we have described in previous issues of *Follow the Script*, Health Canada approves drugs by examining clinical-trial data that a pharmaceutical company submits for review. If the data shows that the drug is safe and effective, it will be approved for the specific medical condition, dosage, and patient group studied in the clinical trials. When an approved drug is used differently than specified by Health Canada's approval, it is called "off-label" use.

Obtaining Health Canada's approval of a prescription drug is a rigorous process. See the Winter 2015 issue of *Follow the Script* for an overview of the steps involved.

Although there is not a lot of data about the extent of off-label prescribing, a Canadian Institutes of Health Research (CIHR) study, published in the *Archives of Internal Medicine* showed that it is still relatively uncommon for most health conditions. The study reported that 11 per cent, or one in nine, of prescriptions in Canada are off label.<sup>1</sup> And 79 per cent of those prescriptions "lacked strong scientific evidence" that they actually work. Therefore, we can deduce that for about 20 per cent of drugs used off label, there is good evidence that supports their effectiveness and safety.<sup>2</sup>

### Older drugs are more commonly used off label

We usually see off-label prescribing with drugs where the patent has expired. Since they've been on the market longer, the time span available for their use offers more opportunity for experimentation and the discovery of new indications.<sup>3</sup> Sometimes an off-label use becomes a "standard of care." As well, more known risks and side-effects are documented for older products.

While it's not illegal for physicians to prescribe drugs off label, it is illegal for drug manufacturers to *promote* off-label uses. And it is unlikely that clinical evidence supporting a new use will be available from the drug's manufacturer because once a brand-name drug is off patent, there is little financial incentive for the manufacturer to take on the cost of additional research and clinical trials, which is a lengthy and expensive process. Even when the drug is still under patent, the drug manufacturer would require a strong business model and a large potential market to embark on a series of clinical trials for a new indication.

Physicians often find out about alternative drug treatments from their colleagues or through their own experience as off-label prescribing can make sense as an expansion of an approved use. Sometimes a drug manufacturer has completed clinical research for a new indication but has not submitted an application for approval to Health Canada because of economic concerns. Submitting a new indication to Health Canada can be an expensive process, so if the drug will only be used by a small number of people, there's little financial incentive to pursue the new indication. For some common off-label uses there actually is high-quality supporting evidence produced from independent clinical studies; for example, universities frequently undertake their own research and publish the results in medical journals. In fact, a way for physicians to access a drug off label for their patients is to enrol them in a clinical trial.

### Why prescribe a drug off label anyway?

There are some situations in which off-label use is common and may be appropriate, such as when a physician is treating a patient who is not improving with more conventional therapies or patients with rare conditions (a.k.a. orphan diseases) or types of cancer where there aren't many (or any) other treatment options available. When there are no other options, a physician may determine that the potential benefit of experimenting with a drug off label outweighs the risks.

Off-label prescribing is especially common in cancer treatment where drugs that treat one type of cancer are prescribed off label for another type of cancer that shares similar characteristics. Usually there is high-quality clinical evidence available that shows the treatment is safe and effective in more than the approved type of cancer.

### On the other hand...

There can be an increased risk of serious side-effects with off-label use and these often arise in certain types of patients commonly prescribed drugs off-label. For example, pregnant women, children, and seniors are groups not typically included in clinical trials because of potential risk. The absence of testing for these groups means the effects of the drugs on them, both positive and negative, aren't completely known. The lack of evidence doesn't mean a drug is unsafe or ineffective; it means the drugs may not affect people in these groups in the same way as traditional test subjects and may cause unforeseen side-effects.

Another consequence of off-label drug use is that it can lead to wastage when the patient stops using the drug either because it's not having the desired effect or it's causing troublesome side-effects.

### *Prescribed a drug off-label? What patients need to know...*

Patients do not always know when they have been prescribed a drug off label. But a decision to use a drug off label should be made between the physician and the patient (or their caregiver). Here are some things a patient should ask about:

- The drug's approved indications
- Available studies that support the off-label use of the drug
- Other drugs or therapies approved to treat the disease or medical condition
- Effectiveness of the off-label drug versus the approved treatment
- Potential benefits and risks of the off-label treatment
- Benefits plan coverage for the off-label use of the drug
- Applicable clinical trials that the patient could join

## GSC's off-label drug policy

This can be a confusing space for pharmacy benefits managers and/or carriers. While physicians are free to prescribe medication that they feel is in the best interests of their patients, GSC does not typically consider a drug to be an eligible benefit when it is being used off label. We understand that physicians may want to try to experiment with treatment, especially when they have run out of other alternatives, but we need to rely on evidence first and foremost. Our priority is to put plan member safety first, while ensuring appropriate, research-backed utilization of plan sponsor dollars. For those reasons, we do not condone broad-scale off-label prescribing.

For many drugs commonly prescribed off label, our special authorization criteria and evaluation process ensures the drug is being prescribed for the approved uses. In addition, we put rules into the GSC Advantage® system to try and prevent some off-label use. For example, an age restriction can make sure a drug is an eligible benefit only for age groups where treatment has shown to be safe and effective, eliminating off-label use of the product.

### *Not eligible for coverage...*

Examples of some off-label uses that GSC does not approve since they do not have a proven benefit and can involve a risk of serious side-effects:

- **Human chorionic gonadotropin (hCG) for weight loss;** risks include blood clots and depression. HCG is a hormone authorized by Health Canada for female infertility problems.
- **Sodium-glucose co-transporter type 2 (SGLT2) inhibitors for weight loss;** risks include decreased kidney function and frequent genital and urinary infections. This class of diabetes medication is approved to treat type 2 diabetes.
- **Human growth hormone (HGH) to improve athletic performance;** risks include high cholesterol, fluid retention, and diabetes. HGH is approved for use by Health Canada for specific conditions, including failure to grow and muscle-wasting conditions; it is usually prescribed by endocrinologists.
- **Tumour necrosis factor (TNF) alpha inhibitors for gout;** risks include serious infections. These biologic drugs are approved to treat inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), and psoriasis.

Special authorization requests that specifically request approval for a drug being prescribed off label are relatively rare. And, although GSC does not typically approve requests for an off-label use, we feel it's important to have some flexibility to accommodate unique situations. In some circumstances where there is overwhelming supporting clinical evidence for the treatment and it has become a standard of care, we will approve reimbursement for a drug for an off-label use. This is where the art of adjudication meets science. We have noted when conducting analyses of a prior carrier's adjudication, it is not unusual to see very liberal acceptance of off-label reimbursement... a.k.a. "anything goes." We strive to find a thoughtful, middle ground between that and 100 per cent rejection.

In the end, while many off-label uses are benign and can be helpful in some instances, the main concern for insurers and plan sponsors should be that, in off-label situations, they're paying for a drug that could potentially be ineffective, harmful, or may have a cost-effective alternative treatment supported by clinical evidence.

#### Source:

<sup>1,3</sup> *Drug, Patient, and Physician Characteristics Associated With Off-label Prescribing in Primary Care*, JANUARY 2012, [archinte.jamanetwork.com/article.aspx?doi=10.1001/archinternmed.2012.340&etoc#Abstract](http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinternmed.2012.340&etoc#Abstract)

<sup>2</sup> *Association of Off-label Drug Use and Adverse Drug Events in an Adult Population*, January 2016, *JAMA Intern Med.* 2016;176(1):55-63. doi:10.1001/jamainternmed.2015.6058

# BEHIND THE COUNTER



## Dispensing and off-label drug use

To get a real-life pharmacist's point of view on off-label drug use, we talked to GSC pharmacist Andrea Staruch about her experience both behind the counter and as a consulting pharmacist at GSC.

**Follow the Script:** Hello Andrea, thank you for talking with us on this somewhat complicated and sometimes controversial topic. To start with, is it fair to say that GSC doesn't always know when drugs are being prescribed off-label?

**Andrea:** That's fair, many of these drugs are routinely used and are inexpensive, so off-label prescribing of them doesn't typically impact the health of most plan members.

**FtS:** But if we know a drug is commonly used off label, we make it a prior authorization drug?

**Andrea:** Yes, we would need a prior authorization claim to be submitted to us for review and we either approve or decline coverage. We decline most of these requests; we'd only approve one if the off-label use really is a standard of care – that is, it has strong clinical evidence and it's in the guidelines.

**FtS:** Is off-label prescribing an issue when you're dispensing and talking with patients?

**Andrea:** It's a huge issue with geriatric patients. I see quite a bit of this since I'm a certified geriatric practitioner – a lot of these off-label uses are very concerning. The ways drugs interact with our bodies are very different in an old body than in a younger adult. The same applies to children. At different ages, your body can have different responses to drugs.

For instance, there's a lot of prescribing of antipsychotics to geriatric patients even though the patient isn't posing a risk to themselves or anybody else. And studies have shown that antipsychotics shouldn't be used in elderly people. There have been extremely negative outcomes like the increased risk of death in these patients.

**FtS:** We've heard this a few times. Why is it so common that antipsychotics are prescribed incorrectly?

**Andrea:** The drugs are being used for behavioural issues and dementia. They do seem to be commonly used and not just in the geriatric population. Kids with attention-deficit/hyperactivity disorder (ADHD) are prescribed these drugs too. Recently a study was released about the use of antipsychotics by people with developmental disabilities like Down syndrome and autism.

**FtS:** Is this happening with kids and old people because we just want them to be easy to take care of?

**Andrea:** Yes, that's often the case. A lot of times you see geriatric patients on antipsychotics in hospitals and nursing homes. When older people get infections, they get confused, and confused elderly people aren't easy to control and care for... I once saw a patient who had been admitted to the hospital and it turned out that her only issue was she was having a poor reaction to antipsychotics. When we took her off the drugs, she was absolutely fine.

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**FtS:** When you see situations like that in your practice as a pharmacist – specifically, you see a prescription for antipsychotics from a doctor and you know off-label use is a chronic problem – what do you do?

**Andrea:** Often when I see those scripts, it's not the patient bringing it in, it's a family member. So I'll have a conversation with the person who has the patient's power of attorney and see what the situation actually is. And I'll let them know the risks associated with the drug. They have to be able to make an educated decision for the patient.

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**FtS:** Do you talk to the doctor?

**Andrea:** Usually I will. I'll ask if this drug is really warranted. However, if an 80-pound, 85-year-old woman is looking after her husband and he's being abusive – and people with dementia can be abusive – then I may be a little more tolerant of prescribing him the anti-psychotics. But if it's someone who in my mind is posing no risk, then I'll definitely make a phone call to the doctor.

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**FtS:** Let's go on to a slightly different topic. In your work here at GSC reviewing prior authorization requests, what are some of the broader patterns you see in off-label use.

**Andrea:** Well, that there are a lot of grey areas. Sometimes there are very rare off-shoot diseases where there hasn't been a research study conducted, so the doctor is extrapolating that a drug for a related disease might be effective. But because it's not an indication for the drug, we have to decline it. But that's not to say it wouldn't work if it was researched through a clinical study. We just don't have enough evidence to say it would work.

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**FtS:** When do you look at a situation and say "I understand why they're doing that"?

**Andrea:** It depends on whether you mean professional understanding or emotional understanding. We see a lot of cancer cases in which the patient has tried every drug under the sun, and the doctor is saying this is the last thing I can think of. We have to decline it because it's not going to work, but emotionally I can see why they don't want to tell the patient there's nothing left to try.

The other situation is when indications are studied after the fact – which are more reliable studies, by the way. The drug is now off patent, so the studies aren't done by the manufacturer. These drugs won't ever have the new indications because when the manufacturer doesn't have a financial interest, they won't pursue Health Canada approval for a new indication. Those kinds of prior authorization requests will likely be approved by us because there's solid evidence that shows the drug is effective.

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**FtS:** Thanks Andrea, this is an interesting topic that we're sure to see come up again.

## DRUG REVIEW AT GSC...

To give you an idea of what drugs might impact your benefits plan next, every quarter *Follow the Script* highlights some of the drugs recently reviewed by GSC's Pharmacy and Therapeutic (P&T) Committee.

GSC CLASSIFICATION <sup>1</sup>	NEW DRUG <sup>2</sup>	GENERAL INFORMATION	COST <sup>3</sup>	COVERAGE DETAILS <sup>4</sup>
<b>RARE DISEASES</b>				
Traditional; Specialty (Tier 5)	Ocaliva™ (obeticholic acid)	<p>Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is a rare and serious chronic liver disease where the immune system attacks the liver causing slow, progressive damage to the bile ducts (small tubes that carry bile out of the liver).<sup>5</sup> Normally bile produced by the liver helps aid in digestion of lipids (fats), so when bile ducts are damaged, bile and other substances cannot be eliminated and instead accumulate in the liver. The toxic bile and other harmful substances cause inflammation which leads to further liver damage. Over time, this results in liver scarring (cirrhosis) and eventually liver failure and/or liver transplantation. While the exact cause of PBC is unknown, it is the leading cause of liver transplants in Canadian women and predominately affects women aged 40-60.<sup>5,6</sup> In 2015, an estimated 11,366 people were diagnosed with PBC.<sup>6</sup></p> <p>There is no cure for PBC but medications such as ursodeoxycholic acid (UDCA), which mimics a naturally occurring bile acid, can be used to slow disease progression. Prior to Ocaliva, UDCA was the only drug approved in Canada for treatment of PBC; however, up to 40 per cent of patients experience a partial or incomplete response to UDCA while five to ten per cent are unable to tolerate UDCA.<sup>7,8</sup></p> <p>Ocaliva is a first-in-class farnesoid X receptor agonist (a key regulator of bile acid) approved by Health Canada to treat PBC. In combination with UDCA, Ocaliva meets an unmet need treating adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.</p> <p>Ocaliva is the first therapy to be approved for PBC in over 20 years and is administered orally once daily.</p>	<p><b>\$\$\$\$</b></p> <p>Approximately \$36,000 per year</p>	<p>→ Specialty drug PPN</p> <p>→ Requires prior approval</p>

### Notes:

<sup>1</sup> Traditional generally refers to small molecule compounds derived from chemical synthesis and also includes drugs not listed in Schedule D of the Food and Drugs Act; Specialty (Tier 5) refers to drugs with an expected annual treatment cost of \$10,000 or more (certain drugs approaching the threshold may also be considered high cost if clinical evidence warrants)

<sup>2</sup> Brand (generic)

<sup>3</sup> Based on manufacturer list price, does not reflect pharmacy markup and dispensing fee. \$ <1,000; \$\$ 1,000–4,999; \$\$\$ 5,000–9,999; \$\$\$\$ 10,000–49,999; \$\$\$\$\$ ≥50,000;

<sup>4</sup> Applicable to all formularies unless otherwise noted. PPN refers to GSC's preferred pharmacy network program.

<sup>5</sup> Primary Biliary Cholangitis, Canadian Liver Foundation, <http://www.liver.ca/liver-disease/types/primary-biliary-cirrhosis.aspx>

<sup>6</sup> Prevalence of Primary Biliary Cholangitis in Canada, First National Study, <http://pbc-society.ca/images/yoshida.pdf>

<sup>7</sup> Primary biliary cirrhosis. *Lancet* 2015; 386:1565-75.

<sup>8</sup> FDA approves Ocaliva for rare, chronic liver disease, FDA News Release, <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm503964.htm>