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FOLLOW THE SCRIPT™

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AN UPDATE ON SEBS

Since we first covered subsequent-entry biologic drugs (SEBs), or biosimilars, in our fall 2014 issue of *Follow the Script*, this hot topic has gotten even hotter. Back then SEBs were just coming on to our radar, and even now Health Canada has approved only three SEBs. But as a number of blockbuster biologic drug patents have expired or are set to expire over the next several years, we expect many more SEBs to come on the market.

To get a new perspective on the role of SEBs, we reached out to Pfizer Canada and had an interesting talk with Gerry Stefanatos, general manager, Global Established Pharma Business, and Vincent Lamoureux, director, Corporate Affairs. With significant experience and expertise in biologics, Pfizer has made a big commitment to the development of SEBs, which it sees as a logical and necessary step to be relevant in the emerging pharmaceuticals landscape. To that end, Pfizer has 14 SEB products either under development or launched someplace in the world.

SEBs in the pipeline

Originator biologic	Number of SEBs in development
Humira®	13
Enbrel®	21
Remicade® (one SEB – Inflectra® – already available and included on GSC formularies)	9
Lantus® (one SEB – Basaglar® – already available and included on GSC formularies)	5
Rituxan®	30
Avastin®	14
Herceptin®	24
Neulasta®	14
Lucentis®	2
Aranesp®	4
Neupogen® (one SEB – Grastofil™ – already available and included on GSC formularies)	52

Let's review...

Before we go any further, let's review our introduction to SEBs from the fall 2014 issue of *Follow the Script*: An SEB is a biologic product that is similar to an approved originator (or innovator) biologic product. To be approved by Health Canada, an SEB application follows the New Drug Submission process and must demonstrate the same clinical outcomes in terms of safety and effectiveness as the originator product. For example, Gerry confirms that the approved indications for Hospira's Inflectra were granted on the basis of similarity between Inflectra and the reference product, Remicade.

What's Inflectra?

The SEB Inflectra has been available in Europe since August 2013 and was approved for use in Canada in early 2014. Its originator product is Remicade. These are anti-inflammatory drugs used to treat rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, fistulising Crohn's disease, and ankylosing spondylitis.

Are SEBs generics?

SEBs often get compared to generic drugs, but they differ in two important ways. First, they are not identical copies of the original products and therefore not interchangeable by pharmacists. Second, unlike generics, SEBs are required to undergo a more complex regulatory approval process that includes original studies demonstrating safety and effectiveness.

As Gerry explains, the regulatory process that SEBs undergo is evidence based and very rigorous. "Data required by Health Canada to support market authorization of SEBs includes quality (chemistry and manufacturing), non-clinical (pharmacology and toxicology), and clinical (pharmacology, safety, and efficacy) information. Demonstration of similarity to the reference biologic drug is required by Health Canada."

As well, the manufacturing of SEBs involves a more complex process than for traditional generic drugs. As a result, SEBs are typically not able to achieve the same price points as generic drugs – the current SEBs approved in Canada are priced 15 to 47 per cent less than originator products whereas generics can be up to 78 per cent less than the brand-name products. However, because biologic drugs are extremely expensive to begin with, the actual dollar savings achieved through the use of SEBs are substantial.

Facing challenges

While SEBs are fairly new in North America, they have been available in Europe for over a decade, where they have been established as safe and effective and are steadily gaining market share in many EU countries. We can learn from the European experience as Canada and the rest of North America face some key challenges to rapidly creating a viable and sustainable market for SEBs, such as:

- → **Physicians are hesitant to prescribe SEBs** as they may not be aware of what SEBs are available or that they offer viable treatment options.
- → **Patients may be resistant to trying an SEB** when they don't understand what SEBs are or that they are as safe and effective as originator products.
- → **Slow movement by payors to support the SEB industry** – at both the provincial plan and private carrier levels despite SEBs offering significant savings to the system.

Overcoming these challenges seems to call for more education, better marketing, additional patient support, and competitive pricing. As more SEBs go through Health Canada's regulatory process, the acceptance of SEBs as an alternative option will undoubtedly increase.

Gerry comments that "CADTH's [Canadian Agency for Drugs and Technologies in Health] additional layer of review provides an added comfort level but it slows down adoption of SEBs in the market. It can be well over two years from the time a NOC [Notice of Compliance] is issued by Health Canada and the provincial reimbursement of the drug. We would like to see evidence-based adoption mechanisms to create a sustainable marketplace for SEBs and get them on the market faster which would lead to greater savings for patients and payors."

Can SEBs be substituted for an originator product?

While a generic drug is an exact copy of a brand-name drug, the same is not true of an SEB and its originator drug. Due to the complex nature of the manufacturing process, they are similar, but not identical; therefore, Health Canada does not consider SEBs and originator products interchangeable. This means that pharmacists

cannot automatically substitute the SEB for the originator biologic – a physician must specifically prescribe the SEB. However, if the originator product is prescribed, the pharmacist can get authorization from the physician to dispense the SEB instead.

Research in Europe, and elsewhere, is underway to study the effects of switching patients from certain originator products to an SEB. All early evidence points to switching being a viable strategy that preserves patient safety while generating the cost savings needed to ensure the sustainability of drug plans. However, further research is needed to conclusively demonstrate the feasibility of switching patients to SEBs. In the meantime, encouraging physicians to prescribe an SEB as the first choice would go a long way to increasing the uptake of these drugs in Canada.

Gerry brings up the interesting point that there are different prescribing mechanisms at play in Europe than we find in Canada. "In Europe, SEBs are mainly used in a hospital context rather than being a prescribing decision made in a Canadian physician's office. Not having to educate physicians one-by-one is a huge accelerator in the adoption of SEBs."

The NOR-SWITCH Study

This study was initiated by the Norwegian federal government to examine the safety and efficacy of switching patients from the biologic Remicade to the SEB Remsima. Norway wants to achieve lower costs for its national pharmacare plan and is investigating SEBs as an opportunity for savings.

NOR-SWITCH is a randomized, double-blind, parallel-group study of adults with a diagnosis of rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, or chronic plaque psoriasis.

The study started in October 2014 and results are expected in January 2017.

Source:
https://clinicaltrials.gov/ct2/show/NCT02148640

GSC's SEB policy

GSC's recently publicized policy lists SEBs as **preferred products under our formularies**. Current users of the originator biologics are grandfathered under the policy. With SEBs costing much less than the originator product, our approach ensures that plan members starting on a new therapy, who can safely and appropriately use an SEB, will be required to do so to receive reimbursement.

Our SEB policy is designed to be flexible and accommodate the rare circumstances when an SEB may not be appropriate for a plan member. For example, in the case of Remicade, some patients may require unique dosing that may not be available through the SEB. In these cases, we will approve the originator product to ensure the plan member can receive the appropriate treatment. In our current experience with SEBs, these situations tend to be extremely rare; for the vast majority of plan members, SEBs are an appropriate option.

With substantial cost savings on the table, we expect to see our approach implemented more widely by other carriers as more SEBs become available and Canadian physicians become more experienced in prescribing.

What's next?

To conclude our meeting with Gerry and Vincent, we asked what the next wave of SEBs will yield. Gerry says that oncology drugs are very important in Pfizer's line up and will be the next "big products" to come to the market. "The adoption of these drugs should be easier as they are generally hospital-based infusions and we expect an accelerated uptake process to be in place. By then, there will be more of a comfort level for SEBs as physicians and patients gain more experience with the concept."

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[1]	NEW DRUG[2]	GENERAL INFORMATION	COST[3]	COVERAGE DETAILS[4]
HEART FAILURE				
Traditional; Maintenance	Entresto™ (sacubitril/ valsartan)	Heart failure (HF) happens when the heart cannot pump enough blood to maintain the needs of tissues and organs. This can result in severe illness or death, particularly in those with reduced "ejection fraction" (amount of blood that is being pumped out of the heart). More than 500,000 Canadians are affected by HF and approximately 56% of these patients have reduced ejection fraction.[5] Entresto is a new first-in-class, orally administered, combination therapy indicated for the treatment of HF in patients with reduced ejection fraction and mild to moderate heart failure. Having demonstrated reduced cardiovascular death and hospitalization, Entresto received positive recommendations from the Canadian Cardiovascular Society, and may begin to replace the current, less expensive, standard treatments – angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). HF is a disease that typically affects the elderly, so individuals aged 65 years and older are most likely to be impacted. This means it will be an incremental cost for plans until it is listed by provincial plans.	$$ Cost of Entresto is more than 20 times higher than the least expensive ACEIs and ARBs used to treat HF.	**Open formulary:** Full benefit **Managed formulary:** Requires prior approval
DIABETES				
Biologic; biosimilar	Basaglar™ (insulin glargine)	Diabetes is recognized as one of the leading causes of death and disability worldwide. In Canada, there are 3.4 million people living with diabetes; this is expected to increase to five million in 2025. Additionally, 57% of Canadians with diabetes reported non-adherence to treatment as a result of high out-of-pocket costs for medications, devices, and related supplies.[6] Basaglar is one of the first subsequent-entry biologics (SEBs) to be approved in Canada. It has been approved by Health Canada as an SEB to the originator product Lantus® for the same indications. With comparable effectiveness and safety to Lantus, Basaglar offers an affordable option for patients who require therapy with long-acting insulin, which accounts for over 50% of all insulin use.[7] Basaglar is a once-daily long-acting insulin that is injected for the treatment of type 1 or type 2 diabetes.	$$ Approximately 15% discount compared to the originator biologic Lantus.	**Open formulary:** Full benefit **Managed formulary:** Requires prior approval

GSC CLASSIFICATION[1]	NEW DRUG[2]	GENERAL INFORMATION	COST[3]	COVERAGE DETAILS[4]
NEUTROPENIA				
Biologic; biosimilar	Grastofil™ (filgrastim)	Filgrastim is commonly used to treat neutropenia, a condition where the body makes too few neutrophils (a type of white blood cell that helps the body fight against infection). Neutropenia can be caused by a number of conditions including cancer, bone marrow transplant, and chemotherapy. Filgrastim works by helping to increase the neutrophils in the body. Grastofil was approved by Health Canada as an SEB for the reference product Neupogen®. Grastofil received approval for all six indications approved for Neupogen based on demonstrated biosimilarity. Grastofil is available in a ready-to-use pre-filled syringe and has greater room-temperature stability compared to Neupogen. These features in addition to the lower cost offer value to patients.	$$$ Approximately 17% discount compared to the originator biologic Neupogen.	**All formularies:** Full benefit Prior authorization is not required because Grastofil replaced Neupogen (which didn't require prior authorization) in our formulary. Neupogen will now require prior authorization in accordance with our SEB policy.

Sources:

[1] Biologic refers to drugs produced through biotechnology and listed in Schedule D of the Food and Drugs Act.

[2] Brand (generic)

[3] 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

[4] Applicable to all formularies unless otherwise noted.

[5] Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006; 355(3): 260-9.

[6] The burden of out-of-pocket costs for Canadians with diabetes. Canadian Diabetes Association. (2011). Available at: www.diabetes.ca/CDA/media/documents/publications-and-newsletters/advocacy-reports/burden-of-out-of-pocket-costs-for-canadians-with-diabetes.pdf.

[7] Based on GSC's book of business during 2015.

BEHIND THE COUNTER

MANAGING PATIENTS WITH DEPRESSION

In each issue of *Follow the Script*, we interview a member of our pharmacy team about a current topic. In this issue, we talk to **Leila Mandlsohn** about dispensing antidepressants and the challenges of managing patients with depression.

Follow the Script: Nice to talk to you again Leila. Let's discuss dispensing antidepressants in the context of our findings in the GSC 2015 Health Study. We featured those results in the June issue of *The Inside Story*®, but I just want to quickly review for our readers. Our data showed that 44 per cent of GSC plan members who were just starting out on antidepressants received a dose at less than the recommended minimum therapeutic level. So our questions begin with: What is the pharmacist's responsibility in all this? They must realize the dosage prescribed is low.

Leila: Yes, pharmacists recognize that the dosage is low. While that may be appropriate in some patients, I think the findings from our study are concerning largely because, if these patients are being treated for depression, there was often no evidence of dose escalation or drug switching. But the big issue for the pharmacist looking after these patients is not knowing enough about the patient and the condition being treated. Some antidepressants can be used to treat more than one condition – like depression, anxiety, eating disorders, obsessive compulsive disorder – and sometimes they are even prescribed "off label" for other conditions such as sleep, nerve pain, and hot flashes. And there are some patients who do need to start an antidepressant at a low dose and just stay there. For example, a frail elderly patient may not be able to tolerate a higher dose or the dose can't be increased because of drug interactions. But the sheer volume of our results indicates that these situations should not be the norm.

FtS: But don't pharmacists talk to patients about why they're taking the drug that's been prescribed?

Leila: They should, but this is what usually happens at the pharmacy: The patient drops off the prescription to the technician who is under great pressure to quickly process it and get the drug dispensed. The meaningful conversation happens when the patient comes to pick up the medication. At that point the pharmacist should be asking why the patient was prescribed the drug, but not all patients will be open to talking about it, especially if there's a mental health issue. Studies have found that patients with mental illness feel stigmatized which can make them unwilling to share information – even with their pharmacists.

FtS: What about the pharmacists – are they confident talking about mental health issues?

Leila: It's not that they are uneducated in mental health; it may be that they feel they don't have the up-to-date skills or the resources necessary to properly assess and manage these patients. Counselling patients with mental illness can be challenging, especially if you practice in a busy community pharmacy. Often there's a lack of privacy and time to really get into a meaningful discussion with a patient. Or they may feel that they lack the training to assess the severity of an

illness and response to treatment. While pharmacists are taught in school to do things like measure blood pressure, examine a rash, and evaluate laboratory values, there's little to no training on how to screen and assess patients with mental illness.

FtS: OK, but as the gatekeeper for drugs, shouldn't a pharmacist call the patient's doctor to find out why the drug has been prescribed and why the dose is so low?

Leila: Yes, ideally every prescription that reaches the pharmacy would include the indication or the reason for use but in the real world that almost never happens. You could try calling the physician but they're often not readily accessible. And even if you get to talk to the physician, generally the answer is that they're starting the patient off on a low dose because of a concern about adverse reactions. Since you don't really know the details of the patient's condition, it becomes very challenging to engage in a discussion about the most appropriate dose for the patient. Most pharmacists assess the potential for harm – is the dose too high, is there an interaction with other drugs the patient is taking, or is there any reason the drug shouldn't be dispensed at all – and promptly dispense the drug. For other illnesses, such as hypertension and diabetes, pharmacists are likely more comfortable and skilled at managing the disease and the patient. That's not the case for mental illness. If a patient with depression doesn't seem to be responding to the drug, you can refer them back to the doctor, but most pharmacists working in a general community practice would be reluctant to make a dose adjustment recommendation to a physician.

FtS: Would you say the system is dysfunctional when it comes to interactions between pharmacists and doctors?

Leila: Unfortunately, yes. Without access to a patient's full medical history, pharmacists are ill-equipped to look at the whole picture so they often focus on the drug and simply preventing harm. They will call a doctor if there's a concern about drug interactions, or the patient is having a reaction to the drug or isn't responding to the treatment, but calling to verbally obtain the patient's history is not efficient in the current pharmacy environment.

FtS: Ideally, how should the system work?

Leila: The model definitely needs to change – there should be a much more collaborative relationship between the patient, pharmacist, and physician. A pharmacist should engage with the patient from the beginning – discuss the drug and dose. The patient likely doesn't know **why** the dose is low, so ideally the pharmacist would be able to access the patient's medical history to find the information necessary. In cases where the information is not available, then you need to be able to talk to the doctor. But that's not happening today – pharmacists don't have access to patient's medical records. And sometimes when you call a physician's office you still encounter issues of hierarchy. There are some instances where doctors and pharmacists engage with each other and the patients, but many do not. To be fair, doctors don't have much time available either, and in a more collaborative system, they could have a lot of pharmacists calling them.

FtS: So what would you suggest to improve the system?

Leila: Our health care system needs to evolve on many levels. Pharmacists need to acquire the confidence and the skills necessary to feel comfortable engaging both with physicians and patients to discuss patient care. And doctors have to acknowledge pharmacists as partners in patient care. The pharmacy itself should also change so that it becomes easier to talk to patients. While there's no question pharmacists need the skills and tools, they also need the right environment and adequate resources to properly care for patients, especially ones with mental illness.