Biosimilars in Canada –
What inflammatory arthritis patients need to know

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Biosimilars in Canada

A biologic “biosimilar” is highly similar to its biologic “originator”

Biosimilars can improve access to biologics and produce significant savings for public and private health care systems

Savings from biosimilars use can modernize “special access criteria,” removing the need for patients to fail on older therapies before approving reimbursement for biosimilars

Savings from biosimilars use can be reinvested into public and private drug formulary budgets making it possible to add new medications coming into the market place

Savings from biosimilars can be invested into non-medication elements of care that patients need, such as specialized nursing, counselling, physio- and occupational therapy

Patients have multiple sources for fact-based information on biosimilars

- Your rheumatologist or rheumatology nurse or support staff
- Public or private drug plan web sites
- Patient organizations such as Arthritis Consumer Experts
- Patient created and led websites such as the Biosim-Exchange. http://biosim.joinhealth.org
Transitioning to a biosimilar

“Policy transition” occurs when a public or private drug plan’s reimbursement policy change necessitate patients to move from their biologic originator to its biologic biosimilar, usually because it is significantly less expensive.

“Medical transition” occurs when a patient, not doing well on their current biologic originator or biosimilar, is transitioned to another biologic originator or biosimilar to regain maximum disease control.

Transitioning is safe and effective

More than 100 research studies exist on patients with inflammatory arthritis, gastrointestinal and skin disease who have successfully policy transitioned from a TNF inhibitor biologic originator to its TNF inhibitor biologic biosimilar.

Prior to transitioning, both rheumatologists and their patients must be fully informed about the policy requiring the transition and have all available information about the biosimilar.

Research on transitioning to a biosimilar from an originator shows no health differences between patients.

Transition should not affect how patients fill biologic prescriptions or receive patient support

Patients will obtain their medication in the same or similar way as their previous biologic.

Biosimilars patient support program coordinator will help organize reimbursement and with other patient needs.

Rheumatologist and patient will monitor the safety and effectiveness of biosimilar as part of routine care.
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Foreword

Biosimilars in Canada – What inflammatory arthritis patients need to know

Biosimilars have been approved for use in Canada since 2009, and in arthritis since 2014. Twelve biosimilars are currently approved by Health Canada with another 15 biosimilars expected to be launched by 2020. Since the European Union (EU) approved the first biosimilar in 2006, and in inflammatory arthritis in 2013, the EU has approved 40 biosimilars.

Based on scientific evidence and the lived experience of patients in North American and Europe, rheumatologists across Canada are now regularly prescribing biosimilars for newly initiated inflammatory arthritis patients, and in full consultation with their patients, beginning to transition them from their biologic originator to its biologic biosimilar.

Provincial and private drug benefit plans have begun implementing policy transition (also called “non-medical switch”) requiring patients to move from their current biologic originator to its biologic biosimilar. Policy transition has been successfully implemented in many European countries and in thousands of inflammatory arthritis patients with no compromise to patient safety, effectiveness or quality of care.

It is important for patients with inflammatory arthritis to learn and understand biosimilars issues and facts, including:

- Safety, efficacy and immunogenicity
- Latest research
- Clinical and patient experiences
- Safety and efficacy monitoring
- Cost savings to patients and to health care systems
- Medical and policy transitioning

Arthritis Consumer Experts (ACE) has produced “Biosimilars in Canada: What inflammatory arthritis patients need to know” to address those needs of patients who want information on biosimilar medicines. It aims to provide answers to questions patients may have on biosimilars and provide them the information tools they need to power and support their conversations with their rheumatologists and other health care providers and ensure science-based continuity of care. If you would like to read more about biosimilar medicines, there are references for further information at the end of this guide or visit jointhealth.org.

Arthritis Consumer Experts thanks Arthritis Research Canada for its review of the content in this guide to ensure scientific and clinical accuracy.
Overview

Biologics overview

Today in North America, Europe and Asia, there are more biologics - originators and biosimilars - in use to treat inflammatory arthritis than in any other disease.

Over the past 18 years in Canada, biologics have become a life-saving treatment option for inflammatory arthritis patients whose disease does not respond, or respond well enough, to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as hydroxychloroquine or sulfasalazine. Biologics are proved to effectively address disease signs and symptoms – like swelling, pain and fatigue – but also may improve mortality and reduce heart disease and other complications of inflammatory arthritis.

Biologics are made from living organisms, such as living cells that have been modified using biotechnology. This allows these living organisms or cells to produce the active substance (the part that works to treat the disease) of the biological medicine. This active substance is then harvested from the cells. The active substance is commonly called a “protein.” Biologics made up of proteins are much larger and more complex in nature than conventional, small molecule medicines, like over-the-counter ibuprofen (e.g. Advil) or by-prescription methotrexate. (See figure 1)

While small molecule medicines are made of pure chemical substances and their structures can be identified, most biologics are complex mixtures of proteins, sugars or nucleic acids that are more difficult to identify or characterize. Because of their complexity, biologics are expensive and time consuming to develop. This can limit patients’ access to such medicines and can make it difficult for the health care system to afford them.

Figure 1

Size and Complexity of Molecular and Biologic Medications

<table>
<thead>
<tr>
<th>Small Molecule</th>
<th>Large Molecule</th>
<th>Large Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong> 21 Atoms</td>
<td><strong>hGH (human growth hormone)</strong> 3000 Atoms</td>
<td><strong>IgG (immunoglobulin G) Antibody</strong> 23,000 Atoms</td>
</tr>
<tr>
<td>Bicycle 20lbs</td>
<td>Car 3000lbs</td>
<td>Business Jet 30,000lbs</td>
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Biologic biosimilars overview

A biosimilar is a biologic that has similar effectiveness, safety, immunogenicity profile and quality, and delivers the same therapeutic benefits to patients as its biologic originator. They are typically prescribed to patients by a rheumatologist. For example:

- etanercept (Brenzys®) and etanercept (Erelzi®) are biologic biosimilar versions of the biologic originator etanercept (Enbrel®);
- infliximab (Inflectra®) and infliximab (Renflexis®) are biologic biosimilar versions of the biologic originator infliximab (Remicade®).

Biosimilars have been approved for use in Canada since 2009 and for use in inflammatory arthritis since 2014. Twelve biosimilars are currently approved by Health Canada with another 15 biosimilars expected to be launched by 2020. The EU approved its first biosimilar in 2006, and in inflammatory arthritis in 2013, and today totals 40 approved biosimilars.

Biosimilars have been used for many years in other diseases, such as diabetes, growth disorders and anaemia. Due to the size, complexity and natural variability of biologic medications, and because biologic medications are made in living cells rather than with chemicals, a biosimilar and its originator can be shown to be similar, but not identical.

For example, the way that etanercept is manufactured makes it impossible to produce an exact copy of the molecule. This differs from other pill-form medications you may have taken before. Medications like methotrexate and ibuprofen are made of small chemical molecules, not proteins. When patents expire on small molecule medications and generic versions are authorized for manufacture, exact copies can be made.

The diagram below (Figure 2) compares development of biologic originators and biologic biosimilars and shows biosimilars are developed in a step-wise fashion, just like their biologic originator (Reference: European Medicines Agency (EMA) consensus information paper 2013).

Figure 2
The diagram below (Figure 3) shows the slight differences that occur between originator and biosimilar because they are both made from living cell lines. The arrows in the diagrams below point to slight differences that do not involve the active or “medicinal” part of the biologic biosimilar. The slight difference is called “glycosylation”, or simply put, sugar molecules. Minor differences between the originator and the biosimilar in clinically inactive components are acceptable and are not known to make a difference in the way the medicine works in the body.

Biologics - originators and biosimilars - are made in “batches.” Batches of biologic originators are slightly different from each other (Figure 4), but those differences are minimal and are not known to affect safety, efficacy or patient outcomes.

For both biologic originators and biosimilars, batch-to-batch differences (i.e., acceptable within-product differences) exist and are expected during the manufacturing process for biologics, and are carefully controlled and monitored by regulatory authorities, such as Health Canada. At the 2017 American College of Rheumatology Annual Scientific Meeting, researchers presented studies that showed the variation between biosimilars and originators is similar to the variation seen in different batches of the originator.

To read more scientific and clinical information about biosimilars, please visit Health Canada’s web site: http://bit.ly/HealthCanadaBiosimilarEN

The biologic biosimilar review process in Canada

A biologic biosimilar enters the market after a biologic originator patent expires, just like a small molecule generic medication does when the brand name medication’s patent expires. And just as generic medications are much lower in price compared to their original versions, so too are biosimilars.

Biosimilars have their own Health Canada review pathway, as do originators (also referred to as “reference” product or medicine). However, Health Canada does not require all studies with the originator repeated with the biosimilar. Because the safety and effectiveness of the biologic originator are already well known, if the biosimilar medicine is very similar in structure and has the same biological activity, not all clinical studies need to be repeated. Instead, studies aim to
show that there are no clinically meaningful differences between the biosimilar and the reference medicine (i.e. to demonstrate biosimilarity).

To be granted regulatory approval from Health Canada, the biosimilar dosage form(s), strength(s), and route(s) of administration must be the same as that of the biologic originator. Further, the active substances (medicinal ingredients) of the biosimilar and the originator must be shown to be similar.

The key principles that Health Canada uses to evaluate biosimilars are aligned with those of other regulators and international organizations such as the EMA, the United States Food and Drug Administration (FDA), and the World Health Organization. Health Canada engaged a broad range of stakeholders when developing the regulatory framework for biosimilars and reviews its approach to regulating biosimilars on an ongoing basis in response to scientific advances, best practices and experience gained.

Since the EU approved the first biosimilar in 2006, it has approved the highest number of biosimilars worldwide, amassing considerable experience of their use and safety. During this period, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their biologic originators.

The EMA in its “Biosimilars in the EU: Information guide for health care professionals” states: “The evidence acquired over 10 years of clinical experience shows that biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines.”

Health Canada’s Biosimilars website landing page provides information about biosimilars including a fact sheet, relevant guidance documents, scientific advice meetings and links to approved drugs.

Benefits to patients and health care systems

Underlying Health Canada’s approach to approving biosimilars is the societal benefit the introduction of biosimilars potentially brings to patients and the health care system.

A 2016 study commissioned by the Patented Medicine Prices Review Board (PMPRB) and conducted by the National Prescription Drug Utilization Information System (NPDUIS), “Potential Savings from Biosimilars in Canada”, estimated potential annual savings for infliximab alone in Canada could range between $91M and $514M in the third year following biosimilar entry.

As reported at a Health Canada Biosimilars Workshop in March 2017: “A competitive and sustainable market for biosimilar and innovator drugs could offer many benefits to the health care system, including broadening access to effective biologic treatments, reducing the cost burden and enabling savings to be re-directed across all areas of health care including funding of new innovative therapies.”
Biosimilars can create three main benefits to patients, the health care system, and society:

1. **Savings from biosimilars use can modernize “special access criteria”**. Currently, patients must try and fail treatment with older and less expensive medications. Because biosimilars are significantly less expensive public and private drug formularies can remove the need for patients to fail on at least some of these older therapies before approving reimbursement for them.

2. **Savings from biosimilars use can be reinvested into public and private drug formulary budgets** making it possible to add new medications coming into the market place, and by doing so, expanding patient medication choice.

3. **Savings from biosimilars can be invested into non-medication elements of care that patients need**, such as specialized nursing, counselling, physiotherapy and occupational therapy, among other important elements of a holistic inflammatory arthritis treatment plan.

**Extrapolation**

Because of the way biosimilars are developed, it is not always necessary to carry out clinical studies with the biosimilar in all the diseases for which the originator has been shown to work. Instead, it may be possible to extend safety and efficacy data from studies in one disease to cover others. This is known as extrapolation.

An indication is the use of a drug to treat a disease or medical condition. Many biologics (originators and biosimilars) are approved to treat more than one “indication” (disease or medical condition). The term extrapolation is often used to refer to Health Canada’s approval of a biosimilar for indications where clinical studies were not done. Because a biosimilar is very similar in structure and function to a biologic originator with proven safety and efficacy, clinical studies do not need to be repeated for each indication.

Instead, Health Canada may approve a biosimilar for use in more than one indication because of the similarity between the biosimilar and the biologic originator. Patients and physicians can have confidence in the use of a biosimilar in each indication approved by Health Canada.

Biosimilars can receive all indications (diseases/conditions) held by the biologic originator based on the “totality of evidence” obtained from all comparative analyses between the biosimilar and biologic originator.

The indications approved for a particular biosimilar depend on the following factors:

- Indications may be patented at different times and indications under patent and data protection cannot be approved;
- The biosimilar manufacturer chooses which indications they wish to seek for the product. Health Canada does not force a manufacturer to apply for indications that the manufacturer does not wish to have; and,
- Health Canada may decide not to approve a biosimilar for a certain indication based on scientific and benefit/risk-based considerations.
Post marketing surveillance: How the safety of biosimilars is monitored after authorization

Tracking the efficacy, safety and value to patients and the health care system of both biologic originators and their biosimilars is important. Patients and their physicians rely on this “real world data” when they are making treatment decisions. Health Canada monitors the safety of all medications on the market, including biosimilars. Specifically, they:

- Conduct market surveillance
- Monitor adverse reaction reports
- Investigate complaints and problem reports
- Take action as appropriate

Each manufacturer must do its part for drug safety:

- Set up a system to monitor reported side effects;
- Report any new information received about serious side effects to Health Canada;
- Notify Health Canada about any studies with new safety information;
- Request authorization for any major changes to:
  - the manufacturing process,
  - dose regimen, or
  - recommended uses of the drug.

Biosimilars in development

Figure 5
Twelve biologic biosimilars are currently approved by Health Canada. Numerous biosimilars are currently under development globally (Figure 5). Health Canada expects a significant increase in submissions as patent/data protections expire in Canada. Currently, Health Canada is seeing a significant increase in the number of pre-submission and pipeline meetings with biosimilar manufacturers.

Experts predict another 15 biosimilars to be launched in Canada by 2020.

**Biosimilars library**

**Health Canada Biosimilars Landing Page**
- Provides information about biosimilars including a fact sheet, relevant guidance documents, scientific advice meetings and links to approved drugs.

**Peer reviewed research articles**
Biosimilars: Frequently asked questions

What is a biologic?

Today in North America, Europe and Asia, there are more biologics – originators and biosimilars – in use to treat inflammatory arthritis than in any other disease.

Over the past 18 years in Canada, biologics have become a life-saving treatment option for inflammatory arthritis patients whose disease does not respond to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as hydroxychloroquine or sulfasalazine.

Biologics are made from living organisms, such as living cells that have been modified using biotechnology. This allows these living organisms or cells to produce the active substance of the biological medicine. This active substance is then harvested from the cells. The active substance is commonly called a “protein.” Biologics made up of proteins are much larger and more complex in nature than conventional, small molecule medicines such as over-the-counter ibuprofen (e.g. Advil) or by-prescription methotrexate.

While small molecule medicines are made of pure chemical substances and their structures can be identified, most biologics are complex mixtures of proteins, sugars or nucleic acids that are more difficult to identify or characterize. Because of their complexity, biologics can be very expensive and time consuming to develop. This can limit patients’ access to such medicines, and can make it difficult for the health care system to afford them.

What is a biologic biosimilar?

A biosimilar is a biologic that has similar effectiveness, safety, immunogenicity profile and quality and delivers the same therapeutic benefits to patients as its biologic originator. They are typically prescribed to patients by a rheumatologist. For example:

- etanercept (Brenzys®) and etanercept (Erelzi®) are biologic biosimilar versions of the biologic originator etanercept (Enbrel®);
- infliximab (Inflectra®) and infliximab (Renflexis®) are biologic biosimilar versions of the biologic originator infliximab (Remicade®).

Due to the size, complexity and natural variability of biologic medications, and because biologic medications are made in living cells rather than with chemicals, a biosimilar and its biologic originator can be shown to be similar, but not identical.

For example, the way that etanercept is manufactured makes it impossible to produce an exact copy of the molecule. This differs from other medicines you may have taken before. Medications like methotrexate and ibuprofen are not proteins so when they are manufactured, exact copies can be made. These generic drugs are small molecules that are chemically synthesized and contain identical medicinal ingredients to their brand name reference products.

A biologic biosimilar enters the market after a biologic originator patent expires, just like a small molecule generic medication can do when the brand name medication’s patent expires. And just the way generic medications are much lower in price compared to their original versions, so too are biosimilars.
How long have biosimilars been available?
Biosimilars have been used for many years in other diseases, such as diabetes, growth disorders and anaemia. Biosimilars have been approved for use in Canada since 2009 and for use in inflammatory arthritis since 2014. Twelve biosimilars are currently approved by Health Canada with another 15 biosimilars expected to be launched by 2020. Since the European Union approved the first biosimilar in 2006, and in inflammatory arthritis in 2013, the EU has approved 40 biosimilars.

Are biosimilars generic biologics?
When a drug patent expires, pharmaceutical companies can copy that branded drug, and sell it for significantly less as a generic. Generic medications are copies of brand-name medications, have the same active ingredient, and are the same as those brand name medications in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.

If they meet Health Canada’s safety and efficacy requirements, biosimilars are allowed to enter the marketplace when the patent of the biologic originator expires. Biosimilars, like generic medications, are lower priced versions of brand name drugs and are approved through different abbreviated pathways that avoid duplicating costly clinical trials. But biosimilars are not the same as generic medicines (a medicine which contains exactly the same molecule as an existing non-biological medicine, such as aspirin or ibuprofen). This is because unlike non-biological medicines, biologics cannot be exactly copied and are developed and manufactured following the same strict quality requirements as any other biologic, using state-of-the-art methods and manufacturing.

My rheumatologist and I are thinking about choosing a biosimilar for my treatment: Is it going to be safe and effective?
Like any medicine approved by Health Canada, biosimilars can be expected to be safe and effective treatment options when they are used appropriately in their approved indications. Instructions for use are provided in the product monograph and package leaflet.

As with any treatment, it is important to have a thorough conversation with your rheumatologist about all the available therapeutic options, their safety, benefits and risks, and the differences between the medications, before coming to a decision.

What should I do if I suspect I have a side effect?
As for any other medicine, in cases where you suspect you may have a side effect, both you and your rheumatologist or pharmacist should report it. This helps authorities to continuously monitor the safety of medicines in the wider population. At the time of writing this document, no specific biosimilar-related safety issues have been identified for the currently Health Canada approved biosimilars.
**Why have biosimilars been developed and approved?**

Biologics are treatments that can help patients with serious diseases such as cancer and inflammatory arthritis. However, they are complex and can be very expensive and time consuming to develop. This can limit patients’ access to such medicines and can make it difficult for the health care system to afford them.

Like legislated generic drug savings in Canada, biosimilars have the potential to improve patient access to biologics and save public and private health care systems billions of dollars now and over the coming years. A study commissioned by the Patented Medicine Prices Review Board (PMPRB) and conducted by the National Prescription Drug Utilization Information System (NPDUIS), “Potential Savings from Biosimilars in Canada”, estimated potential annual savings for infliximab alone in Canada could range between $91M and $514M in the third year following biosimilar entry.

As reported at a Health Canada Biosimilar Workshop in March 2017: “A competitive and sustainable market for biosimilar and innovator drugs could offer many benefits to the health care system, including broadening access to effective biologic treatments, reducing the cost burden and enabling savings to be re-directed across all areas of health care including funding of new innovative therapies.”

**Why aren't all studies conducted by the biologic originator maker repeated with the biologic biosimilar maker?**

Because the safety and effectiveness of the biologic originator are already well known, if the biosimilar is very similar in structure and has the same biological activity, not all clinical studies need to be repeated. Instead, studies aim to show that there are no clinically meaningful differences between the biosimilar and the biologic originator.

**Why can biosimilars be approved for indications for which no clinical studies have been done? What is ‘extrapolation’?**

Because of the way biosimilars are developed, it is not always necessary to carry out clinical studies with the biosimilar in all the diseases for which the originator has been shown to work. Instead, it may be possible to extend safety and efficacy data from studies in one disease to cover others. This is known as extrapolation.

An indication is the use of a drug to treat a disease or medical condition. Many biologics (originators and biosimilars) are approved to treat more than one “indication” (disease or medical condition). The term extrapolation is often used to refer to Health Canada’s approval of a biosimilar for indications where clinical studies were not done. Because a biosimilar is very similar in structure and function to a biologic originator with proven safety and efficacy, clinical studies do not need to be repeated for each indication.

Instead, Health Canada may approve a biosimilar for use in more than one indication because...
of the similarity between the biosimilar and the biologic originator. Patients and physicians can have confidence in the use of a biosimilar in each indication approved by Health Canada.

**Why are some biosimilars approved to treat fewer diseases than the originator?**

An indication is a use of a medication to treat a specific disease or medical condition. A biosimilar may be approved for all or some of the indications of the originator.

The indications approved for a particular biosimilar depend on the following factors:

- Indications may be patented at different times and indications under patent and data protection cannot be approved;
- The biosimilar manufacturer chooses which indications they wish to seek for the product. Health Canada does not force a manufacturer to apply for indications that the manufacturer does not wish to have; and,
- Health Canada may decide not to approve a biosimilar for a certain indication based on scientific and benefit/risk-based considerations.

**What is immunogenicity and how is it addressed for biosimilars?**

The immune system has evolved to recognize foreign proteins in the body. Biologics are usually injected into the body and the immune system often reacts to them. This reaction is referred to as the immunogenicity of the product. Sometimes immunogenicity can only be detected using sophisticated laboratory tests and has no impact on the patient. In other cases, immunogenicity can impact patient safety or how well the medication works. For these reasons, studies showing that there are no clinically meaningful differences in immunogenicity between the biosimilar and biologic originator are required for authorization of a biosimilar. In addition, a risk management plan is required by Health Canada for all biologic drugs, including biosimilars. This plan must explain how the manufacturer plans to monitor immunogenicity after the biosimilar is authorized.

**How is the safety of biosimilars monitored after authorization?**

Health Canada monitors the safety of all medications on the market, including biosimilars. Health Canada:

- Conducts market surveillance
- Monitors adverse reaction reports
- Investigates complaints and problem reports
- Takes action as appropriate

Each manufacturer must do its part for drug safety:

- Set up a system to monitor reported side effects
- Report any new information received about serious side effects to Health Canada
- Notify Health Canada about any studies with new safety information
- Request authorization for any major changes to
  - the manufacturing process,
  - dose regimen, or
  - recommended uses of the drug.
Biologics are “advanced therapy” treatments – meaning they are used after conventional disease modifying anti-rheumatic drugs (csDMARDs), such as methotrexate – that can help patients with serious autoimmune diseases, like cancer and inflammatory forms of arthritis. They are made from complex large molecules that come from living cells. Biologics are time consuming to research, develop and manufacture, making them expensive when they come into the market place. Health care systems limit reimbursement access to biologics through “special access criteria” – a patient must be, or get, very sick before publicly or privately funded drug formularies will pay for them. As a result, all patients who medically need a biologic therapy may not qualify for reimbursement coverage because the criteria are too difficult to meet.

Since the entry of biologics into the Canadian market, the use of biologics has been higher in Canada than in most comparable international markets. In 2016, 7 out of the top 10 selling medications in Canada were biologics. The relatively higher use of biologics means Canadians have the most to gain from potential biosimilar savings.

A biologic “biosimilar” enters the market after a biologic “originator’s” patent expires, like a small molecule generic medication does when the brand name medication’s patent expires. And just the way generic medications are much lower in price compared to their original versions, so too are biosimilars in comparison to their originators. They have the same safety and efficacy yet are significantly less expensive, and the cost savings to the health care system can result in positive benefits to patients and society not related to the medicines themselves. Specifically, biosimilars can create three main benefits to patients, the health care system, and society:

1. **Savings from biosimilars use can modernize “special access criteria”**. Currently, patients must try and fail treatment on older, less expensive medications. Because biosimilars are significantly less expensive public and private drug formularies can remove the need for patients to fail on these older therapies before approving reimbursement for them.

2. **Savings from biosimilars use can be reinvested into public and private drug formulary budgets** making it possible to add new medications coming into the market place, and by doing so, expanding patient medication choice.

3. **Savings from biosimilars can be invested into non-medication types of care** that patients need, such as specialized nursing, counselling, physio and occupational therapy, among other important elements of a holistic inflammatory arthritis treatment plan.

Like legislated generic drug savings, biosimilars reimbursement policy has the potential to improve access to biologics and save public and private health care systems billions of dollars, now, and over the coming years. As reported at a Health Canada Biosimilar Workshop on March 20, 2017: “A competitive and sustainable market for biosimilar and innovator drugs could
offer many benefits to the health care system, including broadening access to effective biologic treatments, reducing the cost burden and enabling savings to be re-directed across all areas of health care including funding of new innovative therapies.”

A study commissioned by the Patented Medicine Prices Review Board (PMPRB) and conducted by the National Prescription Drug Utilization Information System (NPDUIS), “Potential Savings from Biosimilars in Canada”, estimated potential annual savings for infliximab alone in Canada could range between $91M and $514M in the third year following biosimilar entry.

A study that looks at biosimilar use and cost in Canada under provincial drug plans in 2016 (excluding Quebec) found that if half of the Remicade claims has been Inflectra instead, the cost difference would have been more than $102 million.*

Biosimilar transition overview

Transitioning from a biologic originator to a biologic biosimilar

Since the introduction of biosimilars in Europe in 2006 “real-world” policy implementation, prescribing and use has been well researched and documented. In particular, the European experience of rheumatologists successfully working with their patients to transition them from a biologic originator to a biologic biosimilar has helped inform policy transition development in Canada. Today, the international inflammatory arthritis community has the most biosimilar experience of any disease community, with tens of thousands of patients safely and effectively transitioned to a biosimilar.

Transitioning terminology

Transitioning (sometimes referred to as “switching”) generally refers to a one-time change from a biologic originator to a biologic biosimilar.

There are two types of transition; a “medical transition” and a “policy transition”

1. “Medical transition” occurs when a person no longer responds and receives most or full benefit from the medication. Loss of response or “loss of efficacy” requires a person to change their medication(s).

   In the case of a patient not doing well on their biologic originator or biologic biosimilar, they would be medically transitioned either to a different biologic originator or biosimilar to regain maximum disease control. This is a carefully considered decision taken between the patient and their rheumatologist. Transitioning at the right time, when medically required, is important to achieving the best disease control and patient outcomes.

2. “Policy transition” (sometimes referred to as “non-medical switching”) requires patients to move from their current biologic originator to its biologic biosimilar, usually because it is significantly less expensive.

Research highlights on transitioning from a biologic originator to a biosimilar

Biosimilar transition clinical trials and registry data findings are regularly reported at the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) annual scientific meetings. There are now more than 100 research studies, in rheumatology, gastroenterology, dermatology and other diseases, which collectively show little to no clinical differences between biosimilars and their biologic originators.

For those who policy transitioned to a biosimilar and lost efficacy, the reasons for the loss of efficacy were historically generally the same, and at the same rate, as in those who lost efficacy on the originator.

Currently available research presented at the most recent ACR and EULAR annual meetings indicates that a single transition from a biologic originator to one of its biologic biosimilars is safe and effective; there is no scientific rationale to expect that transitioning among biosimilars of
the same biologic originator would result in a different clinical outcome but patient perspectives should be considered (see Library at end of this document for specific transition studies).

- Data from first randomized trial - “NOR-SWITCH” study of transitioning from a biologic originator to its biosimilar was presented at the EULAR and ACR 2016 Annual Scientific Meetings by Norwegian researchers
- Data showed no differences in disease worsening between patients who were transitioned from the infliximab originator (Remicade) to the infliximab biosimilar Remsima (approved as Inflectra in Canada);
- NOR-SWITCH immunogenicity data was presented at EULAR 2017 and no significant differences between Remicade and Remsima were reported

- Registries in Norway, Denmark, Germany and Sweden are tracking patients’ “real world” transition experience and reporting continued safe and effective use of biosimilars.

**Having an evidence-based biosimilar transition conversation with your healthcare professional**

During a biosimilar transition conversation in a consultation between a healthcare professional (HCP) and patient, the choice of wording used by HCPs to describe transitioning is important for patient understanding and empowerment (e.g. using the proper term "biosimilar" vs. words like “copy”, “cheaper version”).

Specifically, the things that rheumatologists, nurses and pharmacists must be able to clearly explain to their patients are the safety, quality and benefits of biosimilars; from the patient outcomes perspective, they are statistically the same as their originator.

Another key at the time of transitioning is for the HCP to be able to provide the patient education materials in “easy-to-read”, objective language to help them understand the principles of biosimilars and the reasons for transition and the scientific evidence that supports it.

To learn more about what patients can expect about transitioning, view Arthritis Consumer Experts’ Biosimilar Education Videos at: https://biosim.jointhealth.org/resources

**Health Canada’s biosimilar transitioning statements**

At a Health Canada Biosimilars Workshop in March 2017 - Regulation of Biosimilars: Hot Topics - Catherine Parker, Director General Biologics and Genetic Therapies Directorate Health Canada, stated:

- Health Canada considers well-controlled transitions from biologic originator to biologic biosimilar in an approved indication to be acceptable;
• Health Canada recommends that a decision to transition or “switch” a patient being treated with a biologic originator drug to a biosimilar, or between any biologics, be made by the treating physician in consultation with the patient, taking into account any policies of the relevant jurisdiction.

Public drug plan and private health insurers’ positions on biosimilar transitioning

Federal, provincial, territorial and private insurance drug plans have begun implementing policy transition, which moves patients from their current biologic originator to its biologic biosimilar. A key benefit of transitioning patients is hundreds of millions of dollars in cost savings to the health care system. Biosimilars have the potential to improve access to biologics (both originators and biosimilars) and save public and private health care systems billions of dollars now, and over the coming year.

The arthritis community is working with both public and private health insurers to shape plans to reinvest some of the cost savings towards the reimbursement of new medicines coming into the marketplace, and importantly, towards improving other aspects of inflammatory arthritis care, such as expanding rheumatology nursing services and other supports identified by patients.

Transition vs interchangeability

It is important to note that transitioning is not the same thing as “interchangeability”.

In Canada, interchangeability often refers to the ability for a patient to be changed from one medication to another deemed therapeutically “equivalent” by a pharmacist, without the knowledge or approval of the doctor who wrote the original prescription. There are varying definitions of interchangeability in different provinces.

Health Canada’s Interchangeability Statement

• Health Canada’s authorization of a biologic biosimilar is not a declaration of equivalence to the biologic originator;
• The authority to declare two products interchangeable rests with each province and territory.

Transition experience and policy in Europe

Policy transition has been successfully implemented in many European countries and in tens of thousands of inflammatory arthritis patients with no compromise to patient safety or quality of care. European Union (EU) member countries generally agree that EU authorized biosimilars are considered alternative therapeutic options to their respective biologic originators, under the supervision of a clinical decision maker. The majority of countries, including England, Norway, Denmark, Germany, Netherlands, Belgium, France, and Portugal support physician led transitioning for biosimilars.

In the EU, like in Canada, the ruling regulatory body (European
Medicines Agency, the European equivalent to Health Canada) leaves the decision on biosimilar transitioning to individual member countries (comparable to federal, provincial and territorial jurisdictions or private drug plans decision making in Canada).

The EU Consortium of Individual Regulators in 2017 concluded that because of the high similarity, there is no reason to believe that the body’s immune system would react differently to the biosimilar compared with the original biologic upon a switch. This view is supported by the current experience with biosimilars on the market and by literature data. (Kurki et al. – Interchangeability of biosimilars: A European perspective) 

**Biosimilars library**

- Health Canada Biosimilars Landing Page
- Health Canada’s 2017 Biosimilars Workshop: Summary Report

**Transition studies**

Biosimilars policy transition
Frequently asked questions

Does authorization by Health Canada mean that a biologic biosimilar will be funded through drug benefit programs?

When Health Canada approves a biosimilar for use in the market place, funding is not guaranteed through drug benefit programs. In Canada, federal, provincial, territorial and private plans reimburse drugs. It is up to each jurisdiction to make their final formulary listing and reimbursement decisions.

Can a biologic biosimilar be used interchangeably with its biologic originator medication?

Health Canada’s authorization of a biosimilar is not a declaration of equivalence to the originator. There are varying definitions of interchangeability. In Canada, the term often refers to the ability for a patient to be changed from one drug to another considered equivalent drug by a pharmacist, without the intervention of the doctor who wrote the prescription. In Canada, the authority to declare two medications interchangeable rests with each federal, provincial and territorial drug formulary program, according to its own rules and regulations.

What does transitioning mean?

Transitioning refers to a one-time change from one medication to another, whether medically necessary or through a reimbursement policy change.

“Medical transition” occurs in the case of a patient, not doing well on their current biologic originator or biosimilar, who is transitioned to another biologic originator or biosimilar, based on a decision by the patient and their rheumatologist. Transitioning when medically required is important to achieving the best disease control and outcomes.

“Policy transitions” (“non-medical switching”) necessitate patients to change their medicine of choice to another, typically less expensive, medicine, not for a medical reason. In the case of biologics, policy transitioning would mean moving a patient from their biologic originator to its biologic biosimilar, usually because it is significantly less expensive.

If I am currently being treated with a biologic originator, can I be transitioned to its biosimilar?

Policy transitions can occur when the biologic originator’s patent expires and a biosimilar to it is approved for use. Health Canada considers well-controlled switches from a biologic originator to its biologic biosimilar in an approved indication to be acceptable. Research on transitioning to a biosimilar from a biologic originator from the European League Against Rheumatism and
American College of Rheumatology annual meetings shows no health differences between patients.

Prior to transitioning patients, both rheumatologists and their patients must be fully informed about the policy requiring the transition and have all available information about the biosimilar, such as details about the reimbursement policy, patient program information, including contact names and phone numbers.

There are several places patients transitioning from one biologic to another (whether from originator to biosimilar, originator to originator, or biosimilar to originator) can go for information and support, including:

- Your rheumatologist or rheumatology nurse or support staff
- Biologic patient support program
- Public or private drug formulary web sites
- Patient organizations such as Arthritis Consumer Experts and
- Patient created biosimilars websites, such as the Biosim•Exchange

**Why are public and private payers transitioning patients from biologic originators to biologic biosimilars as they become available?**

When patents expire, pharmaceutical companies can develop and bring to market a biosimilar version of the biologic originator, which creates competition and lowers medication costs. Like legislated generic drug savings in Canada, biosimilars have the potential to improve patient reimbursement access to biologics and save public and private health care systems billions of dollars now, and over the coming years.

A study commissioned by the Patented Medicine Prices Review Board (PMPRB) and conducted by the National Prescription Drug Utilization Information System (NPDUIS), “Potential Savings from Biosimilars in Canada”, estimated potential annual savings for a single biologic originator, like infliximab, in Canada could range between $91M and $514M in the third year following biosimilar entry.

**What benefits do biologic biosimilars bring to patients and health care systems?**

Specifically, biosimilars can create three main benefits to patients, the health care system, and society:

1. **Savings from biosimilars use can modernize** “special access criteria”. Currently, patients must try and fail on treatment with older and less expensive medications. Because biosimilars are significantly less expensive public and private drug formularies can remove the need for patients to fail on at least some of these older therapies before approving reimbursement for them.

2. **Savings from biosimilars use can be reinvested** into public and private drug formulary budgets making it possible to add new medications coming into the market place, and by doing so, expanding patient medication choice.
3. **Savings from biosimilars can be invested into non-medication types of care** that patients need, such as specialized nursing, counselling, physiotherapy and occupational therapy, among other important elements of an holistic inflammatory arthritis treatment plan. The arthritis community is working with public and private payers to reinvest some of the cost savings to new innovative medicines coming into the marketplace and, importantly, improve other aspects of arthritis care.

**Will the biologic biosimilar be as safe and effective as the biologic originator?**

A biosimilar is a biologic that has highly similar effectiveness, safety, immunogenicity profile and quality, and delivers the same therapeutic benefits to patients as its biologic “originator”. They are typically prescribed to patients by a rheumatologist. For example:

- etanercept (Brenzys®) and etanercept (Erelzi®) are biologic biosimilar versions of the biologic originator etanercept (Enbrel®);
- infliximab (Inflectra®) and infliximab (Renflexis®) are biologic biosimilar versions of the biologic originator infliximab (Remicade®).

As with any treatment, it is important to have a thorough conversation with your rheumatologist about all available therapeutic options, their safety, benefits and risks, and the differences between the medications, before coming to a decision.

**Will biosimilar manufacturers provide patient support at the same levels as offered by biologic originator manufacturers?**

You will continue to be supported and obtain your biosimilar in the same way as you did for the biologic you were previously taking. Your rheumatologist will give you the name of the patient support program for your biosimilar and they will help you organize reimbursement and other patient needs. You and your rheumatologist will monitor the safety and effectiveness of your biosimilar as part of your routine care.

**What research or “real world” experience supports my insurer mandating a policy transition?**

There have been more than 100 transition studies in rheumatology, gastroenterology, dermatology and other diseases, which collectively show little to no clinical differences between anti-TNF inhibitor biosimilars and their biologic originators. Currently available research presented at the most recent ACR and EULAR annual meetings indicates that a single transition from a biologic originator to one of its biologic biosimilars is safe and effective.

Data from the “NOR-SWITCH” study of transitioning from a biologic originator to its biosimilar by Norwegian researchers showed no differences in disease worsening between patients who were transitioned from the infliximab originator (Remicade®) to the infliximab biosimilar Remsima (approved as Inflectra® in Canada). NOR-SWITCH immunogenicity data
showed no significant differences between Remicade and Remsima. Registries in Norway, Denmark, Germany and Sweden are tracking patients’ “real world” experience of transitioning to biosimilars and reporting nearly identical results.

Am I likely to experience side effects after transitioning?

As you have already been successfully treated with the originator, you are unlikely to experience any new side effects after transitioning. As always, your rheumatologist will monitor your treatment carefully, just like they did with your previous biologic, whether it was an originator or a biosimilar. If you feel you are experiencing a significant side effect, contact your rheumatologist who will be able to assess whether it is the medication or some other reason.
About ACE

Arthritis Consumer Experts (ACE) is a national patient-led organization that provides free science-based information and education programs in both official languages to people with arthritis. ACE serves people living with all forms of arthritis by helping them take control of their disease and improve their quality of life. Founded and led by people with arthritis, ACE actively advocates on arthritis health and policy issues at meetings, conferences and through ACE's JointHealth™ family of programs and its online news channel, Arthritis Broadcast Network. ACE's organizational and staff conduct is guided by a strict set of publicly available guiding principles as well as seeks council from its advisory board comprised of leading scientists, medical professionals and informed people with arthritis.

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ACE also received unsolicited donations from its community members (people with arthritis) across Canada.

ACE thanks funders for their support to help the nearly 6 million Canadians living with osteoarthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and the many other forms of the disease.

Disclaimer

The material contained in this guide is provided for general information only. This guide should not be relied on to suggest a course of treatment for a particular individual or as a substitute for consultation with qualified health professionals who are familiar with your individual medical needs. It is meant to inform the discussion that you have with health care professionals, as well as others who play a role in your treatment and care. Should you have any health care related questions, you should contact your physician.
Biosimilars in Canada – What inflammatory arthritis patients need to know

About this Guide

This guide has been prepared by Arthritis Consumer Experts (ACE) in collaboration with its advisory board comprised of leading scientists and medical professionals and will be updated and improved regularly as new research, information, and treatments on biosimilars become available.

Founded in 2000, ACE is Canada’s largest national arthritis patient-led organization and leading provider of evidence-based information, education programming and sustained government advocacy. ACE actively advocates on arthritis health and policy issues at meetings, conferences and through ACE’s JointHealth™ family of programs and its online news channel, Arthritis Broadcast Network.

ACE has been a leader in biosimilars discussions since 2009, sharing information with stakeholders through free research-based workshops, webinars and education programs. Drawing from this experience, ACE has created the Biosim•Exchange, an information hub for consumers to get the latest biosimilars news, research findings and background analysis as well as public and private health insurance formulary policy and listing decisions.

This guide will be updated online and available for download in PDF format at http://biosim.jointhealth.org.

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