Arthritis Talks: Biologics, Biosimilars, JAK inhibitors

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Webinar tips

- Use the **Q&A** section to ask the presenters your questions. Some of the questions will be chosen for the live question period at the end of the webinar.
- Click on the **Chat** box to connect with other participants and the Arthritis Society's chat moderator.
- If you have further issues, email arthritistalks@arthritis.ca

Overview

[1]
Biologics and Biosimilars

[2]
JAK Inhibitors
Tips to optimize therapy

[3]
Questions

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What are biologics, biosimilars and JAK inhibitors?

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Biologics

Biologics are a group of drugs that are genetically engineered proteins which are derived from animals or microorganisms.

- Not synthetically produced, but are made in a living system, often using DNA technology
- Complex large molecules and are mixtures which are not identical from batch to batch
  Used in the treatment of many immune related conditions, and many others
- Very targeted treatments as they are engineered to bind to a specific target such as a cytokine (controls the immune system)
- Often require refrigeration to maintain shelf life
- Have “mab” as part of the name – **m**onoclonal **a**nti**b**ody

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Biosimilars

Biosimilar are the subsequent entry biologic that has demonstrated similarity to the originator biologic

- Requires chemical testing and clinical testing showing similarity
  - Comparative analytical data
  - Comparative pre-clinical data
  - Comparative clinical data
- All are branded and have a tradename or brand name
  - E.g. originator/reference - Humira
  - E.g. biosimilars – Abrilada, Amgevita, Hadlima, Hulio, Hyrimoz, Idacio, Simlandi, Yuflyma
- Cannot be interchanged in Canada, what is prescribed must be dispensed
  - All biosimilars of the same molecule have the same molecule name (e.g. adalimumab)
- Have effects and side effects which are clinically indistinguishable

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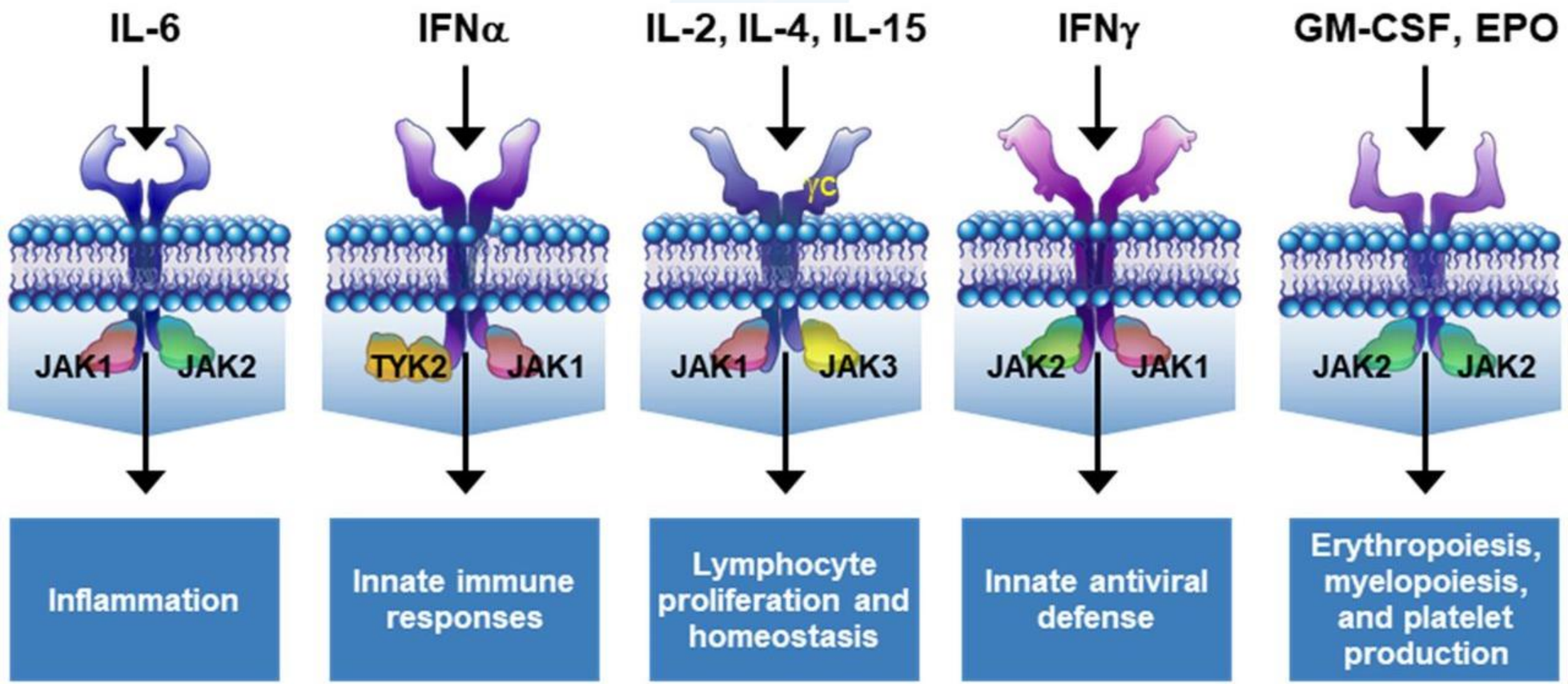
JAK (Janus Kinase) Inhibitors

JAK (Janus Kinase) inhibitor belong to a group of DMARDs (Disease-Modifying Anti-rheumatic drugs) which impairs the body's immune system and helps prevent damage to joints

- Available as tablets and capsules for oral use



JAK Inhibitors

- Used in the treatment of many conditions; rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, atopic dermatitis, and other conditions
- Cibinqo (abrocitinib), Inrebic (fedratinib), Jakavi (ruxolitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib)
- May be associated with heart problems, blood clots and some cancers.
  - People with potential related risks including cardiovascular risk factors or heart disease or are prone to blood clots should consider other options for treatment first, and discuss with their healthcare professional

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Final Notes – biologics, biosimilars, JAK inhibitors

- Biologics are complex molecules used to treat a variety of diseases are stored in the refrigerator, must be injected under the skin or by IV infusion
- Biosimilars are highly similar to the reference biologic in all relevant structural and functional attributes including safety and efficacy
- Biologics and JAK inhibitors can take
- JAK Inhibitors are a new category of drugs for use in conditions that involves autoimmune activity
- Unusual to be treated with any combination of a biologic, biosimilar and JAK Inhibitors
  - Methotrexate is often used in combination with biologics/biosimilars and JAK inhibitors

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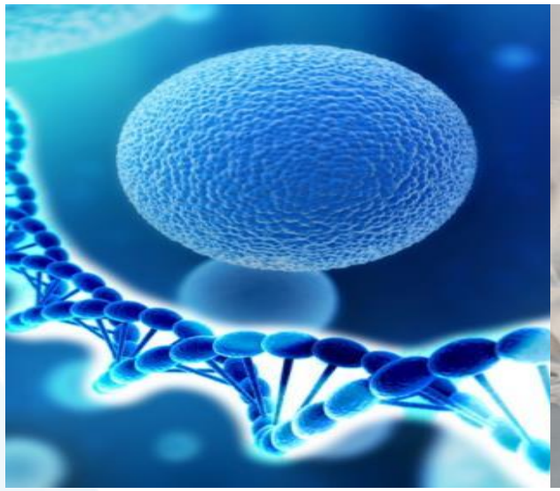
Some originator medications have many biosimilars. How are they different and how do you know which will work best?

Manufacturing of Biologics




Modify host cells → **Grow cells** → **Extract, refold, purify** → **Formulate to stable finished drug product**

(e.g., bacteria, yeast, mammalian) to produce recombinant proteins

under controlled conditions (fermentation, upstream process)

to generate drug substance (downstream process)

vial, syringe, cartridge

Adapted from EGA Handbook on biosimilar medicines; available from http://www.egagenerics.com/index.php/publications/
http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/06/WC500107832.pdf

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Biologics are More Complex than Small Molecules

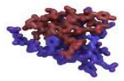
Synthetic

1x

Acetylsalicylic acid (ASA)
“Aspirin”
0.18kDa

Bacteria, Yeast

Protein
(no sugars)

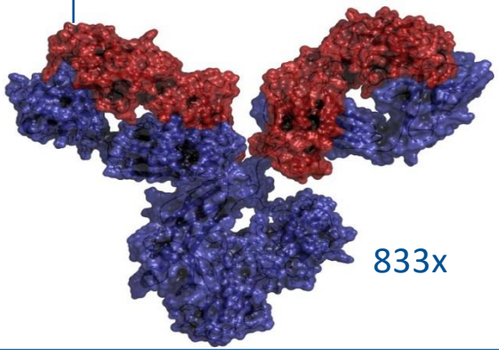


32x

Recombinant Insulin
~5.8 kDa

Mammalian

Glycoprotein
(with sugars)



833x

Monoclonal antibody
~150 kDa

Complexity

kDa: kilodalton

Adapted from: Kozlowski S, *et al*. *N Engl J Med* 2011;365(5):385–8; Revers L & Furczon E. *Canadian Pharmacists Journal* 2010;143(3):134–9;
Revers L & Furczon E. *Canadian Pharmacists Journal* 2010;143(4):184–91; http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf
Accessed July 10, 2015; accessed May 2, 2016; http://www.drugbank.ca/drugs/DB00945, accessed May 2, 2016; http://www.drugbank.ca/drugs/DB00073, accessed May 2, 2016; http://www.drugbank.ca/drugs/DB00030; accessed May 2, 2016.

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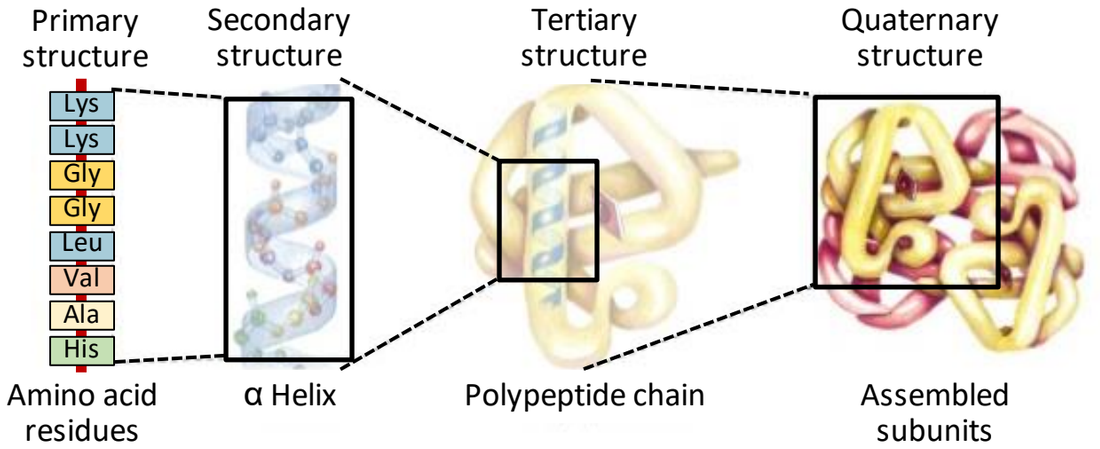
A Biosimilar is Designed to be Comparable to the Reference Product in All Parameters

- Identical amino acid sequence (primary structure)
- **Highly similar higher-order structure** (secondary, tertiary and quaternary structures)
  - Affinity
  - Selectivity
  - Pharmacokinetic profile
  - Functional activity
  - Solubility
  - Immunogenicity



Clinically relevant attributes of the biosimilar must be within the narrow variability range of the reference product – based on Health Canada requirements

Adapted from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed July 10, 2015.
Image source: https://www.slideshare.net/mujahidahuja/protein-structure-69630269.
Kirchhoff CF *et al*. *Biotech & Bioengin* 2017;114(12):2696-705.

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Some originator medications have many biosimilars. How are they different and how do you know which will work best?

- Once an originator biologic's patent expires, other manufacturers can market their version of the molecule as a biosimilar.
  - Some molecules have only a few biosimilar whereas adalimumab has 8 biosimilars
  - These versions are highly similar with comparable structure and have clinical effects shown in studies to be not clinically different.
  - All biosimilars have been studied in people with one of the conditions, but not in all the patient conditions as the originator
  - Often 35 to 50% lower in cost compared to the originator
  - Each version has its own Patient Support Program (PSP) who are independent and do not communicate with each other
    - PSPs do communicate with your physician and pharmacy as needed to assist with navigation of coverage and financial assistance

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When Health Canada Approves a Biosimilar

- The quality, safety and efficacy of the biosimilar are **highly similar** to the reference biologic drug
- If Special Authority or Exceptional Access is approved for the reference biologic it will be approved for the biosimilar
- There are **no clinically meaningful** differences between the biosimilar and the reference biologic drug
- The **stringent practices by Health Canada** for all approved drugs with respect to Good Manufacturing Practices and regular audits are applied
- Patient and healthcare professionals can have **confidence in the quality, safety and efficacy**
- It is possible to have different excipients (e.g. preservatives and stabilizers) in the different biosimilar versions

Adapted from:
Health Canada. About Biosimilars: What we know and what we want to know. January 19, 2018.
Available at: https://www.slideshare.net/NatalieRichardson7/biosimilars-presentation-health-canada?from_action=save
Health Canada. Good Manufacturing Practices Guide for Drug Products (GUI-0001)-Summary. Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/gmp-guidelines-0001.html

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Biosimilar Development Represents a Paradigm Shift

	Generic	Biologic	Biosimilar
Time to Market (years)	2 – 3	8 – 10	**7 – 8**
Clinical Studies	Bioequivalence studies in healthy volunteers	Phase I – III efficacy and safety studies	**Comparative pharmacokinetic and Phase III studies**
Patients (n)	20 – 50	800 – 1000	**~500**
Post-approval activities	Pharmacovigilance	Phase IV, Risk Management, Plan including Pharmacovigilance	**Phase IV, Risk Management Plan including Pharmacovigilance**

Adapted from:
Windisch J. *Int J Clin Rheumatol* 2015;10(6):501-10.
Kirchhoff CF *et al*. *Biotech & Bioengin* 2017;114(12):2696-705.

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Which one is best?

- Biosimilars may vary in their injector pen or syringe
  - Size, shape, style, need size, and pressure needed to inject
- Biosimilars can have different excipients (other ingredients, preservative, diluent, etc.) – e.g. adalimumab may be contain citrate or citrate-free
- Costs are essentially equal among biosimilars, but PSPs are different and may offer different types of support (e.g. financial assistance, vaccines, lab tests, etc.)
- You can select your preferred pharmacy where you receive your medication
- You can select your preferred infusion clinic where you receive your infusion
- Supply shortages can occur

The best one is the one that has the most suitable injector pen/syringe, compatible excipients, adequate financial coverage, PSP that is supportive, and drug with suitable storage requirements (some have longer room temperature storage)

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What if the biosimilar I switch to does not work as well?

What if the biosimilar I switch to does not work as well?

Clinical studies have demonstrated the effects of biosimilars are clinically equivalent to the originator

- Is the change in response an allergic reaction or different effect
- As a result of differences in excipients, there could be a slightly different effect for some people – review contents
- Check the administration of the medication is proper – new injector pen, new infusion site, different pre-treatment protocol, etc.
- The disease flares, waxes, wanes and is often unpredictable, so the lack of response may just be a flare that may have occurred regardless
- Determine if there may be an association to changes in lifestyle and stress level

What if the biosimilar I switch to does not work as well?

- You may be experiencing the nocebo effect – that is experiencing a negative effect due to a belief that the therapy is worse or won't work
  - This is the opposite of the "Placebo" effect
  - There may be a perception from what is read on the internet or how someone has described or educated you about biosimilars
- Most payers (public and private plans) require an "adequate trial" of the biosimilar before switching back to the originator with coverage
  - Check your options with your private health insurance plan
    - Some payers require a trial of another biosimilar before covering the originator
  - Document your response, keeping notes of reactions/response and the dates and duration of use
  - Speak with your physician about the response and discuss the options available
    - Some physicians recommend changing to a therapy with a different mechanism or a different drug if there is a concern of antidrug antibodies

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I have tried several biologic treatments, each for about 6 months. Is there a concern with switching biologics?

The response to a drug therapy with inflammatory conditions like rheumatoid arthritis can be very individual

- Some people respond well to the first drug they try
- Some may have a long-term response and some a short-term response
  - Can be due to developing anti-drug antibodies (the body attacking the biologic drug, which is a protein)
  - Check injection technique for SC administration – common to have variable dosing due to not pressing the button hard enough, not waiting long enough before removing the needle, not injecting in the right location, missing doses, drug stored improperly, etc
- Give the therapy an adequate time for response, 6 to 12 months, initial response may be seen in 3 months. May need to stop if severe side effects or allergic reaction.
- Can respond to a drug with same mechanism or change to a different mechanism for better response – no clear evidence
  - Adjunctive treatment with methotrexate is often beneficial – some practitioners recommend restarting methotrexate

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How are JAK inhibitors different than biologics and biosimilars?

How are JAK inhibitors different than biologics and biosimilars?

	Administration route	Dosing	Available since	Used with MTX	Increased risk of infection	Cardiovascular risk
Biologics	SC / IV	Weekly to every 6 months	1998	Yes	Yes	No
JAK Inhibitors	Oral tablets and capsules	Daily to twice a day	2012	Yes	Yes	Yes

- Treatment may begin with either a biologic or JAK inhibitor
- JAKs may have an earlier onset of effect in a few days to 2 weeks, whereas biologics often take several weeks
- Maximum benefit for biologics and JAKs occurs in 3 to 6 months
- Speak with your Specialist – carry out shared informed decision making
- Infusions require administration at a clinic
- SC injection can be done at home by yourself or a caregiver

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These medications are very costly. What are some ways to find help in covering these medications?

Access to Medications – Cost Issues

- Not all medicines are publicly listed (covered by the province or federal plan)
- Private health insurance may cover these medicines – not all are the same
- For the more costly medicines, prior authorization is required, that is forms need to be completed by your physician, e.g. Special Authority, Exceptional Access, Special Authorization, etc.
  - Systematic trial of therapies – stepping up (e.g. Mtx plus others – leflunomide, sulfasalazine, azathioprine, tacrolimus, cyclosporine, gold, docycycline)
  - Check with your public plan (provincial Pharmacare) about coverage
    - In BC, Fair PharmaCare requires you to file your income tax and qualify for Special Authority)
  - Check with your private plan about coverage requirements and what steps are needed to access coverage
    - Spousal plans may have different requirements
    - Watch for yearly limits and lifetime limits (max amount paid)

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Access to Medications

- Discuss options with your physician and potentially identify a few and discuss with your pharmacist regarding cost and possible coverage (pharmacist may be able to determine your NET out of pocket costs)
  - May need to wait for response from Patient Support Program
- Patient Support Program (PSP) – offer financial support, based on need, individualized to patient need
  - Different product may have different supports in place
  - Speak with PSP if you have financial difficulty
  - Where private health plan requires a deductible payment, PSP may help
  - Depending on province, some drugs have a patient assistance card (Co-Pay Card)
    - Speak with a pharmacist familiar with these therapies

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Rituximab has a B-Cell drug effect, and seems to work well but has side effects which are difficult, are there other options?

Rituximab has a B-Cell drug effect, and seems to work well but has side effects which are difficult, are there other options?

- Rituximab is a biologic and currently is the only therapy that binds specifically to the antigen CD20 (a human B-lymphocyte-restricted differentiation antigen, Bp35) – located on B-Cells – and depletes circulating B-Cells
  - There is currently no other available drug that targets B-Cells
  - There are therapies being studied, none which are close to approval
  - Infusion related reactions can be reduced by:
    - Take acetaminophen prior to infusion and in 4 hours
    - Infusing the drug slower or pausing the infusion
    - Pre-treating with methylprednisolone, diphenhydramine
    - Doses of hydrocortisone and/or diphenhydramine during infusion
- Belimumab (Benlysta) inhibits the survival of B-Cells by binding to the B Lymphocyte Stimulator (BLyS)
  - Is only approved for use in systemic lupus erythematosus (SLE) and active lupus nephritis

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Where can I find more information to make informed medication decisions?

Information Resources

- Be careful of unreliable and non-credible websites
- Canadian resources preferred, developed by licensed healthcare professionals
- Pharmacists, Rheumatology Nurse, Rheumatologist
- Arthritis Society Canada (https://arthritis.ca/)
- Canadian Arthritis Patient Alliance (https://arthritispatient.ca)
- Arthritis Research Canada (https://www.arthritisresearch.ca/)
- RheumInfo (https://rheuminfo.com/)
- Arthritis Consumer Experts (https://jointhealth.org/)
- Patient Support Program – represents only one product by one manufacturer

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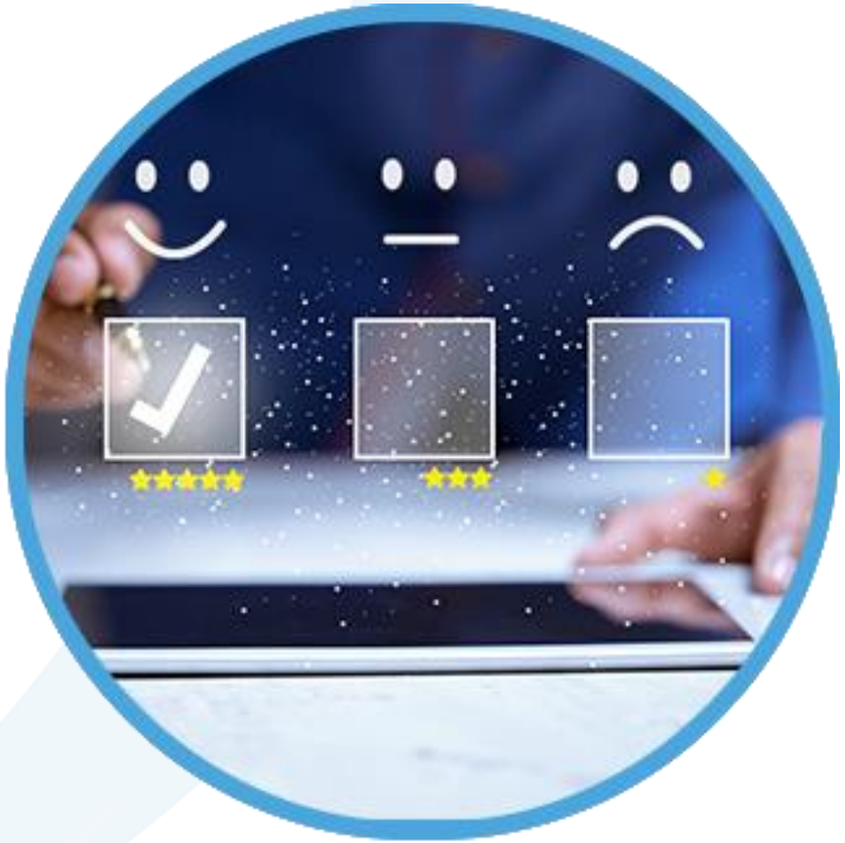
Any final thoughts or recommendations?

Questions

Tell us what you think…



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Upcoming Events

December

6 p.m. ET

Arthritis Talks: Unlocking Physical Activity with Assistive Devices
featuring Tara Stier and Michael Polhmann

Learn about:

- Similarities and differences between biologics and biosimilars
- Benefits of physical activity for people living with arthritis
- Simple exercises for people with arthritis and how much activity is appropriate
- Practical solutions and aids to get you moving
- How assistive devices can help you become more physically active

Register at:

Visit arthritis.ca/ArthritisTalks or click the link in your email inbox


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