ARTHRITIS ALLIANCE OF CANADA
"HOT TOPIC" REVIEW

SUBSEQUENT ENTRY BIOLOGICS

AAC Member Lead: Issue was brought forward by Arthritis Consumer Experts, The Arthritis Society and Canadian Rheumatology Association.

BACKGROUND

Subsequent entry biologics (SEBs) describe a group of medications that are administered by subcutaneous injection or intravenous infusion and are similar, but not the same, as their originator biologics such as infliximab (Remicade®), adalimumab (Humira®), and etanercept (Enbrel®).

Health Canada defines SEBs as a "biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug." While Health Canada uses the term "subsequent entry biologic," the term "biosimiliar" or "follow-on biologic" is also used in other regulatory jurisdictions.

Arthritis patients are on the "front line" of policy making, as SEBs to treat autoimmune forms of arthritis are the first SEBs to enter the Canadian marketplace, with several other therapeutic classes on the horizon.

Inflectra® is the brand name of the SEB that received approval through a Notice of Compliance from Health Canada on January 15, 2014. It is a subsequent entry biologic to infliximab (Remicade). Inflectra® is similar, but not identical, to infliximab and is approved for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and psoriasis (PsO).

A cost-effectiveness recommendation by CADTH for Inflectra® was made on December 19, 2014. Based on this recommendation, each of the provinces is now considering whether to include it on their formularies, or not.

As of February 2, 2015, Inflectra has been added in Quebec to the Liste de Médicaments d'Exception for the Health Canada approved indications (RA, PsA, AS and PsO). The National Institute of excellence in health and social services (INESSS) has positioned Inflectra and Remicade (for the four indications) in the same category and is applying a "lowest price alternative (PPB)" to this category, forcing a patient to pay the difference ($290 /100mg) for continuing on Remicade. INESSS recognizes that clinicians might have some concerns regarding switching patients to a new biologic drug. INESSS highlights the fact that physicians can provide full coverage of Remicade to their patient if they hand write on the prescription: "pas de substitution" or "no substitution."

SIMILAR BUT NOT THE SAME

Medications made with small, chemically manufactured molecules (e.g. acetylsalicylic acid, the active ingredient in aspirin) are made through a relatively simple process. After a manufacturer's patent for a particular medication, like aspirin, expires, other companies can easily make exact copies of the active ingredient of the brand name version. These are known as generics.

Biologics, however, are large and complex protein molecules made in a process that starts with living cells and a manufacturing process can have a significant impact on the final drug product. It is impossible to make an exact copy of a biologic drug because the manufacturing process is proprietary to the original manufacturer. After the patent expires, different companies are only able to make "similar" versions of the originator biologic. Even minor differences from the originator biologic may change the way a SEB acts in the body. The distinction is important to physicians and patients since there is no guarantee a SEB will be equally effective or be as safe as its innovator reference product. As a result, clinical trials will always be required for approval of SEBs.

HOW ARE SEBs REGULATED?

Unlike generics, approval of a SEB is not a declaration of pharmaceutical or therapeutic equivalence to the originator biologic. Generic drugs are pharmaceuticals and are approved through the abbreviated new drug process; SEBs are biologics and are approved under the new drug submission process.

Health Canada reviews the manufacturing process, data on the comparability of the SEB to the reference product and the non-clinical and clinical data supplied by the SEB manufacturer to establish similarity to the originator product. At the end of the review, Health Canada can approve the product for one or more indications of the reference product based on clinical trial information showing comparability of response and safety. Health Canada may approve some indications without clinical data in that disease based on the response in a different indication. This is called indication extrapolation. Approval of a SEB is not a declaration of bioequivalence with the reference product and post-approval, SEBs are regulated like any new biologic medicine.

HOW ARE SEBs REIMBURSED ON DRUG FORMULARIES?

Individual provinces and insurance plans will make decisions about SEB listings on drug formularies. As SEBs are not bioequivalent to the reference product, it is unlikely they will be listed as interchangeable with the original product. Public and private payers, however, may prefer one product over another, opening up the possibility that a SEB could replace the original biologic that a patient had previously been prescribed due to potential cost advantage.

SEB "INTERCHANGEABILTY"

"Interchangeability" refers to the ability to switch from one bioequivalent medication to another considered to be its generic equivalent. This type of substitution is most common with small-molecule generic drugs (e.g. Lipitor vs generic atorvastatin), and often happens

automatically at the pharmacy (without physician knowledge or involvement) because of cost differences. Therapeutic Substitution refers to the switching from one product in the same class to a non-bioequivalent product in the same class, which is thought to be therapeutically equivalent (e.g. Lipitor vs Crestor). However, SEBs are not identical copies or "generics" of the original biologic drug; small differences between products can cause unexpected outcomes.

Because SEBs and innovator biologics are not identical, interchangeability or therapeutic substitution at the pharmacy, could lead to uncontrolled switching (i.e. without physician oversight) between products. This may be problematic, as patients could develop antibodies that may affect efficacy and safety of the medication. Health Canada does not support automatic substitution of SEBs and recommends that physicians make well-informed choices when considering switching a patient's biologic medicine.

SEB NAMING

Arthritis consumer and health professional groups, and other disease organizations, have called for distinct non-proprietary and brand naming for any and all SEBs entering the Canadian marketplace. They did so because of the need to minimize confusion about which medication was being prescribed or taken, and equally important, to accurately attribute adverse events to the appropriate product (SEB or originator biologic).

Health Canada has decided to follow the non-proprietary naming protocol for biologics (including SEBs) that is ultimately recommended by the World Health Organization (WHO). In the interim, Health Canada has allowed Inflectra to use the same nonproprietary name (infliximab) as the originator biologic (Remicade). This will complicate post-marketing surveillance if adverse events are reported as "infliximab" only, without clearly distinguishing the products (Inflectra or Remicade). At the request of a number of regulatory jurisdictions, the WHO is working to address the issue of non-proprietary naming for SEBs. Currently, it is unclear what the patient support program and post market surveillance plan is for Inflectra in Canada.

SEB POTENTIAL BENEFITS

SEBs may offer patients & physicians a choice in the treatment of autoimmune forms of arthritis at a reduced acquisition cost. The additional treatment option an SEB may provide is compromised if public and private payers decide to reimburse them in a preferential manner to the originator biologic.