Mandatory Generic Substitution For Immunosuppressant Transplant Drugs

Is it the safest and healthiest policy for patients?

The potential for uncontrolled generic switching of immunosuppressant transplant drugs, such as tacrolimus or cyclosporine, due to mandatory generic substitution plans, can negatively impact patient (plan member) safety and health outcomes, resulting in higher costs. Does your drug benefit plan have proper safeguards to avoid this scenario?

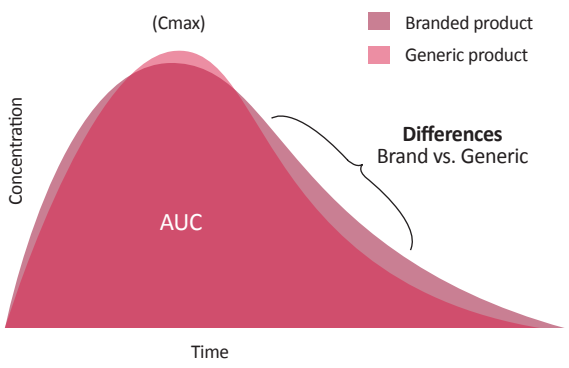
Are mandatory generic substitution plans the best solution for all drugs?

Mandatory generic substitution plans assume all brand drugs and their corresponding generics are equivalent and will have similar clinical outcomes and adverse effects for patients. Generic equivalencies are based on Health Canada bioequivalence standards as well as provincial legislation, regulations, and/or policies.

In a mandatory generic substitution plan, plan sponsors will reimburse pharmacies and plan members only the price of the lowest generic equivalent of the brand drug. Pharmacists can substitute interchangeable generics at the pharmacy without consultation or approval by the physician. Pharmacy purchasing practices can also influence which drug a patient receives, as generic suppliers can change based on cost and availability. This is important as Health Canada requires a generic manufacturer to prove that its drug is bioequivalent to the brand or reference drug, but does not have to show bio-equivalence to other generic versions.

Generic substitution plans, in general, achieve their goal of providing similar clinical outcomes at a lower cost to the plan sponsor and member. These practices have been a mainstay for both public and private drug benefit plans over the last few decades. However, in a number of circumstances, the uncontrolled switching from brand to generic drug, or between different generic formulations, may result in less optimal treatment. Plan sponsors must balance the need for cost containment while having plan members receive appropriate treatment by ensuring processes are in place for plan design exceptions.

Bioequivalence Testing



Key Pharmacokinetic Parameters

- Area under the curve (AUC)→ marker of drug exposure
- Peak drug concentration achieved following dosing (Cmax)

What exceptions should be considered?

There are a number of immunosuppressant transplant drugs that should be considered as exceptions in mandatory generic substitution plans. These drugs have been designated as 'Critical Dose Drugs' (CDDs) by Health Canada. In 2012, Health Canada published an update to its 'Guidance Document – Comparative Bioavailability Standards: Formulations Used for Systemic Effects,' which defines bioequivalence standards and exceptions. One important exception involves CDDs, which are defined as 'drugs where small differences in dose and blood levels may lead to serious therapeutic failures and/or serious adverse reactions which may be life-threatening, or result in hospitalization, persistent disability or incapacity, or death.' A CDD has a narrow therapeutic range where blood levels, clinical response and toxicity are closely linked. Health Canada has designated several drugs within this category, including the immunosuppressant transplant drugs: cyclosporine (Neoral®), sirolimus (Rapamune®), and tacrolimus (Prograf®).

In the 'Guidance Document,' Health Canada has not established guidelines or standards for generic substitution of CDDs. However, a number of European regulatory bodies have created exceptions for tacrolimus. For example, in Spain and the United Kingdom, oral generic formulations of tacrolimus are branded by name. Prescribing and dispensing should be done by brand name only to minimize the risk of inadvertent switching between products, which has been associated with reports of toxicity.[1-4] In Denmark, generic substitution of oral tacrolimus is not allowed.[5] Norway now recommends that tacrolimus should not be substitutable at pharmacies. The Italian Medicines Agency issued a statement 'that oral tacrolimus may not be interchanged without careful therapeutic monitoring under the strict supervision of a transplant specialist, and the chemist should always dispense the commercial name as prescribed by the physician'.[6]

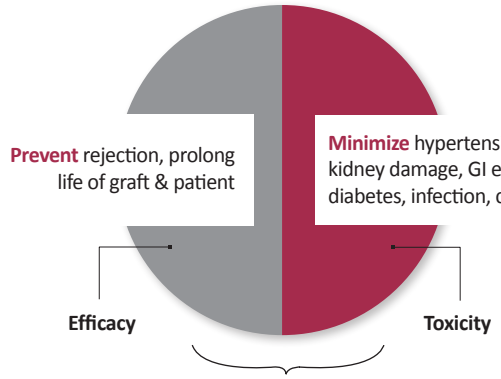
There are also a number of Canadian examples for exception approval processes of critical dose immunosuppressant transplant drugs, two of which are in Ontario and Quebec.

In Ontario, the Special Drugs Program (SDP) covers the full cost of certain outpatient drugs used to treat a number of serious conditions. Included in the program is Neoral® (cyclosporine) for treatment in solid organ or bone marrow transplant if prescribed by a physician on the medical staff of a Group O hospital, under the Public Hospitals Act.[7]

In Quebec, Liste de médicaments published by the Régie de l'assurance maladie du Québec (RAMQ) includes cyclosporine as a narrow therapeutic index drug (Schedule VII). Cyclosporine is therefore exempt from the province's lowest cost available policy and Neoral® is reimbursed when prescribed by a physician.[8]

Canada's provincial drug plan and private drug benefit managers can utilize these experiences for other critical dose immunosuppressant transplant drugs when generics become available. The importance is paramount because as of this writing it is expected Health Canada will approve generic oral tacrolimus in the near future without such exceptions in place.

Desired Outcomes for Immunosuppressant Therapy in Transplantation



Optimize Balance
Between Efficacy and Toxicity

What are the unique patient considerations for transplant drugs?

With the advent of newer drug therapies, one-year kidney graft survival rates have improved, from 65% in 1975 to over 97% in 2009 (Canadian Organ Replacement Register, 2011, CIHI). Success in transplantation relies on managing the body's immune response to optimize graft survival. The usual approach is 'triple therapy' for long-term maintenance, including one of the following CDDs: Prograf® (tacrolimus immediate release capsules), Advagraf® (tacrolimus extended release capsules) or Neoral® (cyclosporine capsules and solution). The goal for optimizing therapy in these patients is to find the appropriate balance between drug efficacy and toxicity while preventing graft rejection.

"The appropriate management of immunosuppressive drug therapy is critical to success in transplantation. The level of the drug in blood is used as a surrogate marker to gauge an individual patient's level of immunosuppression. Drugs like Prograf® (tacrolimus) require close blood level monitoring to ensure that the level of drug in the blood remains in the desired target range. As the therapeutic range is narrow, changes in exposure may compromise patient outcomes," says Jennifer Harrison, Pharmacy Clinical Site Leader with the University Health Network in Toronto.

Acute kidney graft rejection may be a consequence of inappropriate dosing, which may result in hospitalization, more intensive intravenous immunosuppressive therapy, infection, possible shortening of graft life or actual loss of graft function. The patient may also experience other complications or adverse effects from intensified therapy. Unintended consequences for a plan sponsor may include an increase in disability costs and absenteeism for its plan member.

What are the recommendations of healthcare professionals for the prescribing and dispensing of critical dose drugs?

In light of the potential problems with generic substitution of CDDs, in particular in relation to unsupervised switches

in immunosuppressive transplant therapy, healthcare professionals through advisory meetings, consensus conferences and surveys in the U.S., Europe, and Canada, have made the following recommendations:[9-11]

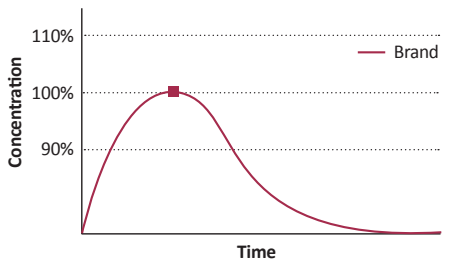
1. Generic immunosuppressant use should be approached with caution.
2. If a generic is used, it should be prescribed from the day of transplantation rather than switching when there is high risk of graft rejection.
3. Formulation switches should be initiated only by physicians; repetitive switches (between generic drugs or between generics and the brand drug) should be avoided.
4. Patient education is essential. Patients should be informed when switches occur.
5. Following any formulation switch, blood level monitoring should occur until stable immunosuppression is established.
6. More extensive data should be made available regarding the efficacy and safety of generic immunosuppressive therapy for proper use and monitoring.

Harrison further states that, "There is widespread consensus in the transplant community that blood level and clinical monitoring is required with any dose or product change, whether a switch from a brand to a generic drug, or from one generic drug product to another. In the setting of mandatory generic substitution, where drug product selection is defined by the insurer and dispensed at the retail pharmacy, the prescriber may not be informed of drug product switches. Without timely prescriber notification, the requisite monitoring cannot be performed, which poses a significant patient safety concern."

In a number of circumstances, the uncontrolled switching from brand to generic drug, or between different generic formulations, may result in less optimal treatment. **Plan sponsors must balance the need for cost containment while having plan members receive appropriate treatment** by ensuring processes are in place for plan design exceptions.

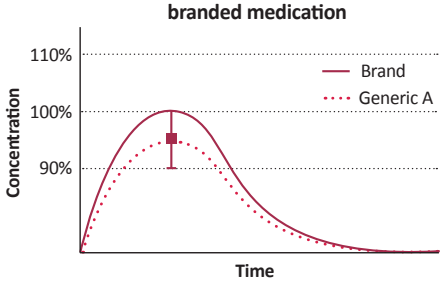
The Case: Substituting Critical Dose Immunosuppressant Transplant Drug Generic A for Brand

On leaving hospital, patient receives a **two-month supply of branded medications**



Blood level profile of patient's branded medication

After two months, patient's pharmacist **dispenses Generic A in place of his branded medication**



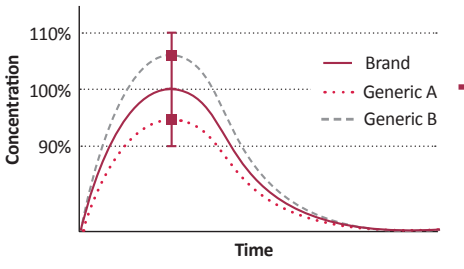
Generic A is bioequivalent to patient's branded medication

= **Bioequivalence does not mean clinical equivalence**

The Case: Substituting Critical Dose Immunosuppressant Transplant Drug Generic A and Generic B

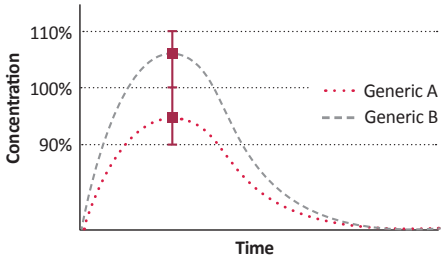
(Generics may not be bioequivalent with each other)

After six months, patient's pharmacist **dispenses Generic B in place of Generic A**



Generics A and B are both bioequivalent to patient's branded medication

Patient may be switching between drugs that are not bioequivalent with each other



Generic B may not necessarily be bioequivalent to Generic A

= **May have variability in blood levels between generics. Variability with critical dose immunosuppressant transplant drugs is associated with poor outcomes**

"There is widespread consensus in the transplant community that blood level and clinical monitoring is required with any dose or product change, whether a switch from a brand to a generic drug, or from one generic drug product to another. In the setting of mandatory generic substitution where drug product selection is defined by the insurer and dispensed at the retail pharmacy, the prescriber may not be informed of drug product switches..." —*Jennifer Harrison, University Health Network*

What are the new management challenges and action plans for integrating generic transplant drugs into Canadian drug benefit plans?

With the anticipated Health Canada approval of generic oral tacrolimus, and with the knowledge that additional critical dose drugs used in immunosuppressive transplant therapy will likely have generic versions available in future years, it is imperative that guidelines, standards and policies are established (public and private) for these drugs to balance cost, clinical response, and positive patient outcomes.

The challenges appear to be complex and do not fit into the standard practice of mandatory generic substitution plans, where exception processes for using critical dose drugs are primarily reactive (i.e., at the pharmacy), thus potentially delaying therapy. There needs to be an understanding from all stakeholders that while generic formulations of critical dose immunosuppressant transplant drugs have been approved as safe for use by Health Canada, uncontrolled substitution for these drugs may be unsafe.

Below are some suggestions for managing CDD immunosuppressant transplant therapy for plan sponsors, plan members, and healthcare professionals:

1. Drug substitution exception policies should be implemented for these drugs in certain circumstances, such as switching after a patient is stabilized.
    a. Establish standardized proactive exception processes at the drug plan design level for these drugs (prior to prescribing by a physician).
2. Formulation switches should be initiated only by physicians experienced in transplantation; repetitive switches (between generic brands) should be avoided.
    a. Following any formulation switch, blood level monitoring MUST occur until stable immunosuppression is established.
3. Pharmacists must inform patients and physicians if switches occur.
4. Create proactive mechanisms to ensure that blood levels are monitored.

Due to the complexity and immediacy of the current situation with possible uncontrolled mandatory substitution of generic critical dose drugs in transplant therapy, plan sponsors should proceed with proactive plan design exception and monitoring changes to ensure appropriate therapy and safety for their plan members.

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