Important Safety Information on Tacrolimus - Risk of Graft Rejection due to Medication Errors: Inadvertent Switching between Different Oral Formulations

2019/07/22

Audience

Healthcare professionals including general surgeons, transplant surgeons, nephrologists, hepatologists, gastroenterologists, transplantation nurses, hospital and community pharmacists, and transplant centres.

Key messages

- **Graft rejection and other adverse reactions from either under- or over-exposure to tacrolimus have been reported when patients received the wrong formulation of oral tacrolimus.**
- **The three different oral tacrolimus formulations available in Canada are not interchangeable. Inadvertent switching between formulations without appropriate dosing adjustments and monitoring could lead to graft rejection and other adverse reactions.**
- **If a prescriber intends to switch between formulations, careful medical supervision and therapeutic monitoring are required. Dose adjustments may be necessary to maintain blood levels in the therapeutic range.**
- **In order to prevent inadvertent switching between tacrolimus formulations, healthcare professionals are advised to:**
    - **Add prominent descriptors for the different formulations (e.g., 'IMMEDIATE release, 'EXTENDED release', or 'PROLONGED release') when identifying tacrolimus products, including on written orders, on the drug selection screens of prescribing and dispensing information systems, and in storage locations.[1]**
    - **Use brand/product names throughout the medication use process to confirm which specific formulation is intended for the patient.**
    - **Consider an automated alert for computerized prescriber and pharmacy order entry that includes a warning that these formulations are not interchangeable, as well as a dosing frequency reminder.**
    - **Fully explain the medication and the different formulations to patients and/or their caregivers, and encourage them to talk to their healthcare professional if they notice a change in their medication.**
- **Health Canada has worked with the manufacturers of tacrolimus products to implement naming and labelling strategies to highlight the product formulation.**

What is the issue?
Graft rejection and other adverse reactions have been reported as a consequence of medication errors where patients received the wrong formulation of oral tacrolimus.

Products affected

Brand/Product Name	Strength	Manufacturer
Immediate Release Capsule		
ACH-TACROLIMUS	0.5mg, 1mg, and 5mg	Accord Healthcare Inc.
APO-TACROLIMUS	0.5mg, 1mg, and 5mg	Apotex Inc.
JAMP-TACROLIMUS	0.5mg, 1mg, and 5mg	Jamp Pharma Corporation
PROGRAF®	0.5mg, 1mg, and 5mg	Astellas Pharma Canada, Inc.
RAN-TACROLIMUS	5mg	Sun Pharma Canada Inc. (formerly Ranbaxy Pharmaceuticals Canada Inc.)
SANDOZ TACROLIMUS	0.5mg, 1mg, and 5mg	Sandoz Canada Inc.
Extended Release Capsule		
ADVAGRAF®	0.5 mg, 1 mg, 3 mg, and 5 mg	Astellas Pharma Canada, Inc.
Prolonged Release Tablet		
ENVARSUS PA™	0.75 mg, 1 mg, and 4 mg	Endo Ventures Ltd. Importer: Paladin Labs Inc.

Background information
Tacrolimus is an immunosuppressant drug given orally to prevent or treat organ transplant rejection. Tacrolimus has a narrow therapeutic index, and even minor differences in blood levels can cause graft rejection and other adverse reactions. Three distinct formulations with different dose requirements (see products affected) are authorized in Canada, which could increase the potential for inadvertent switching to the wrong product and lead to dosing errors.

Cases of graft rejection from under-exposure and other adverse reactions such as decreased renal function resulting from over-exposure to tacrolimus have been

reported internationally as a consequence of confusion about the different formulations. Health Canada has received 9 reports of medication errors in Canada where distinct formulations of tacrolimus products were inadvertently switched. None of the Canadian reports resulted in graft rejection reactions. Two Canadian reports described renal effects.

If a prescriber intends to switch between formulations, careful medical supervision and therapeutic monitoring are required. Dose adjustments may be necessary to ensure that blood levels remain in the therapeutic range.

To reduce the potential for product confusion, Health Canada has worked with manufacturers of tacrolimus products to implement product naming and labelling strategies to highlight the product formulation.

Information for consumers

Tacrolimus is a medication used to help prevent or treat organ rejection after transplant. There are 3 different oral tacrolimus formulations with different dose requirements available in Canada: immediate-release capsules, extended-release capsules, and prolonged-release tablets. Different formulations of tacrolimus are not interchangeable.

Health Canada has received reports of medication errors in which patients received the wrong type of tacrolimus. Serious side effects such as organ transplant rejection may result from taking the wrong formulation of tacrolimus.

Patients should take the same type of tacrolimus medication, and should not be switched to a different formulation except under advice and supervision of their doctor.

Patients should contact their healthcare professional immediately if they notice any changes in the appearance, dose, brand/product name or packaging of their medication.

Patients or their caregivers should contact their healthcare professional for more details about this new safety information.

Information for healthcare professionals

Healthcare professionals are advised to:

- Add prominent descriptors for the different formulations (e.g., 'IMMEDIATE release', 'EXTENDED release', or 'PROLONGED release') wherever these names appear, including on written orders and on the drug selection screens of prescribing and dispensing information systems and in storage locations.
- Use brand/product names (see Products affected) when prescribing and confirm which specific formulation is intended for the patient prior to dispensing tacrolimus products.
- Consider an automated alert for computerized prescriber and pharmacy order

entry that includes a warning that these formulations are not interchangeable, as well as a dosing frequency reminder.

- Remind patients to talk to their healthcare professional if they notice any changes in the appearance, dose, brand/product name or packaging of their medication.

Action taken by Health Canada

Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site (https://healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php) on the Healthy Canadians Web Site. This communication will be further distributed through the MedEffect™ e-Notice email notification system as well as social media channels including LinkedIn and Twitter.

Report health or safety concerns

Health Canada's ability to monitor the safety of marketed health products depends on healthcare professionals and consumers reporting adverse reactions and medical device incidents. Any case of graft rejection or other serious or unexpected adverse reactions in patients receiving tacrolimus should be reported to the appropriate manufacturer (see "Products affected") or Health Canada.

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Tel : 1-800-667-4708

Astellas Pharma Canada, Inc.
675 Cochrane Drive, Suite 500, West Tower
Markham, Ontario, L3R 0B8
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Jamp Pharma Corporation
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Paladin Labs Inc.
100 Boulevard Alexis-Nihon, Suite 600
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Tel : 1-888-867-7426

Sandoz Canada
110 De Lauzon
Boucherville, Québec, J4B 1E6
Tel : 1-800-343-8839

Sun Pharma Canada Inc.
126 East Drive
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Tel: 1-866-840-1340

To correct your mailing address or fax number, contact the appropriate manufacturer.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate
E-mail: mhpd-dpsc@canada.ca
Telephone: 613-954-6522
Fax: 613-952-7738

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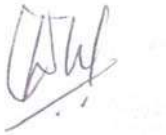

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Patrizia Franco
Senior Director, Regulatory Affairs
Jamp Pharma Corporation

Reference

1. Prograf and Advagraf Mix-up [Internet]. Toronto: Institute for Safe Medication Practices Canada; 2009 Jun. [accessed July 4 2019]. Available from: http://www.ismp-canada.org/download/safetyBulletins/ISMPCSB2009-5-PrografandAdvagrafMix-up.pdf