IMPORTANT SAFETY INFORMATION ON MYCOPHENOLATE-CONTAINING PRODUCTS AND SERIOUS RISK OF TERATOGENICITY

2016/01/18

Audience

Physicians, pharmacists, and nurses, working in nephrology, cardiology, internal medicine, obstetrics and gynaecology, and involved in the care of patients with transplants.

Key messages

- **Mycophenolate is a human teratogen, which increases the risk of spontaneous abortions and congenital malformations following exposure during pregnancy.**
- **New contraindications will be added to the CellCept® (mycophenolate mofetil) and MYFORTIC® (mycophenolate sodium) Canadian Product Monographs to strengthen safety information for use:**
  - **during pregnancy due to the mutagenic and teratogenic potential**
  - **in women of childbearing potential who are not using highly effective contraceptive methods**
  - **in women who are breastfeeding**
- **Healthcare professionals should ensure that women and men taking mycophenolate products understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult a physician if there is a possibility of pregnancy.**

What is the issue?

A cumulative review of birth defects has confirmed that mycophenolate is a human teratogen. The evidence showed an increased rate of congenital malformations and spontaneous abortions associated with mycophenolate in comparison with other immunosuppressants.

Products affected

CellCept (mycophenolate mofetil) – all dosage forms (capsules, tablets, oral suspension, injection).

MYFORTIC [mycophenolic acid (as mycophenolate sodium)] **-** tablets.
All generic versions of mycophenolate-containing products.

Background information
CellCept (mycophenolate mofetil) is indicated for the prophylaxis of organ rejection in adult patients receiving allogeneic renal, cardiac or hepatic transplants.
It is also indicated for the prophylaxis of organ rejection in pediatric patients (2 to 18 years of age) receiving allogeneic renal transplants.

MYFORTIC (mycophenolate sodium) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants.

CellCept (mycophenolate mofetil) or MYFORTIC (mycophenolate sodium) are administered in combination with cyclosporine and corticosteroids.

Congenital malformations, including multiple malformations, have been reported post-marketing, in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy.

The following malformations were most frequently reported:
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos);
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly);
- Cardiac abnormalities such as atrial and ventricular septal defects;
- Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations (such as spina bifida).

Based on evidence from medical literature, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy, compared to 2 to 3% of live births in the overall population and approximately 4 to 5% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil. Cases of spontaneous abortions have been reported in 45 to 49% of patients exposed to mycophenolate mofetil during pregnancy, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.

Information for consumers
The drugs CellCept and MYFORTIC are both used after kidney transplantation to help prevent organ rejection. CellCept is also used after heart and liver transplantation to help prevent organ rejection.

Women and men taking either of these products should understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult a physician if there is a possibility of a pregnancy.

Consumers with any questions about their CellCept or MYFORTIC treatment should contact their healthcare professional for more information.

Information for health care professionals
Before the start of treatment with mycophenolate-containing products, female and male patients of reproductive potential should be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning.

Before starting therapy with any mycophenolate-containing product, women of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL; the second test should be performed 8 to 10 days after the first one and immediately before starting any mycophenolate-containing product. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Women of child bearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Sexually active men should be informed to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. Men should be informed not to donate sperm/semen during therapy or for at least 90 days following discontinuation of mycophenolate. In addition, female partners of male patients should be informed to use highly effective contraception during treatment and for a total of 90 days after the last dose of any mycophenolate containing product.

Patients should be informed not to donate blood during treatment or for at least 6 weeks following discontinuation of any mycophenolate-containing product.

Action taken by Health Canada
Health Canada, in collaboration with Hoffmann-La Roche Limited and Novartis Pharmaceuticals Canada Inc., is communicating this important safety information to health care professionals and to the public through its Healthy Canadians Web site (www.healthycanadians.gc.ca) and MedEffect™ e-Notice.

Health Canada is working with Hoffmann-La Roche Limited and Novartis Pharmaceuticals Canada Inc., to update the Canadian Product Monographs for their respective products to include these contraindications.

Report health or safety concerns
Managing marketed health product-related side effects depends on healthcare professionals and consumers reporting them. Any case of spontaneous abortions and congenital malformations or other serious or unexpected side effects in patients receiving CellCept (mycophenolate mofetil) should be reported to Hoffmann-La Roche Limited, and in patients receiving MYFORTIC (mycophenolate sodium) should be reported to Novartis Pharmaceuticals Canada Inc., or Health Canada.

Hoffmann-La Roche Limited
Drug Safety Department
7070 Mississauga Road
Mississauga, Ontario, L5N 5M8
Toll free: 1-888-762-4388
Fax: 905-542-5864
E-mail: mississauga.drug_safety@roche.com

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Boulevard
Dorval, Quebec, H9S 1A9
Toll free: 1-800-363-8883
www.novartis.ca/en/util/contact/product.shtml

To correct your mailing address or fax number, contact Hoffmann-La Roche Limited.

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.public@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Sincerely,
Original signed by:

Hany Moselhi, M.D.
Vice President, Medical Affairs
Hoffmann-La Roche Ltd.

Original signed by:
Monique Lacroix for:

Jean Godin, M.D.,
Vice-President and Chief
Scientific Officer
Novartis Pharmaceuticals
Canada Inc.

If you require this information in an accessible format, please contact Roche at 1-800-561-1759.