Important Safety and Efficacy Information on ISTODAX® (romidepsin) – Restricted Access Program

Bristol Myers Squibb™

2023/03/20

Audience
Healthcare professionals including hematologists, hemato-oncologists, and pharmacists at hospitals and units specialized in the use of cytotoxic chemotherapy.

Key messages

- In 2013, ISTODAX (romidepsin) was authorized under a Notice of Compliance with conditions (NOC/c) for the treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy, pending the results of trials to verify its clinical benefit.
- The Phase 3 confirmatory study failed to demonstrate ISTODAX, in combination with chemotherapy, was more effective than chemotherapy alone at delaying the progression of PTCL (see Background Information). However, there is no evidence of new safety issues with ISTODAX monotherapy.
- As such, ISTODAX will be withdrawn from the Canadian market once treatment is completed for patients currently using ISTODAX.
- ISTODAX should **not** be initiated in new patients. ISTODAX is now available only under Celgene Inc.'s, a Bristol-Myers Squibb company, Restricted Access Program.
- Healthcare professionals are advised to:
    - Discuss with their patients whether to continue treatment with ISTODAX.
    - Enroll patients who will continue to receive ISTODAX in the Restricted Access Program.
- The Canadian Product Monograph (CPM) for ISTODAX has been updated to reflect this new information. Health Canada will continue to work with the manufacturer throughout the market withdrawal process.

What is the issue?
In 2013, ISTODAX (romidepsin) was authorized under a Notice of Compliance with conditions (NOC/c) for the treatment of patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy, pending the results of trials to verify its clinical benefit.

ISTODAX is now available only under Celgene Inc.'s, a Bristol-Myers Squibb company, Restricted Access Program and should not be initiated in new patients. This is based on a Phase 3 confirmatory study that failed to demonstrate ISTODAX, in combination with chemotherapy, was more effective than chemotherapy alone at delaying the progression of PTCL.

Products affected
ISTODAX (romidepsin); Lyophilized powder for solution; 10mg/vial; Intravenous infusion

Background information
ISTODAX (romidepsin) is a histone deacetylase inhibitor. It is indicated for the treatment of patients with relapsed/refractory PTCL who are not eligible for transplant and have received at least one prior systemic therapy.

In 2013, ISTODAX was authorized under a NOC/c based on results from a Phase 2, open-label, multi-centre, single arm, international clinical study in 131 patients with PTCL who had failed at least one prior therapy.

Continued authorization was contingent on verification of clinical benefit in a Phase 3, multi-centre, randomized study comparing efficacy and safety of romidepsin plus cyclophosphamide, doxorubicin, vincristine and prednisone (Ro-CHOP) versus cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) alone in subjects with untreated PTCL. The confirmatory study did not meet the primary efficacy endpoint of progression-free survival in the overall study population and did not confirm the clinical benefit of the Ro-CHOP regimen as a first-line treatment for PTCL. There were no clinically meaningful improvements in the secondary efficacy endpoints (objective response rate, complete response, overall survival). Additionally, an increase in Treatment Emergent Adverse Events with Ro-CHOP compared to CHOP was noted.

At this time, the clinical benefit of ISTODAX monotherapy for the treatment of relapsed/refractory PTCL in patients who are not eligible for transplant and have received at least one prior systemic therapy remains unconfirmed. The monotherapy safety profile of ISTODAX remains unchanged.

As such, ISTODAX will remain on the Canadian market until the last patient completes treatment, then it will be withdrawn. New patients should not be initiated on ISTODAX outside of an investigational setting.

Information for consumers
ISTODAX is a prescription medicine used to treat people with a type of blood cancer called peripheral T-cell lymphoma (PTCL), who cannot receive a stem cell transplant and have disease which has come back after having tried at least one other treatment by mouth or injection.

ISTODAX was authorized with conditions based on promising evidence of clinical effectiveness following Health Canada's review. The manufacturer agreed to complete more studies to ensure that the drug works the way it was expected.

In a recent study, previously untreated PTCL patients received ISTODAX with a combination of chemotherapy agents. This study failed to show that ISTODAX plus chemotherapy was more effective than chemotherapy alone at delaying the progression of PTCL.

Patients should discuss any questions or concerns about this information with their healthcare professional. Patients should inform their healthcare professional if they are experiencing any side effects while receiving ISTODAX.

Information for healthcare professionals
Healthcare professionals are advised of the following:

- ISTODAX is now available only under Celgene Inc.'s, a Bristol-Myers Squibb company, Restricted Access Program.
- ISTODAX should not be initiated in new patients.
- Confirm **within 3 days** of this communication (March 20, 2023) the number of patients currently being treated with ISTODAX by following the link and/or QR code sent with this letter. Celgene Inc., a Bristol-Myers Squibb company, will subsequently provide an enrolment form and further documentation to eligible healthcare professionals.
- Enroll **within 10 days** of this health product risk communication (March 20, 2023) patients continuing to receive ISTODAX in the Restricted Access Program.
- For more information on the Restricted Access Program, contact Celgene Inc., a Brystol-Myers Squibb company, Medical Information Services at 1-866-463-6267 or medical.canada@bms.com.
- ISTODAX will be withdrawn from the Canadian market once the last patient completes treatment with ISTODAX.

Action taken by Health Canada
Health Canada has worked with the manufacturer to update the CPM for ISTODAX to include this new information. Health Canada will continue to work with the manufacturer throughout the market withdrawal process.

Health Canada is communicating this important information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site. This communication will be further distributed through the MedEffect™ e-Notice email notification system.

Report health or safety concerns
Managing marketed health product-related side effects depends on healthcare professionals and consumers reporting them. Any case of serious or unexpected side effects in patients receiving ISTODAX should be reported to Celgene Inc., a Bristol-Myers Squibb company, or Health Canada.

Celgene Inc., a Bristol-Myers Squibb company
2344 Alfred-Nobel Blvd
Suite 300
Saint-Laurent, QC
H4S 0A4
Tel: 1-866-463-6267

To correct your mailing address or fax number, contact Celgene Inc., a Bristol-Myers Squibb company.

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:

Pharmaceutical Drugs Directorate
E-mail: pharma_drug_enquiries-renseignements_medicaments_pharma@hc-sc.gc.ca
Telephone: 613-957-0368
Fax: 613-952-7756

Original signed by
Franck Chenu
Senior Director, Medical Affairs
Celgene Inc., a Bristol-Myers Squibb company