Important Safety Information on BCR-ABL Tyrosine Kinase Inhibitors [GLEEVEC® (imatinib mesylate), TASIGNA® (nilotinib), BOSULIF™ (bosutinib), SPRYCEL® (dasatinib), ICLUSIG® (ponatinib hydrochloride)] and Risk of Hepatitis B Reactivation

2016/05/04

Audience

Healthcare Professionals (medical oncologists, hematologists, gastroenterologists, oncology nurses, pharmacists) pharmacy associations, medical associations, chiefs of medicine in hospitals, hospital pharmacy chiefs) and patient groups.

Key messages

- **Cases of reactivation of hepatitis B virus (HBV) have occurred in patients who are chronic carriers of HBV after they received BCR-ABL tyrosine kinase inhibitors (TKIs). Some cases of HBV reactivation resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.**
- **It is recommended that:**
  - **Patients be tested for HBV infection before initiating treatment with BCR-ABL TKIs.**
  - **Experts in liver disease and in the treatment of HBV be consulted promptly before initiating treatment in chronic HBV carriers (including those with active disease) and in patients who test positive for HBV infection during treatment.**
  - **Patients who are carriers of HBV requiring treatment with BCR-ABL TKIs be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.**
- **The Canadian prescribing and consumer information for BCR-ABL TKIs will be updated to reflect this new safety information.**

What is the issue?

A recent review of data from clinical trials and postmarketing experience has shown that HBV reactivation can occur in chronic HBV carriers, after they received BCR-ABL TKIs. Some of these cases included acute hepatic failure or fulminant hepatitis leading to liver transplantation or death. These case reports indicate that HBV reactivation may occur at any time during BCR-ABL TKI treatment. Some of these patients had a documented history of hepatitis B. An increase in viral load or positive serology after initiating treatment with a BCR-ABL TKI occurred with HBV reactivation. For other cases, the serologic status at baseline was not known. HBV reactivation is considered to be a class-effect of BCR-ABL TKIs, although the mechanism and the frequency of HBV reactivation during exposure is not known at

this time.

Products affected (Including any generic versions)

Brand Name	Generic Name	Manufacturer
GLEEVEC	imatinib mesylate	Novartis Pharmaceuticals Canada Inc.
TASIGNA	nilotinib	Novartis Pharmaceuticals Canada Inc.
BOSULIF	bosutinib	Pfizer Canada Inc.
SPRYCEL	dasatinib	Bristol-Myers Squibb Canada
ICLUSIG	ponatinib hydrochloride	ARIAD Pharmaceuticals, Inc.

Background information

BCR-ABL TKIs are used for the treatment of specific types of blood cancers, including Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL), and less commonly, other types of cancers.

A recent review of clinical trials and reports received in the post-marketing period as well as published medical literature indicate that cases of HBV reactivation have occurred in patients who are carriers for the virus after receiving BCR-ABL TKIs. In some of the cases, HBV reactivation caused acute liver failure or fulminant hepatitis requiring liver transplantation or death. HBV reactivation occurred at different points during therapy, with cases reported worldwide between three weeks and more than 8 years after starting treatment.

Although no mechanism for HBV reactivation has been identified to date, based on a review of the available evidence, HBV reactivation is considered to be a class effect of BCR-ABL TKIs.

Information for consumers

Talk to your doctor, pharmacist or nurse before taking GLEEVEC (imatinib mesylate), SPRYCEL (dasatinib), TASIGNA (nilotinib), BOSULIF (bosutinib), or ICLUSIG (ponatinib hydrochloride) and let them know if you have ever had or might now have a hepatitis B or liver infection. This is because these drugs could cause hepatitis B virus to become active again, which can be fatal in some cases.

Signs and symptoms of hepatitis include: weight loss, fever, abdominal pain, nausea and vomiting followed by yellowing of the skin (jaundice). It is important to be carefully checked by your doctor for signs of this infection before treatment is started.

Information for healthcare professionals

Patients should be tested for HBV infection status before initiating treatment with BCR-ABL TKIs. Healthcare professionals should consult experts in liver disease and in the treatment of HBV promptly before starting treatment with BCR-ABL TKIs in patients with positive HBV serology (including those with active disease) and in patients who test positive for HBV infection during treatment.

Healthcare professionals should closely monitor patients who are carriers of HBV, who are currently on or require a BCR-ABL TKI treatment for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. The Canadian Product Monographs will be updated to reflect this new safety information.

Action taken by Health Canada
Health Canada, in collaboration with the appropriate manufacturers including manufacturers of generic versions (see "Products affected") will update the Canadian prescribing and consumer information.

Report health or safety concerns
Managing marketed health product-related side effects depends on healthcare professionals and consumers reporting them. Any adverse event or other serious or unexpected side effects to BCR-ABL TKIs should be reported to the appropriate manufacturer (see "Products affected") or to Health Canada.

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Québec, H9S 1A9
1-800-363-8883
www.novartis.ca/en/util/contact/product.shtml

Pfizer Canada Inc. Canada
17 300 Trans-Canada Highway
Kirkland, Québec, H9J 2M5
1-800-463-6001

Bristol-Myers Squibb
2344, boul Alfred-Nobel, suite 300
Saint-Laurent, Quebec, H4S 0A4
1-866-463-6267
Email: Safety_Canada@bms.com

ARIAD Pharmaceuticals, Inc.
c/o Paladin Labs Inc.
100 Blvd Alexis-Nihon, Suite 600
Saint-Laurent, Quebec, H4M 2P2
1-888-867-7426
Email :Medinfo@paladinlabs.com

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
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