Health Canada Endorsed Important Safety Information on Pradaxa™/Pradax® (dabigatran etexilate)

December 21, 2012

Dear Health Care Professional:

Subject: Pradaxa™/Pradax® (dabigatran etexilate): New contraindication in patients with prosthetic heart valves requiring anticoagulant treatment due to their valvular status

Boehringer Ingelheim (Canada) Ltd. (BICL), in consultation with Health Canada (HC) , would like to inform you about important new safety information relating to the use of Pradaxa™ (dabigatran etexilate), also known as Pradax®, in patients with prosthetic heart valves. Based on recent information, the Pradaxa™ Product Monograph (PM) will be revised to include a new contraindication for use in patients with prosthetic heart valves requiring anticoagulant treatment due to their valvular status.

This change is based on interim results from a phase II trial (RE-ALIGN) which compared dabigatran etexilate and warfarin in a total of 252 patients with prosthetic heart valves. The study investigated a dose range of 150 mg twice daily to 300 mg twice daily in patients with recent mechanical heart valve replacement surgery (within the current hospital stay) and in patients who received mechanical heart valve replacement more than three months before. More thromboembolic events (mainly strokes, and symptomatic/asymptomatic prosthetic valve thrombosis) and more bleeding events were observed with dabigatran etexilate than with warfarin, especially in patients who were randomised post-surgery, i.e., soon after mechanical valve placement. As a result, Boehringer Ingelheim decided to discontinue the study and update the worldwide labelling to contraindicate the use of Pradaxa™ in patients with prosthetic heart valves.

- A 12-week open-label randomized study comparing dabigatran etexilate with warfarin was discontinued as a result of an interim analysis showing numerical excess of thrombosis, that included valve thrombosis, stroke and myocardial infarction in patients with recent mechanical heart valve placement receiving dabigatran.
- Pradaxa™ is now contraindicated for use in patients with prosthetic heart valves requiring anticoagulant treatment due to their valvular status.
- Health care providers are reminded to strictly follow the recommended conditions of use for Pradaxa™.

BICL is working closely with HC to update the product label accordingly.

Pradaxa™ (dabigatran etexilate) is an oral anticoagulant authorized for sale in Canada for the prevention of venous thromboembolic events in patients following hip or knee replacement surgery and for the prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.[1] Pradaxa™ is currently not recommended for use in patients with prosthetic heart valves, with or without atrial fibrillation, see WARNINGS AND PRECAUTIONS, Cardiovascular, *Patients with Valvular Disease* of the current Product Monograph.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious or unexpected adverse reactions in patients receiving Pradaxa™ should be reported to Boehringer Ingelheim (Canada) Ltd, or to Health Canada:

Boehringer Ingelheim (Canada) Ltd.,
5180 South Service Rd. Burlington, ON, L7L 5H4
Tel: 1 (800) 263-5103 Ext. 87233. http://www.boehringer-ingelheim.ca/en/contact.html

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, please contact Health Canada at:
Marketed Health Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca Telephone: 613-954-6522 Fax: 613-952-7738

The Pradaxa™ Product Monograph[1] as well as a copy of this letter can be found on the Boehringer Ingelheim (Canada) Ltd., website at: http://www.boehringer-ingelheim.ca/en/human_health/our_products.html

Sincerely,
original signed by

Mathias Knecht, M.D.
Vice President, Medical and Regulatory Affairs
Boehringer Ingelheim (Canada) Ltd.

References:

1. Pradaxa™ Product Monograph, dated November 28, 2012
http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp