Health Canada Endorsed Important Safety Information on INNOHEP® (tinzaparin sodium)

2010-10-14

Dear Health Care Professional:

Subject: Updated Safety Information for the Use of INNOHEP® (tinzaparin sodium) in Elderly Patients with Renal Impairment – The IRIS clinical trial

LEO Pharma, in consultation with Health Canada, would like to inform you of important updated safety information regarding INNOHEP (tinzaparin sodium) related to results from a clinical study that was stopped prematurely (IRIS – Innohep in Renal Insufficiency Study) due to the observance of increased mortality. This study involved the use of therapeutic doses of INNOHEP for the treatment of acute venous thromboembolism (VTE) in elderly patients with renal impairment.

INNOHEP is a low molecular weight heparin. It is authorized for the prevention of postoperative VTE in patients undergoing orthopaedic surgery and in patients undergoing general surgery who are at high risk of developing postoperative VTE; the treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE); and the prevention of clotting in indwelling intravenous lines for haemodialysis and extracorporeal circulation in patients without high bleeding risk.

Based on the observations in IRIS:

- The study was halted by the Data Safety Monitoring Committee due to an interim finding of an increase in all-cause mortality in patients who received INNOHEP compared to unfractionated heparin (UFH).
- INNOHEP is not recommended in elderly patients over 70 years of age with renal impairment.
- INNOHEP should be used with caution in patients with moderate to severe renal impairment; in all cases of impaired renal function, patients should be closely monitored.

The IRIS study was an international, multicentre, prospective, open, centrally randomised, parallel group study comparing treatment doses of INNOHEP (175 IU/kg once daily; N=269) and UFH (N=268) for the initial treatment of DVT and/or PE in elderly patients with renal impairment (i.e., patients ≥ 70 years with CrCl ≤ 30 mL/min or patients ≥ 75 years with CrCl ≤ 60 mL/min). An interim safety analysis revealed a difference in mortality between the treatment groups and the study was subsequently stopped. The all cause mortality rates for patients at the 90-day follow up were 6.3% (17/268) in the UFH group and 11.5% (31/269) in the INNOHEP group. There was no clear explanation for this difference; however mortality was not due to recurrent VTE or bleeding.

The Canadian Product Monograph for INNOHEP has been revised to include this updated safety information and can be accessed at www.leo-pharma.com/canada or at Health Canada's Drug Product Database at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php.

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 serious or unexpected adverse reactions in patients receiving

INNOHEP should be reported to LEO Pharma Inc. or Health Canada at the following addresses:

LEO Pharma Inc.
123 Commerce Valley Drive East, Suite 400
Thornhill, Ontario, L3T 7W8
or call toll free Medical Info at: 1-800-263-4218
or fax at: 905-886-6639
or e-mail at: medical-info.ca@leo-pharma.com

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). The Reporting Form is also in the Canadian Compendium of Pharmaceuticals and Specialties.

For other inquiries related to this communication, please contact Health Canada at:
Marketed Health Products Directorate (MHPD)
E-mail: mhpd_dpsc@hc-sc.gc.ca
Tel: (613) 954-6522
Fax: (613) 952-7738

To change your mailing address or fax number, contact the Market Authorization Holder (Industry).

LEO Pharma is committed to providing you with the most current information to assist you in the management of your patients. Should you have any questions or require additional information regarding the use of INNOHEP, please contact the Medical Information Department of LEO Pharma Inc. at 1-800-263-4218.

A copy of this letter and the Public Communication are available on the Health Canada Web Site at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index-eng.php.

Sincerely,

original signed by

Kenneth Kobayashi, MD, FRCPC
Vice President, Research & Development
LEO Pharma Inc.

Reference:
A. Leizorovicz. Tinzaparin compared to unfractionated heparin for initial treatment of deep vein thrombosis in very elderly patients with renal insufficiency-the IRIS trial. Blood (ASH Annual Meeting Abstracts), 2008; 112: 434.