



May 31, 2012

Discontinuation of Refludan® [lepirudin (rDNA) for injection]

Dear Health Care Professional:

After careful consideration, Bayer HealthCare would like to inform you that we will discontinue marketing Refludan® [lepirudin (rDNA) for injection] on **May 31, 2012** and no further product is expected to be shipped to wholesalers in the United States after that date. It is important to emphasize that these actions are not related to safety concerns.

Bayer HealthCare has had a manufacturing and supply agreement in place with a third-party manufacturer that permitted the sale and distribution of Refludan® by Bayer in the U.S. The third-party manufacturer of Refludan® has permanently ceased production of the product, which has led to the product's discontinuation in the U.S. Bayer has notified the Food and Drug Administration that no further product is expected to be shipped to wholesalers in the U.S. as of May 31, 2012.

Bayer anticipates the supply of Refludan® will be depleted by mid-2013.

Refludan® [lepirudin (rDNA) for injection] is indicated for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications (TEC).¹ We encourage you to discuss treatment alternatives with your patients. Recommendations for use of anticoagulants other than Refludan® are described in treatment guidelines for HIT.²

We regret any inconvenience this decision may have on your practice and we very much appreciate your support for Refludan®. Should you have any questions, please call Bayer Customer Service (877-229-3750) or Bayer Medical Communications (888-842-2937).

Important Safety Information

Refludan® is contraindicated in patients with known hypersensitivity to hirudins or to any of the components in Refludan®.

Hemorrhage can occur at any site in patients receiving Refludan®. While patients are being anticoagulated with Refludan®, the anticoagulation status should be monitored closely using an appropriate measure such as the aPTT.

Intracranial bleeding following concomitant thrombolytic therapy with rt-PA or streptokinase may be life-threatening. There have been reports of intracranial bleeding with Refludan® in the absence of concomitant thrombolytic.

For patients with increased risk of bleeding, a careful assessment weighing the risk of Refludan® administration vs its anticipated benefit has to be made by the treating physician. In particular, this includes the following conditions: recent puncture of large vessels or organ biopsy, anomaly of vessels or organs, recent cerebrovascular accident, stroke, intracerebral surgery, or other neuraxial procedures, severe uncontrolled hypertension, bacterial endocarditis, advanced renal

impairment, hemorrhagic diathesis, recent major surgery, recent major bleeding (eg, intracranial, gastrointestinal, intraocular, or pulmonary bleeding), and recent active peptic ulcer.

With renal impairment, relative overdose might occur even with standard dosage regimen. Therefore, the bolus dose and the rate of infusion must be reduced in patients with known or suspected renal insufficiency.

Formation of antihirudin antibodies was observed in about 40% of HIT patients treated with Refludan®. This may increase the anticoagulant effect of Refludan® possibly due to delayed renal elimination of active lepirudin-antihirudin complexes. No evidence of neutralization of Refludan® or of allergic reactions associated with positive antibody test results was found.

Serious liver injury (eg, liver cirrhosis) may enhance the anticoagulant effect of Refludan® due to coagulation defects secondary to reduced generation of vitamin K-dependent coagulation factors.

There have been reports of allergic and hypersensitivity reactions including anaphylactic reactions. Serious anaphylactic reactions that have resulted in shock or death have been reported. These reactions have been reported during initial administration or upon second or subsequent reexposure(s).

Concomitant treatment with thrombolytics (eg, rt-PA or streptokinase), coumarin derivatives (vitamin K antagonists), and drugs that affect platelet function may increase the risk of bleeding.

The most common hemorrhagic adverse events observed in clinical trials were bleeding from puncture sites and wounds (14.1%), anemia or isolated drop in hemoglobin (13.1%), other hematoma and unclassified bleeding (11.1%), hematuria (6.6%), gastrointestinal and rectal bleeding (5.1%), epistaxis (3.0%), hemothorax (3.0%), and vaginal bleeding (1.5%).

The most frequent nonhemorrhagic adverse events observed in clinical trials were fever (6.1%), abnormal liver function (6.1%), pneumonia (4.0%), sepsis (4.0%), allergic skin reactions (3.0%), heart failure (3.0%), abnormal kidney function (2.5%), unspecified infections (2.5%), multiorgan failure (2.0%), pericardial effusion (1.0%), and ventricular fibrillation (1.0%).

For important risk and use information, please consult the full Prescribing Information enclosed.

Regards,



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Vice President
U.S. Medical Affairs, Hematology
Bayer HealthCare

References:

1. Refludan® [Prescribing Information]. Wayne, NJ: Bayer Healthcare Pharmaceuticals; 2006.
2. Linkins L-A, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention Of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:2 suppl e495S-e530S; doi:10.1378/chest.11-2303.