



NSU College of Pharmacy  
Drug Information & Resources Center  
**N e w s l e t t e r**

03-July-2003

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## Question of the Day...

What commercially available antithrombotic is, in essence, a recombinant protein originally obtained from the spit of a leech?

hint: the official name of the leech is *Hirudo medicinalis*.

## In the News

### **Pfizer's experimental program saves Florida millions**

<http://main.pslgroup.com/news/industrynews.nsf/IndustryNewsId/9F366128AB57A0EB85256D5D00619123?opendocument&id=>

During its first year of operation, an experimental program designed by Pfizer to help Florida's sickest Medicaid patients appears to have saved the state \$15.9 million while reducing hospital stays by 12.6 percent, a news source says. The figures come from a report issued jointly by Pfizer and the state that examines the first seven months of the programme, which uses case managers to target high-risk patients suffering from high blood pressure, asthma, diabetes and heart failure. Under the plan, Pfizer promised to save the state \$33 million over two years in return for getting all of its drugs approved for Medicaid patients without having to offer discounts, the news source reports. Included in the total savings was \$8.2 million that Pfizer contributed to hire 55 case managers. The drugmaker also gave \$200,000 worth of drugs to community health centres. The remaining \$7.5 million in savings came from better care for 4,810 high-risk patients, the news source reports. Florida's Medicaid director said that he expects better savings the longer the patients' care is managed. According to the report, 48 percent of patients with hypertension saw a drop in blood pressure, and diabetes patients had a 4 percent decline in glucose levels. Patients who joined the programme at the very beginning saw a 27 percent reduction in hospital days, the report said. But overall, trips to the emergency room decreased only 1 percent. Critics of the plan say that the state could realise \$64 million a year in savings by making pharmaceutical companies offer drug discounts and omitting the disease management programme, a figure which is disputed by

state and federal officials. Researchers with the state legislature's Office of Program Policy Analysis and Government Accountability say they will be looking closely at how the report derived its \$7.5 million savings estimate, the news source says.

### **First and Only Head-to-Head Survival Study in Heart Failure Comparing Two Beta-Blocking Agents Reveals Patients Live Longer On Carvedilol Than on Metoprolol**

<http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/07-03-2003/0001976425&EDATE=>

Results from the longest and largest trial ever conducted in heart failure -- the Carvedilol or Metoprolol European Trial (COMET) -- will be published in the Saturday, July 5, 2003 issue of The Lancet. The study showed that carvedilol, a newer, comprehensive beta-blocking medication reduced all cause mortality by 17 percent ( $p=0.0017$ ), cardiovascular mortality by 20 percent ( $p=0.0004$ ) and prolonged median survival by 1.4 years more than metoprolol tartrate, a traditional selective beta-blocking medication. Carvedilol is marketed as Coreg(R) in the U.S. and Dilatrend(R) in Europe. "The results of COMET provide clear evidence of the survival benefits of carvedilol over metoprolol in the treatment of chronic heart failure and suggest that carvedilol prolongs the life of patients by 1.4 years compared to metoprolol," commented Professor Philip Poole-Wilson, Chairman of the COMET Steering Committee. "Carvedilol's significant survival benefit could mean thousands of lives saved each year." The COMET investigators wanted to determine whether carvedilol, which has properties beyond those of traditional beta blockers, would reduce mortality and morbidity more than a beta-one selective blocker in patients with heart failure. They concluded that carvedilol has a significantly greater beneficial impact on survival than metoprolol. The study results also were presented on June 23 at the Heart Failure 2003 meeting organized by the European Society of Cardiology, in Strasbourg, France. Carvedilol Saved More Lives Than Metoprolol (Tartrate)"For years, physicians have wondered if there are important differences among beta blockers used for the treatment of heart failure," said Milton Packer, M.D., Director, Heart Failure Center and Professor of Medicine, Columbia University College of Physicians and Surgeons in New York, N.Y. "The results of the COMET study suggest that the additional properties of carvedilol beyond beta-one blockade do influence survival. The results of the COMET study add even more weight to what is already a wealth of data demonstrating the important benefits of carvedilol. In the U.S., Coreg (carvedilol)\* is marketed by GlaxoSmithKline and is the only beta-blocking agent FDA approved to improve survival in mild to severe heart failure. Coreg is also approved for use in left ventricular dysfunction following a

heart attack (with or without symptomatic heart failure) where it also significantly improves survival. Coreg also is indicated for the treatment of essential hypertension. In Europe, Dilatrend (carvedilol) is marketed by Roche and is approved for congestive heart failure, angina pectoris and hypertension. COMET was initiated in 1996, with 3,029 patients from 15 European Countries and 317 centers enrolled in a multi-center, double-blind, and randomized parallel group trial. In the study, 1,511 patients with chronic heart failure were assigned carvedilol and 1,518 to metoprolol. Patients were required to have chronic heart failure, a previous hospital admission for a cardiovascular reason, an ejection fraction of less than or equal to 0.35 and to be treated optimally with diuretics and angiotensin converting enzyme inhibitors unless not tolerated. The co-primary endpoints were all-cause mortality and the composite endpoint of all-cause mortality or all-cause hospital admission. All patients were followed up for more than 45 months (175,447 patient months) following the trial, and follow up was concluded on November 15, 2002. The trial accumulated over 1,000 deaths.

### **NEJM : Fragmin Trumps Warfarin In Cancer Patients**

[http://biz.yahoo.com/djus/030709/1736001362\\_1.html](http://biz.yahoo.com/djus/030709/1736001362_1.html)

A new study showed a Pfizer Corp. drug was more effective in preventing blood clots in cancer patients than a commonly used generic drug, prompting a recommendation that the Pfizer preparation should become the standard anti-clotting treatment in cancer cases. The study and recommendation are both carried in Thursday's issue of the New England Journal of Medicine. The study was funded by Fragmin maker Pharmacia Corp., which was recently acquired by Pfizer, and led by researchers at McMaster University in Hamilton, Ont. The study and accompanying "perspective" article by a clotting expert unconnected to Pfizer may lead to expanded use of Fragmin by cancer patients in the U.S. and doctors prescribing it for other patients who are at risk from life-threatening thrombosis and embolisms. Fragmin, developed by Pharmacia, is much more expensive than warfarin and must be injected daily by patients. Warfarin is more convenient because it is taken orally, but its use often requires weekly monitoring through pricey laboratory tests. Last year, world-wide sales of Fragmin were \$270 million. The drug was first approved in Germany in 1985 and approved in the U.S. in 1995 by the Food and Drug Administration. But it is more commonly used overseas, according to a Pfizer spokeswoman, and is approved for clot prevention here only for patients undergoing hip-replacement surgery and certain angina and heart-attack patients. Blood clots, also called thromboses, kill up to 200,000 people yearly. Fragmin is a low-molecular-weight heparin, a blood-thinner commonly used in combination with warfarin. Heparin is often given intravenously in medical centers, while the low-molecular-weight version can be injected by the patients themselves. In the new study, half of a group of 672 cancer patients at

sites from Australia to Spain were given the standard treatment of a week of Fragmin followed by six months of warfarin, and the rest got Fragmin for a week followed by a reduced dose of Fragmin instead of warfarin. Despite the treatment, 16% of the warfarin patients suffered from recurring blood-clots during the six month period compared to 8% of those taking Fragmin. Mark Levine, an oncologist at McMaster and the study's leader, said cancer patients have particular problems with orally administered warfarin because during chemotherapy, "cancer patients are sick and vomiting," so dose levels vary. To monitor the patients requires regular laboratory tests to make sure their blood isn't thinned so much that internal bleeding occurs. Because it is injected, like insulin is by diabetics, Fragmin goes into the bloodstream at a predictable level, based on body-weight, eliminating the need for regular monitoring. Dr. Levine said cancer patients are prone to blood clots because many cancers induce clotting and so do many treatments. He is starting work on a study of the cost-effectiveness of the Fragmin treatment compared to warfarin. Dr. Levine said Fragmin isn't particularly costly compared to other cancer therapies, so expects it will prove cost-effective by avoiding the lab tests and extra hospitalizations needed by warfarin patients. Roger L. Bick, a thrombosis expert at University of Texas Southwestern Medical School in Dallas who wrote the editorial in the New England Journal, said low-molecular-weight heparin, the chemical term for Fragmin, is "way more effective than warfarin across the board." He already uses it in preference to warfarin for many of his patients, whether or not they have cancer.

### **Topamax (topiramate) associated with oligohidrosis and hyperthermia in children**

<http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#topama>

Ortho-McNeil and FDA revised the WARNINGS and PRECAUTIONS sections of the prescribing information to provide updated information about oligohidrosis (decreased sweating) and hyperthermia, which have been reported in topiramate-treated patients. Oligohidrosis and hyperthermia may have potentially serious sequelae, which may be preventable by prompt recognition of symptoms and appropriate treatment. Reports have primarily involved children. Most cases have occurred in association with exposure to elevated environmental temperatures and/or vigorous activity, and children should be observed closely under these conditions.

### **Generic Paroxetine Analog Gets Final Approval**

[http://biz.yahoo.com/rc/030707/health\\_synthon\\_1.html](http://biz.yahoo.com/rc/030707/health_synthon_1.html)

Synthon Pharmaceuticals Ltd., a privately held drugmaker, said on Monday it received U.S. regulatory approval to sell an antidepressant that contains the same active chemical used in GlaxoSmithKline's Paxil. Paxil is expected to face U.S. generic competition from Apotex Corp. and other generic

drugmakers by 2005, but it is fighting those companies in court. Synthon's drug is not considered an exact copycat, but could still erode Glaxo's \$3 billion in annual sales from Paxil because the new drug contains paroxetine, the main ingredient in Paxil. Synthon said it would launch its drug in the fourth quarter or earlier. Synthon's product has been available in Europe for more than two years. The U.S. drugs market is the world's most lucrative because the United States does not have price controls on pharmaceuticals. Synthon's Paroxetine will be a brand product composed of paroxetine mesylate. Paxil<sup>®</sup> is composed of paroxetine hydrochloride. The chemical difference between the two products is that the inactive part of the salt (mesylate or hydrochloride) is separated from the active paroxetine molecule in the gastrointestinal tract, leaving only the active paroxetine molecule to be absorbed into the bloodstream and provide the intended therapeutic effect.

### **FDA Approves Combination Blood-Sugar Monitor/Insulin Pump**

[http://biz.yahoo.com/djus/030707/1706001110\\_2.html](http://biz.yahoo.com/djus/030707/1706001110_2.html)

The Food and Drug Administration (FDA) has cleared the first device for diabetics which integrates a glucose meter and an insulin pump with a dose calculator into one device. The new device could be the first step in the development of a fully automated glucose monitoring and insulin delivery system using wireless technology to beam data to the two components. The product, which will retail for \$5,995 and be shipped starting July 21, will take over the task of complicated diabetes math, said Deanne McLaughlin, a spokeswoman for Medtronic MiniMed, the Medtronic subsidiary that is selling the device. Diabetics have to factor in how their body reacts to insulin, then use ratios to tabulate how much insulin they will need based on the amount of carbohydrates in a planned or already consumed meal. "Patients sometimes round up or round down," Ms. McLaughlin said. "That's when you get inaccuracies." Inaccuracies can be dangerous for diabetics, whose bodies don't properly use insulin, the hormone that helps cells turn sugar and starches into energy. Insulin levels that are too high or too low can cause a range of illnesses including blindness, kidney failure, impotence and heart disease. The device, which isn't available in any other country, combines the Medtronic MiniMed Paradigm 512 insulin pump with Becton, Dickinson's Paradigm Link Blood Glucose Monitor. To use the system, patients prick their finger and place a blood droplet on a diabetes test strip. The strip is inserted in the glucose monitor that gives a reading, which in five seconds is sent automatically to the insulin pump. This transmission prevents errors that occur when patients input data manually, the FDA said in a statement. Using the patient's personal information, including target blood-glucose level, the pump recommends how much insulin should be taken. Diabetics can choose that or a different amount of insulin. The pump keeps track of how much insulin is already in the body and records the time and amount of insulin delivered over time.

### **Red Clover No Relief for Hot Flashes-US Study**

<http://reuters.com/newsArticle.jhtml?type=scienceNews&storyID=3056406>

Red clover extract, advertised as a substitute for hormone therapy, offered menopausal women no more relief from hot flashes than a placebo, according to a study published in this weeks JAMA.

Many women who suffer menopausal symptoms are seeking an alternative to hormone replacement therapy after a recent study showed long-term use of the most popular estrogen-progestin Combination increased the risks of heart disease, breast cancer and dementia. The new study said interest in red clover extract stemmed in part from reports that Asian women suffer fewer hot flashes and other menopausal symptoms because their diets are rich in isoflavones, natural compounds found in soy products and legumes such as chickpeas. "Hot flashes are the primary reason that women seek medical attention for menopausal symptoms," Jeffrey Tice of the University of California, San Francisco, wrote in the latest study. The results of the 12-week study appeared in the Journal of the American Medical Association, which has previously published reports rebuking the efficacy of other herbal remedies. In this trial, 250 menopausal women experiencing at least five hot flashes a day were given one of two isoflavone products made from red clover extract -- Promensil or Rimostil -- or a placebo. All of the women experienced a comparable decline in hot flashes of between 34 percent and 41 percent, though Promensil, reduced them more quickly. "Although the study provides some evidence for a biological effect of Promensil, neither supplement had a clinically significant effect on hot flashes or other menopausal symptoms when compared with placebo," the report said. Novogen Ltd, the Australia-based maker of Promensil and Rimostil that funded the study, said the findings overstated the "placebo effect." In a statement, the company said previous studies showed women taking a placebo had symptoms decline by no more than 20 percent. But a Duke University reproductive endocrinologist, Dr. Claude Hughes, said in a telephone interview that the placebo effect can vary widely in such studies of menopausal symptoms. Hughes said he often starts his menopausal patients with diets rich in soy foods, such as tofu, then tries isoflavone extracts, then moves on to hormone replacement therapy. "It's a matter of finding what works," Hughes said.

### **Pfizer, Glaxo Lower Some AIDS Drug Prices**

<http://apnews1.iwon.com/article/20030710/D7S6LBI80.html>

Pfizer Inc. and GlaxoSmithKline on Wednesday became the latest drug companies to slash prices of their AIDS drugs for cash-strapped, state-run programs that treat the poor, uninsured and underinsured. "Who is John Galt?" Pfizer said it will provide millions of dollars of drugs either free or at greatly reduced prices to AIDS Drug Assistance Programs, or ADAPs,

which are run by the states and U.S. territories using a combination of state and federal funds to treat patients. Pfizer spokesman Nehl Horton said the exact amount of its donation would depend on states' needs but the company wouldn't disclose it anyway. Meanwhile, GlaxoSmithKline said it will provide a \$20 million package of cash and credits to the programs. GlaxoSmithKline is the market leader in AIDS treatments. Together, seven companies have agreed to contribute more than \$50 million to assist the ADAP programs, according to the National Alliance of State and Territorial AIDS directors. Bristol-Myers Squibb Co. is the only drug company that hasn't reached an agreement with the ADAP programs, however a company spokesman said it is close to reaching a deal. The latest agreement comes as Congress begins to negotiate funding for the ADAP programs for fiscal 2004, and AIDS activists say the amounts under consideration fall short of needs. Funding shortfalls have caused 15 of the 57 ADAP programs to either start a patient waiting list or restrict access to medicines.

### **Anti-Malaria Pill Comes With Risk Guide**

<http://apnews1.iwon.com/article/20030709/D7S68FJ00.html>

People prescribed Lariam to prevent malaria before a trip abroad will now get a government-ordered brochure along with the pills describing what to do if some rare but serious side effects strike. "Peanut" The FDA announced Wednesday that every Lariam prescription now will come with a medication guide that explains its pros and cons in consumer-friendly language. The new warnings stress that some people shouldn't take the drug: those with active or recent depression, a history of other psychiatric disorders, or epilepsy. The guide also advises patients who suddenly experience psychiatric side effects to promptly contact a doctor - they may need to stop the Lariam and switch to another anti-malaria pill. Last year, the FDA strengthened warnings on the drug's label that it can cause some rare but potentially serious psychiatric side effects, ranging from anxiety and dreams to hallucinations, depression, occasionally even psychotic behavior. FDA's Dr. Leonard Sacks said the new guide addresses concerns that the information was still not reaching those who need it. About 800 Americans a year return home infected with malaria, most because they didn't know to take the pills or skipped them from worry about side effects. Most of the several million Americans who travel to malaria-plagued countries come home healthy thanks to one of several protective drugs. Lariam is the most prescribed among them. The guide will not imply that Lariam is a worse choice than other anti-malaria pills, Sacks said. Each has side effects, and Lariam has advantages that make it an important option.

### **AstraZeneca's Crestor wins backing of FDA advisory panel**

<http://main.pslgroup.com/news/industrynews.nsf/IndustryNewsId/AA74E9ABB561D01585256D5E004BD09E?opendocument&id=>

An FDA advisory panel voted unanimously Wednesday to recommend that the agency approve AstraZeneca's Crestor, in dosages of 5 milligrams to 40 milligrams, news sources report. Crestor is a key drug for AstraZeneca and is part of the company's strategy for filling the gap in sales that Prilosec lost to generic competition. One investment firm forecasts \$300 million in sales for Crestor if it receives final approval this year and \$2.3 billion in sales in 2007. Other analysts predict peak sales of \$3 billion. There has been some concern about Crestor's potential for kidney toxicity at higher doses. The advisory panel has recommended that kidney function tests be performed when patients are given the 40-milligram dose, and some panellists noted that the drug at the higher dosage didn't appear to significantly improve LDL levels over the 20-milligram dose, a news source says. Crestor will compete with Pfizer's Lipitor, which is currently the world's top-selling prescription drug, Merck's Zocor and Bristol-Myers Squibb's Pravachol. The FDA is slated to decide on Crestor by August 12. The drug is currently approved in 24 other countries.

### **Barr Voluntary Recalls Some Nortrel 7/7/7**

<http://news.moneycentral.msn.com/ticker/article.asp?Feed=RTR&Date=20030709&ID=2694018&Symbol=US:BRL>

Barr Laboratories Inc. (BRL) on Wednesday said it is voluntarily recalling three lots of its Nortrel 7/7/7-28 day oral contraceptive because they might have been improperly packaged, perhaps increasing the risk of pregnancy. The Woodcliff Lake, New Jersey-based company said the recall affects Lots 290122001, 290122002 and 290122003, involving about 470,000 packages. It said it is implementing the recall because two people told the company the color-coded tablets in their blister cards were in the wrong sequence. Barr said the first, or top, row should contain yellow tablets, the second blue tablets, the third peach tablets and the fourth white tablets. It said the colored tablets contain active hormonal ingredients. Any woman who takes the tablets in the wrong sequence might face an increased risk of pregnancy, or changes to her menstrual cycle, including delayed bleeding, irregular bleeding or spotting, it said. Barr said women taking the product should examine their blister cards to confirm the proper sequencing. It said it has notified the U.S. Food and Drug Administration of the recall. Questions can be directed to a Barr hotline at 1-800-222-0190 extension 33302.

### **Democrats Kill Medical Malpractice Bill**

[http://story.news.yahoo.com/news?tmpl=story&cid=534&ncid=534&e=18&u=/ap/20030710/ap\\_on\\_go\\_co/congress\\_malpractice](http://story.news.yahoo.com/news?tmpl=story&cid=534&ncid=534&e=18&u=/ap/20030710/ap_on_go_co/congress_malpractice)

Senate Democrats on Wednesday killed legislation limiting the ability of medical malpractice victims to win monetary damages, rejecting Bush administration claims that caps would halt frivolous lawsuits and ease a health care crisis. The 49-48 vote was 11 short of the 60 needed to overcome

Democratic objections. The outcome fell largely along party lines, and both sides sought political gain in the bill's wreckage. "Time and time again this Senate races to protect special interest groups and forgets the families and children and elderly people across America who are the victims of" medical errors, said Sen. Dick Durbin, D-Ill. He disputed claims that malpractice caps would reduce insurance costs, and he attacked the measure as an attempt to help the American Medical Association, HMOs, drug companies and the manufacturers of medical devices. President Bush (news - web sites), who has made legal reform a priority, issued a statement expressing disappointment. "The nation's medical liability system is badly broken, and access to quality health care for Americans is endangered by frivolous and abusive lawsuits," he said. "The medical liability crisis is driving good doctors out of medicine, and leaving patients in many communities without access to both basic and specialty medical services." The measure, similar to a bill that cleared the House earlier this year, would have limited non-economic damages, commonly known as pain and suffering, to \$250,000. Punitive damages would be capped at the greater of \$250,000 or twice the amount of economic damages, which cover medical expenses, loss of wages, funeral expenses and similar costs. States would be permitted to enact higher limits.

Additionally, the measure called for limiting the amount of money attorneys could pocket if they work on a case on a contingency fee. The bill would have applied to malpractice suits against doctors, hospitals or health care providers, as well as the manufacturer, distributor or seller of a medical product. In many respects, the bill seemed doomed to failure from the outset. Republicans brought it to the floor without committee hearings or debate, steps that often lead to progress toward bipartisanship. At the same time, the clash of powerful, competing special interests was evident throughout the debate. The AMA, American Association of Hospitals and American Insurers Association, traditional Republican allies and heavy donors to GOP campaigns, all supported the measure. The Association of Trial Lawyers of America (news - web sites), a reliable ally of Democrats and major donor to their campaigns, opposed it. The vote "could be a very potent political issue" next year, particularly in states the AMA has identified as suffering from a medical malpractice crisis, said Sen. George Allen (news, bio, voting record), R-Va., chairman of the Senate GOP campaign committee. But Sen. John Edwards (news, bio, voting record), D-N.C., a trial lawyer before entering politics, and a presidential hopeful, sounded eager to argue the other side before the voters. "We should protect good doctors and the patients who depend on them," said Edwards, who broke off presidential campaigning to return to the Capitol and cast his vote on the measure. "but we shouldn't pad insurance company profits and hurt people who already have suffered immensely." Republicans saw it differently. "Almost one in three physicians in my state of Missouri are considering leaving their practices altogether because they cannot afford" the cost of medical malpractice premiums, said Sen. Kit Bond, R-Mo. "...The cause of that quite

frankly is the unrestrained plaintiffs' legal actions asserting all sorts of noneconomic and economic damages." Both during debate on the Senate floor, and in news conferences around the Capitol complex, both sides brought victims of inadequate medical care to Washington to buttress their arguments. Republicans repeatedly pointed to individuals who suffered disabling injuries after failing to find needed emergency treatment at nearby hospitals because the needed specialists no longer practiced - an attempt to demonstrate a need to restrain the price of malpractice insurance. For their part, Democrats showcased victims of malpractice, men, women and children grievously injured through medical errors - hoping to undermine the GOP claim that a \$250,000 cap was the maximum that should be allowed, no matter how grievous the impairment. On the vote, 45 Democrats, two Republicans and one independent voted to bottle up the bill. Forty-nine Republicans were in favor of advancing it. Durbin and Sen. Lindsey Graham, R-S.C., outlined an alternative that would have relied on a series of actions to reduce malpractice premiums. They proposed lifting antitrust exemptions that insurance companies enjoy for malpractice insurance, providing tax credits for doctors and hospitals hardhit by rising premiums, and using a voluntary nationwide program to report medical errors. Their alternative also included sanctions for lawyers who file unwarranted suits.

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JAMA 2003;290 157

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Phytoestrogen Supplements for the Treatment of Hot Flashes: The Isoflavone Clover Extract (ICE) Study: A Randomized Controlled Trial

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Correction: Tenofovir Disoproxil Fumarate  
RJ Nestor 1148 [www.theannals.com](http://www.theannals.com)

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### **Website of the Day**

Drug Digest  
<http://www.drugdigest.org/DD/Home>

"DrugDigest is a noncommercial, evidence-based, consumer health and drug information site dedicated to empowering consumers to make informed choices about drugs and treatment options." This site is one of the better commercial sites on the Web. It includes a strong drug-drug interaction reference (with herbals), a drug reaction comparison feature, extensive information on a wide array of diseases, and a very extensive medical glossary. I like this site. Give it a look.

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### ***Answer of the Day***

Refludan (lepirudin) is a highly specific direct thrombin inhibitor indicated for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications (TECs). The drug is identical

to natural hirudin (one of the most potent anticoagulants known, found in leech saliva) except for substitution of leucine for isoleucine at the N-terminal end of the molecule and the absence of one sulfate group.