

# Emerging Drug List

## FONDAPARIN (FONDAPARINUX) SODIUM



**Generic (Trade Name):** Fondaparin (Fondaparinux) sodium (Arixtra®)

**Manufacturer:** Sanofi-Synthélabo and Organon

**Indication:** For the prevention of venous thromboembolic events following orthopedic surgery.

**Current Regulatory Status:** Fondaparin sodium (also known as ORG-35140/SR-90107A) was submitted to the U.S. FDA for priority review in mid February, 2001 and in August, 2001 received an approvable letter for the United States. Similarly, it is also undergoing review for the above indication in Europe and in Canada. It is unknown when this product will be commercialized in Canada, and it is only obtainable in this country via clinical trial programs.

**Description:** A well-recognized consequence of orthopedic surgery is the augmented risk for experiencing a thromboembolic event. Due to the significant morbidity and mortality associated with this complication, recommendations have been published addressing how to prevent and manage such a development. Thromboprophylaxis can be achieved via numerous mechanisms, in particular using pharmacologic means. The mainstay of therapy consists of a group of medications, collectively known as anticoagulants. Each exhibits its mechanism of action by altering or interrupting the normal coagulation cascade.

**Current Existing Treatments:** There has been much research in developing newer and better anticoagulant preparations. Fondaparin sodium is a synthetic pentasaccharide that has selective activity, indirectly inhibiting factor Xa. This is a novel mechanism of action in terms of preventing the generation and growth of thrombi. It exhibits concentration-dependant inhibition of factor Xa (by antithrombin), without inhibiting thrombin itself. After subcutaneous administration, peak anti-Xa levels are achieved within one to three hours. Metabolism of fondaparin is minimal, and its half-life ranges from 13 to 17 hours.

The options for post-orthopedic surgery venous thromboembolism (VTE) prophylaxis are numerous. The alternatives commercialized in Canada include heparin (Heparin Leo® - Leo Pharma), warfarin (Coumadin® - Dupont Pharma), and low molecular weight heparins. These agents consist of dalteparin sodium (Fragmin® - Pharmacia Canada Inc.), enoxaparin sodium (Lovenox® - Aventis Pharma Inc.), nadroparin calcium (Fraxiparine® - Sanofi-Synthelabo), or tinzaparin sodium (Innohep® - Leo Pharma). Other anticoagulants include danaparoid sodium (Orgaran® - Organon Canada Ltd), ancrod (Viprinex® - Abbott Labs Inc.), and lepirudin (Refludan™ - Aventis Pharma Inc.), but these selections are less likely to be used in the absence of



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specific circumstances (e.g., heparin-induced thrombocytopenia). Not all of these agents specifically hold the exact indication as fondaparin.

**Cost:** A cost for this product was not obtainable when this review was prepared. In online indexing systems, several articles discussing clinical development and trials (Phase II) aimed at determining optimal dose were found. Much of this work was presented in December, 2000 at the 35th American Society of Health-Systems Pharmacists Midyear Clinical Meeting in Las Vegas, Nevada.

**Evidence:** The largest body of work to date consists of four unpublished phase III trials, entitled EPHEBUS, PENTAMAKS, PENTHIFRA and PENTATHLON 2000 which enrolled over 7000 patients world-wide (i.e., Latin America, Australia, Canada, Europe, USA). Each study randomized participants to receive one of two agents, fondaparin sodium 2.5 mg sc once daily or enoxaparin sodium (at approved doses) for the prophylaxis of thromboembolism associated with major orthopedic surgery (i.e., elective hip replacement, elective knee replacement). All therapies commenced post-surgery (specific time not reported), and were continued for approximately one week in duration. Adjudicated VTE (occurring up to 11 days post surgical procedure) was the primary endpoint.

The incidence of DVT was 4.1, 12.5, 8.3 and 6.1% versus 9.2, 27.8, 19.1 and 8.3% in patients treated with fondaparin sodium and enoxaparin sodium, respectively. Mortality rates, although the specifics are not reported, were similar between treatment groups. Bleeding rates (clinically relevant bleeding, minor bleeding, bleeding complications) were again comparable between treatment arms. A transfusion ( $\geq 2$  units) or decrease in hemoglobin ( $\geq 2$ g/dL) was reported in 2.3 and 2.7% of patients treated with fondaparin sodium and enoxaparin sodium, respectively.

**Adverse Effects:** Like other anticoagulant products, bleeding is the more frequent adverse effect reported in clinical trials. Data concerning adverse effects not related to coagulation were not presented in published clinical studies. In the data available thus far, thrombocytopenia deemed as clinically significant, has not been reported.

**Conclusion:** Fondaparin is a new anticoagulant product, differing in mechanism of action from those agents currently marketed. The benefits touted for this agent include its pharmacokinetic profile, allowing for once daily administration, the minimal necessity for laboratory monitoring, and its targeted site of action (which should lend to less bleeding complications). It has been shown to be efficacious in clinical trials, although publication of this information in full will allow for closer examination of the data. There are also

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ongoing studies exploring the use of fondaparin sodium in the treatment of VTE, and the results of these studies will be interesting to determine whether fondaparin holds any benefit over other standard agents.

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The contents of this bulletin are current as of August 2001.

This series highlights drugs not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

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