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UK Medicines Information Pharmacists Group

NEW MEDICINES ON THE MARKET

Evaluated information for the NHS

FONDAPARINUX (ARIXTRA[▼])

Summary

- Fondaparinux is a pentasaccharide and the first to be marketed of a new class of antithrombotics that selectively inhibit activated factor X without inactivating thrombin itself. Fondaparinux is licensed for the prevention of thromboembolic events in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgery.
- Unlike the low molecular weight heparins, fondaparinux is synthetic.
- In phase III studies subcutaneous fondaparinux was statistically significantly more effective than enoxaparin at preventing venous thromboembolism after major orthopaedic surgery (exact odds ratio [95% CI] = 0.45 [0.37-0.54]).
- In phase III studies comparing fondaparinux with enoxaparin, there was a tendency towards higher major bleeding rates in fondaparinux patients. However, an analysis of bleeding rates in the fondaparinux patients, related to the time of fondaparinux initiation, found that there was a significant reduction in the incidence of major bleeding when fondaparinux was initiated six or more hours after wound closure compared to less than six hours. At present, fondaparinux cannot be reversed and has a half life of 17 hours.
- As the efficacy and safety of more than nine days' therapy with fondaparinux has not been established, fondaparinux is not licensed for long-term prophylaxis of thromboembolism. However, fondaparinux has been studied or is currently being investigated in indications other than the licensed indication, including the treatment of proximal deep vein thrombosis and pulmonary embolism, ST-segment elevation acute myocardial infarction and unstable angina and the prevention of clotting in the extracorporeal circulation during haemodialysis.
- A nine-day course of fondaparinux is considerably more expensive than treatment for the same period with one of the low molecular weight heparins currently on the market.

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FONDAPARINUX

Approved Name:	Fondaparinux sodium
Brand Name: (Manufacturer):	Arixtra▼ (Sanofi Synthelabo)
Presentation:	Clear, colourless solution for injection in pre-filled syringes. Each syringe contains 2.5 mg fondaparinux in 0.5 ml solution.
BNF Therapeutic Class:	Parenteral anticoagulants, BNF 2.8.1.
Licensed Indications:	Prevention of venous thromboembolic events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgery.
Dosage and Administration:	Recommended dose: 2.5 mg once daily postoperatively by subcutaneous injection while the patient is lying down. Initial dose should be given 6 hours after surgical closure, provided that haemostasis has been established. Continue treatment for 5-9 days. Sites of administration should be alternated (see Summary of Product Characteristics [SPC]).
Sector of Use:	Hospital [Y] Primary Care [N]

Therapeutic Comment:	As a selective inhibitor of factor Xa that does not inactivate thrombin itself, fondaparinux represents a new class of antithrombotics. Like low molecular weight heparins (LMWH), fondaparinux can be given once daily in a fixed dose. Unlike LMWH, however, fondaparinux is synthetic. Although considerably more expensive than LMWH, studies indicate that fondaparinux is a more effective thromboprophylactic than enoxaparin after major orthopaedic surgery. Its efficacy in other indications is yet to be proven.
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Cost and Course Details:	Course of 9 days (9 doses): £64.51
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Treatment Alternatives:	For course of 9 doses (high risk/orthopaedic surgery):
[Prices from MIMS August 2002]	Dalteparin* (5000 i.u. daily) £25.41
	Enoxaparin (40 mg daily) £40.64
	Tinzaparin (4500 i.u. daily) £34.48

* Hip surgery dose is higher

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INTRODUCTION

Over one hundred years ago, stasis, hypercoagulability and venous injury were identified as the causes of intravascular thrombosis. These three factors are still used to explain the development of post surgical deep vein thrombosis [1]. Asymptomatic venous thromboembolism is common following major orthopaedic surgery. Contrast venography has shown the prevalence of total deep vein thrombosis at 7-14 days after orthopaedic surgery to be 50-60% in patients not receiving prophylaxis. In studies using routine lung scans for pulmonary embolism, between 7 and 11% of patients had a high probability scan at 7-14 days after total hip replacement or total knee replacement surgery [2]. Because of this, systematic thromboprophylaxis is required after major orthopaedic surgery. LMWH, such as enoxaparin, are often used in preference to heparin as they can be given in a fixed subcutaneous dose, once or twice daily. Fondaparinux, the first of a new class of antithrombotic agents, has recently been licensed in the UK and can be given in a fixed dose once daily.

PHARMACOLOGY

Fondaparinux is a synthetic pentasaccharide, which displays antithrombin mediated selective inhibition of activated factor X (factor Xa). On binding to antithrombin, fondaparinux induces an irreversible conformational change in the molecule, exposing an arginine residue, which binds to and inhibits factor Xa [3]. As a result of factor Xa inhibition, prothrombin to thrombin conversion is prevented and the coagulation cascade interrupted. In the presence of fondaparinux, the natural neutralisation of factor Xa is potentiated by about 300 times. Fondaparinux does not affect platelet function or inactivate thrombin itself [4].

PHARMACOKINETICS

(See SPC for full details)

The bioavailability of fondaparinux following subcutaneous administration is 100% and the drug has an elimination half-life of about 17 hours in healthy, young subjects. There is no evidence that fondaparinux is metabolised; the kidneys excrete between 64 and 77% of unchanged compound. Compared to patients with normal renal function (creatinine clearance $[CL_{crea}] > 80$ ml/min) plasma clearance is, respectively, 1.2 to 1.4 times, 2 times and 5 times lower in patients with mild ($CL_{crea} = 50-80$ ml/min), moderate ($CL_{crea} = 30-50$ ml/min) and severe ($CL_{crea} < 30$ ml/min) renal impairment. Fondaparinux has not been studied in paediatric patients or those with hepatic impairment [4].

EFFICACY (See Table 1 for details of trials)

Five published, large, randomised, double blind, comparative, multicentre trials are discussed below [3, 5, 6, 7, 8]. All five investigated the efficacy and safety of fondaparinux in the prevention of venous thromboembolism following major orthopaedic surgery of the lower limbs; one was a phase II dose ranging study.

In the four phase III studies, patients receiving enoxaparin adhered to one of the two dosage regimens recommended in the USA (see Table 1) [5,6,7,8]. Of these, one of the dosage regimens is in line with the current UK recommendations that patients receive enoxaparin 40 mg od, starting around 12 hours before surgery.

The US prescribing information for fondaparinux warns that the timing of the first dose of drug may have influenced differences in efficacy and safety between

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fondaparinux and enoxaparin in the phase III studies [9]. For example, over 85% of fondaparinux patients in each of the four studies received their first dose of fondaparinux between four and eight hours after surgery, as planned, but preoperative enoxaparin doses were sometimes withheld in the two studies that incorporated a preoperative dose in the regimen [9]. In 74% of patients in one of these studies, the first dose of enoxaparin was given an average of 18 hours after surgery instead of 12 hours before as originally intended [9,10]. According to one of the study authors, the preoperative dose of enoxaparin was omitted in several cases in which surgery was carried out shortly after admission and the use of regional anaesthesia was planned. This was in line with the study protocol and European health authority recommendations [11]. Administration of enoxaparin took place 12 hours before surgery in 78% of patients in the other study that used preoperative enoxaparin dosing [9].

The timing of fondaparinux initiation in the phase III studies may have affected rates of major bleeding in fondaparinux patients. Analysis of the fondaparinux bleeding rates showed the incidence of major bleeding to be significantly reduced when the drug was initiated six or more hours after wound closure (incidence of major bleeding: 3.0% [fondaparinux initiation <6 hours postoperatively] versus 1.8% [fondaparinux initiation \geq 6 hours postoperatively], $p=0.028$) [12]. For this reason, the fondaparinux SPC recommends that the first dose be given six hours after surgical closure.

Phase II Study: A dose-dependent reduction in the incidence of thromboembolism was seen with fondaparinux (0.75 mg, 1.5 mg and 3.0 mg/day). Relative to enoxaparin (30 mg bd), the reduction in risk with fondaparinux was 82% in the 3.0 mg group ($p=0.01$) and 29% in the 1.5 mg group ($p=0.51$). The

incidence of major bleeding was not significantly different in the enoxaparin and fondaparinux 3.0 mg groups (3.5% versus 4.5%) [3]. It was determined that a daily dose of fondaparinux of 2.5 mg should be used in the phase III studies detailed below.

Phase III Studies: One study found the incidence of venous thromboembolism after hip fracture surgery to be lower with fondaparinux than with enoxaparin 40 mg od (8.3% vs 19.1%, $p<0.001$). Statistically, treatment groups did not differ significantly with regard to the incidence of major bleeding [5].

Two further studies concluded that fondaparinux was more effective than enoxaparin in reducing the risk of venous thromboembolism after hip replacement surgery [6,7], but the difference in incidence of venous thromboembolism reached statistical significance in only one [7]. There was a non-significant tendency towards a higher incidence of major bleeding in the fondaparinux group in this study [7].

In the other study, the reduction in risk of thromboembolism with fondaparinux relative to enoxaparin (30 mg bd) was 26.3% (95% CI -10.8 to 52.8, $p=0.099$). Analysis of symptomatic venous thromboembolism alone showed that, unlike in the other phase III studies, this event occurred in a significantly higher percentage of fondaparinux patients (1% vs 0.1%, $p=0.0062$). The authors warn that most patients with symptomless venographically proven deep vein thrombosis received anticoagulants at therapeutic doses and may therefore have been at a reduced risk of developing symptoms subsequently. There was no statistically significant difference between groups in terms of major bleeding [6].

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Venous thromboembolism was experienced by significantly fewer fondaparinux patients than enoxaparin (30 mg bd) patients undergoing knee surgery (12.5% vs 27.8%, $p < 0.001$). In this study, however, major bleeding occurred more frequently in the fondaparinux group ($p = 0.006$) [8].

It is of note that over three hundred patients in each of the phase III studies were not assessed for primary efficacy outcomes, however the publications for these studies provide valid reasons for excluding these patients and the numbers of patients unavailable for assessment were similar in both study groups.

A pooled analysis of the results of fondaparinux phase III studies gave estimated venous thromboembolism rates for fondaparinux and enoxaparin of 6.8% and 13.7%, respectively (exact odds ratio [95% CI] = 0.45 [0.37-0.54]) [13]. Estimated major bleeding rates for fondaparinux and enoxaparin were 2.7% and 1.7%, respectively (exact odds ratio [95% CI] = 1.54 [1.11-2.16]) [13]. The incidence of thrombocytopenia in phase III studies was found to be the same in the two treatment groups. No evidence emerged to counter the expectation that fondaparinux, in not binding to platelet factor 4, will be associated with a low risk of heparin induced thrombocytopenia (HIT)-type II. There were also no clear indications during clinical studies that concomitant administration of fondaparinux and oral anticoagulants resulted in unexpected synergistic effects on bleeding [14].

ADVERSE EFFECTS

Adverse effects experienced during clinical trials that investigators considered were possibly related to fondaparinux are listed on the SPC. The following are listed as common ($\geq 1\% < 10\%$) adverse effects:

anaemia, bleeding (at surgical site, gastrointestinal, haematuria, pulmonary, haematoma), thrombocytopenia, purpura, abnormal liver function tests and oedema [4].

CONTRAINDICATIONS AND PRECAUTIONS

(See SPC for full details)

Contraindications: Active clinically significant bleeding, severe renal impairment ($Cl_{crea} < 30$ ml/min), presence of HIT-type II, acute bacterial endocarditis, known hypersensitivity to fondaparinux or its excipients [4].

Precautions: Pregnancy and breastfeeding. Patients at increased risk of haemorrhage, including elderly patients, moderately renally impaired patients ($Cl_{crea} < 50$ ml/min), patients who have undergone spinal/epidural anaesthesia or spinal puncture, patients weighing under 50 kg, patients with severe hepatic impairment [4].

Platelets should be monitored at baseline and end of treatment, especially when follow-up treatment with heparin or LMWH is considered. Concomitant administration of certain drugs should be avoided, such as desirudin, fibrinolytic agents, glycoprotein IIb/IIIa receptor antagonists, heparin, heparinoids, LMWH. See SPC for administration of follow up therapy with vitamin K antagonists or other anticoagulants. Other antiplatelet drugs and NSAIDs should be used with caution and monitored closely [4].

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Table 1: Fondaparinux in the Prevention of Venous Thromboembolism After Major Orthopaedic Surgery: Published Efficacy Studies

Ref No	Design of Study (Publication Type)	Treatments Assessed	Primary Outcome Measures	Results and Comments			
3	RA, DB, C, MC <u>Dose ranging study</u> DVT prophylaxis after total hip replacement surgery, 933 pts treated and 593 included in efficacy analysis. Follow up period was five weeks. (PENTATHLON)	F (0.75, 1.5, 3.0, 6.0 or 8.0 mg) od, sc. First dose: 6 (+/-2) hours postoperatively. E 30 mg bd, sc. First dose: 12-24 hours postoperatively. Treatment for ten days or until BV (minimum of five days)	Incidence of venous thromboembolism* Major bleeding	Incidence (%) by day 10			
					VTE	Major bleeding	
				F (0.75 mg)	11.8	0	
				F (1.5 mg)	6.7	0.5	
				F (3.0 mg)	1.7	4.5	
				F (6.0 mg)†	4.4	16.7	
				F (8.0 mg)†	0	17.3	
				E(30 mg)	9.4	3.5	
5	RA, DB, C, MC Venous thromboembolism prophylaxis after hip-fracture surgery, 1711 pts randomised. 1250 pts included in primary efficacy analysis. Follow-up period was six weeks. (PENTHIFRA)	F 2.5 mg od, sc. First dose 6 (+/-2) hours postoperatively. Second dose ≥12 hours after first E 40 mg od, sc. First dose 12 (+/-2) hours preoperatively. Second dose: 12-24 hours postoperatively. Treatment scheduled to continue until days 5-9 (day 1=surgery)	Incidence of venous thromboembolism* by postoperative day 11 Incidence of major bleeding by postoperative day 11	Incidence (%) by day 11			
					F group	E group	
				VTE	8.3	19.1	p<0.001
				Any DVT	7.9	18.8	p<0.001
				Symptomatic VTE	0.5	0.5	p=1.00
				Proximal DVT	0.9	4.3	p<0.001
				Major bleeding	2.2	2.2	p=1.00
6	RA, DB, C, MC Venous thromboembolism prophylaxis after hip replacement surgery, 2275 pts randomised. 1584 pts included in primary efficacy analysis. Follow-up period was six weeks. (PENTATHLON 2000)	F 2.5 mg od, sc (as for study 5) E 30 mg bd,sc. First dose 12-24 hours postoperatively. Treatment scheduled to continue until days 5-9 (day 1=surgery)	As for study 5	VTE	6.1	8.3	p=0.099
				Any DVT	5.6	8.2	p=0.047
				Symptomatic VTE	0.9	0.1	p=0.0062
				Proximal DVT	1.7	1.2	p=0.42
				Major bleeding	1.8	1.0	p=0.11
7	RA, DB, C, MC Venous thromboembolism prophylaxis after hip replacement surgery, 2309 pts randomised. 1827 pts included in primary efficacy analysis. Follow-up period was six weeks. (EPHESUS)	F 2.5 mg od, sc (as for study 5) E 40 mg od, sc (as for study 5)	As for study 5	VTE	4.1	9.2	p<0.0001
				Any DVT	4.0	9.0	p<0.0001
				Symptomatic VTE	0.4	0.3	p=0.73
				Proximal DVT	0.7	2.5	p=0.0021
				Major bleeding	4.1	2.8	p=0.11
8	RA, DB, C, MC Venous thromboembolism prophylaxis after major knee surgery, 1049 pts randomised. 724 pts included in primary efficacy analysis. Follow-up period was six weeks (PENTAMAKS)	F 2.5 mg od, sc (as for study 5) E 30 mg bd,sc (as for study 6)	As for study 5	VTE	12.5	27.8	p<0.001
				Any DVT	12.5	27.1	p<0.001
				Symptomatic VTE	0.6	1.4	p=0.34
				Proximal DVT	2.4	5.4	p=0.06
				Major bleeding	2.1	0.2	p=0.006

†Assignment of pts to 6.0 and 8.0 mg groups discontinued early due to number of bleeding reports.

* DVT, PE or both. Pts examined for deep vein thrombosis by bilateral leg venography. Lung scan, pulmonary angiography, helical computed tomography or autopsy used to confirm symptomatic pulmonary embolism.

Major bleeding was defined as fatal bleeding, retroperitoneal, intracranial, intraspinal or critical organ bleeding, bleeding that led to reoperation or bleeding with an index of 2 or more (number of units of packed red cells or whole blood transfused plus the haemoglobin values before the bleeding episode minus the haemoglobin values after the episode (g/decilitre))

BV=bilateral venography C=controlled DB=double blind DVT= deep vein thrombosis E=enoxaparin F=fondaparinux MC=multicentre PE=pulmonary embolism RA=randomised VTE=venous thromboembolism