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Study No.: C8843
Title: Multinational/multicentre, non-randomized, open label study to assess efficacy and safety of fondaparinux sodium (ARIXTRA®) use in daily practice in subjects undergoing major orthopedic surgery of the lower limbs
Rationale: Subjects undergoing major orthopedic surgery of the lower limbs are in the highest risk category for developing venous thromboembolism (VTE). Data from several studies support the fact that the risk of VTE persists for at least 4 weeks after elective major orthopedic surgery of the lower limbs, and have shown the need for extended thromboprophylaxis. The purpose of this trial was to evaluate the incidence of symptomatic VTE in subjects from daily practice undergoing orthopedic surgery of the lower limbs treated with fondaparinux sodium (FX) 2.5mg once daily (OD) for 4±1 weeks and to assess the safety of FX.
Phase: IIIb
Study Period: 31 July 2003 to 15 December 2004
Study Design: Non-randomized, open label study.
Centers: 236 in total: Australia 10, Austria 7, Belgium 5, Columbia 3, Denmark 4, Finland 5, France 35, Germany 13, Greece 30, Hungary 12, Italy 43, Mexico 5, The Netherlands 18, Norway 2, Portugal 10, Spain 15, Sweden 7, Switzerland 6, Turkey 6 .
Indication: Prevention of venous thromboembolic events in subjects undergoing major orthopedic surgery of the lower limbs
Treatment: Subjects were assigned to treatment at 6-12 hours post surgery. All subjects received once daily subcutaneous injection (SC) of FX 2.5mg for 4±1 weeks according to local habits. Subjects were divided into those with an epidural indwelling, or deep peripheral catheter, and those without a catheter.
Objectives: To evaluate the incidence of symptomatic VTE and the safety of FX 2.5mg given OD SC for 4±1 weeks in subjects from daily practice undergoing major orthopedic surgery of the lower limbs To document the use of FX whatever the technique of anesthesia/analgesia selected by the investigators To investigate the absence of impact on symptomatic VTE rate of specific recommendations regarding the use of an epidural/deep peripheral postoperative indwelling catheter
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the global occurrence of incidence of symptomatic VTE confirmed by routine tests up to 6 weeks post-surgery and validated by an external independent adjudication committee. The components are defined as symptomatic deep venous thrombosis (DVT), symptomatic pulmonary embolism (PE) and fatal PE.
Secondary Outcome/Efficacy Variable(s): <u>Secondary endpoints:</u> Time to first VTE Incidence of each category of VTE (confirmed symptomatic DVT, confirmed symptomatic PE, confirmed fatal PE) Global incidence of symptomatic VTE + all deaths Global incidence of symptomatic VTE + all bleedings meeting protocol criteria* Global incidence of symptomatic VTE + all bleedings meeting protocol criteria* + all deaths Investigator's global clinical assessment at final visit: wound-healing, outcome of the operative procedure, mobilisation level *Bleedings meeting protocol criteria were defined as: bleedings leading to reoperation at surgical site, bleedings at non surgical site necessitating transfusion of at least 3 units of blood, bleedings in a critical organ [including intracranial, intraocular, retroperitoneal, spinal, pericardial] or fatal bleedings.
Statistical Methods: <u>Statistical methods used:</u> The primary analysis was based on the non-inferiority on global symptomatic VTE rates of the use – compared to the absence of use – of a catheter of analgesia (unadjusted analysis). The statistical assessment of the null hypothesis was based on the 2-sided 90% confidence interval (CI) for the unadjusted Odds-Ratio (OR). The non-inferiority of the “With catheter” group, compared to the “Without catheter” group, was shown if the upper limit of the 2-sided 90% CI of the unadjusted OR was lower than 1.75. The 2-sided 95% CI for the unadjusted OR was also provided and associated to the 2-sided p-value at 5% significance level. Secondary efficacy analyses were based on the time to first VTE using survival analyses. Incidence of each category of VTE (DVT, PE and fatal PE) was also summarized. Finally, global incidence of symptomatic VTE + all deaths, global

incidence of symptomatic VTE + all bleedings meeting protocol criteria and global incidence of symptomatic VTE + all bleedings meeting protocol criteria + deaths were computed on the overall ITT Population and according to the 2 subjects groups – With/Without catheter.

Safety analyses included AEs, SAEs and deaths monitoring. Overall incidence of bleedings meeting protocol criteria was analyzed for the ITT Population and according to the 2 subject groups (With/Without catheter), and then presented by type of bleedings.

Populations analyzed:

The Intent-to-Treat (ITT) population included all subjects who had received at least 1 dose of study drug and was the primary population used for all efficacy, AEs and bleedings summaries and analyses. In addition, subjects with a missing VTE endpoint (ie prematurely withdrawn or lost to follow-up without reporting on the endpoint) were not included in the analyses.

Study Population: Adult male or female subjects (≥18 years) undergoing major orthopedic surgery of the lower limbs, whatever the technique of anesthesia or analgesia, who required at least 3 weeks of prophylaxis were eligible for the study. Subjects were excluded if they had a current active significant bleeding disorder or suffered from any other conditions or situations likely to put them at risk of bleeding.

Number of Subjects:	Total Population	
Planned, N	6000	
Enrolled, N	5713	
Enrolled and Treated (ITT population)	5704	
Completed, n (%)	5345 (93.7)	
Total Number Subjects Withdrawn, N (%)	357 (6.3)	
Withdrawn due to Adverse Events n (%)	299 (5.2)	
Withdrawn due to Lack of Efficacy n (%)	N/A	
Withdrawn for other reasons n (%)	58 (1.0)	
Demographics	Without Catheter	With Catheter
N (ITT)	4074	1630
Females: Males: Missing	Total Population 3775:1928:1	
	Without Catheter	With Catheter
Mean Age, years (SD)	66.7 (12.13)	64.8 (11.00)
Race, n (%)	N/A	N/A
Primary Efficacy Results:		
Incidence symptomatic VTE up to 6 weeks (Subjects in ITT population with an endpoint)	Without Catheter	With Catheter
n/N (%)	41/3852 (1.1)	13/1535 (0.9)
Unadjusted OR (With/Without catheter) [90% CI]	0.79 [0.47; 1.34]	
p-value	0.47	
Secondary Outcome Variable(s):		
Time to first VTE	Without Catheter	With Catheter
Number of subjects reporting an event, n/N (%) (ITT Population)	41/4074 (1.0)	13/1630 (0.8)
Time to first VTE, median days (range)	9 (2-33)	5 (2-32)
Incidence of each category of VTE, n/N (%) (Subjects in ITT population with an endpoint)	Without Catheter	With Catheter
DVT	31/3852 (0.8)	12/1630 (0.7)
Non-PE	4/3839 (0.1)	0/1528 (0)
Fatal PE	6/3839 (0.2)	1/1528 (0.1)
Incidence of symptomatic VTE + all deaths (Subjects in ITT population with an endpoint)	Without Catheter	With Catheter
n/N (%)	55/3852 (1.4)	14/1535 (0.9)
95% CI	[1.1, 1.9]	[0.54, 1.5]
Incidence of symptomatic VTE + all bleedings meeting protocol criteria (Subjects in ITT population with an endpoint)	Without Catheter	With Catheter
n/N (%)	76/3863 (2.0)	20/1539 (1.3)
95% CI	[1.6, 2.5]	[0.8, 2.0]

Incidence of symptomatic VTE + all bleedings meeting protocol criteria + all deaths (Subjects in ITT population with an endpoint)	Without Catheter	With Catheter
n/N (%)	85/3863 (2.2)	21/1539 (1.4)
95% CI	[1.8, 2.7]	[0.9, 2.1]
Investigators global assessment at final visit (ITT population)	Without Catheter	With Catheter
Percentage of subjects with uneventful wound healing	87.3	92.2
Outcome of operative procedure and rehabilitation program (%)		
Excellent	23.7	23.8
Good	66.3	69.4
Fair	8.5	6.0
Poor	1.5	0.8
Safety Results:		
Adverse event results: On therapy AEs were defined as those with onset occurring between the first and last injections of study drug.		
Most Frequent Adverse Events – On therapy	ITT Population N=5704	
Subjects with any AE(s), n (%)	1362 (23.9)	
10 most frequent AEs		
Pyrexia	90 (1.6)	
Nausea	76 (1.3)	
Haematoma	70 (1.2)	
Vomiting	66 (1.2)	
Urinary tract infection	66 (1.2)	
Post-procedural hematoma	57 (1)	
Headache	54 (1.0)	
Constipation	49 (0.9)	
Malaise	39 (0.7)	
Diarrhoea	37 (0.7)	
Pruritus	36 (0.6)	
Anaemia	35 (0.6)	
Serious Adverse Events (fatal and non-fatal) – On therapy, n (%) [n considered by the investigator to be related to study medication]	ITT Population N=5704	
Subjects with any SAE	208(3.65) [49]	
Post procedural haematoma	11 (0.19) [5]	
Dislocation of joint prosthesis	9 (0.16) [0]	
Joint dislocation	7 (0.12) [0]	
Femur fracture	5 (0.09) [0]	
Subcutaneous haematoma	5 (0.09) [1]	
Medical device complication	3 (0.05) [0]	
Incision site haemorrhage	2 (0.04) [1]	
Post procedural haemorrhage	2 (0.04) [1]	
Wound dehiscence	2 (0.04) [1]	
Wound secretion	2 (0.04) [1]	
Blister	1 (0.02) [0]	
Bone fragmentation around implant	1 (0.02) [0]	
Cervical vertebral fracture	1 (0.02) [0]	
Failure of implant	1 (0.02) [0]	
Fracture	1 (0.02) [0]	
Hip fracture	1 (0.02) [0]	

Injury	1 (0.02) [0]
Joint dislocation postoperative	1 (0.02) [0]
Post procedural complication	1 (0.02) [0]
Post procedural pain	1 (0.02) [0]
Tendon rupture	1 (0.02) [0]
Traumatic fracture	1 (0.02) [0]
Postoperative infection	7 (0.12) [0]
Wound infection	7 (0.12) [2]
Infection	5 (0.09) [1]
Pneumonia	5 (0.09) [0]
Arthritis infective	2 (0.04) [0]
Urinary tract infection	2 (0.04) [0]
Arthritis bacterial	1 (0.02) [0]
Bronchitis acute	1 (0.02) [0]
Cholangitis suppurative	1 (0.02) [0]
Diverticulitis	1 (0.02) [0]
Escherichia sepsis	1 (0.02) [0]
Implant site infection	1 (0.02) [0]
Lung infection	1 (0.02) [0]
Skin infection	1 (0.02) [0]
Suture line infection	1 (0.02) [1]
Haematoma	10 (0.18) [9]
Haemorrhage	7 (0.12) [5]
Deep vein thrombosis	3 (0.05) [0]
Circulatory collapse	2 (0.04) [0]
Wound haemorrhage	2 (0.04) [2]
Orthostatic hypotension	1 (0.02) [0]
Phebothrombosis	1 (0.02) [0]
Haemarthrosis	6 (0.11) [5]
Arthralgia	2 (0.04) [0]
Arthropathy	1 (0.02) [0]
Joint contracture	1 (0.02) [0]
Joint range of motion decreased	1 (0.02) [0]
Joint stiffness	1 (0.02) [0]
Ligament disorder	1 (0.02) [0]
Pain in extremity	1 (0.02) [0]
Cerebral artery embolism	1 (0.02) [0]
Cerebral haemorrhage	1 (0.02) [0]
Cerebral ischaemia	1 (0.02) [0]
Cerebrovascular accident	1 (0.02) [0]
Dementia Alzheimer's type	1 (0.02) [0]
Dizziness	1 (0.02) [0]
Haemorrhage intracranial	1 (0.02) [0]
Hypoglycaemic coma	1 (0.02) [0]
Hypotonia	1 (0.02) [0]
Paraesthesia	1 (0.02) [0]
Sciatic nerve neuropathy	1 (0.02) [0]
Sciatica	1 (0.02) [0]
Transient ischaemic attack	1 (0.02) [0]

Abdominal pain	1 (0.02) [0]
Duodenal ulcer	1 (0.02) [1]
Gastric haemorrhage	1 (0.02) [1]
Gastrointestinal disorder	1 (0.02) [0]
Gastrointestinal haemorrhage	1 (0.02) [1]
Ileus	1 (0.02) [0]
Intestinal hypomotility	1 (0.02) [0]
Intestinal infarction	1 (0.02) [0]
Intestinal obstruction	1 (0.02) [0]
Pancreatitis acute	1 (0.02) [0]
Retroperitoneal haemorrhage	1 (0.02) [1]
Atrial fibrillation	3 (0.05) [0]
Acute myocardial infarction	1 (0.02) [0]
Arrhythmia supraventricular	1 (0.02) [0]
Cardiac arrest	1 (0.02) [1]
Cardiac failure acute	1 (0.02) [1]
Myocardial infarction	1 (0.02) [0]
Myocardial ischaemia	1 (0.02) [0]
Tachycardia paroxysmal	1 (0.02) [0]
Inflammation of wound	2 (0.04) [0]
Pain	2 (0.04) [0]
Pyrexia	2 (0.04) [0]
Secretion discharge	1 (0.02) [1]
Swelling	1 (0.02) [0]
Wound necrosis	1 (0.02) [1]
Respiratory failure	4 (0.07) [0]
Acute pulmonary oedema	1 (0.02) [0]
Dyspnoea	1 (0.02) [0]
Hip arthroplasty	1 (0.02) [0]
Pain management	1 (0.02) [0]
Post procedural drainage	1 (0.02) [0]
Rehabilitation therapy	1 (0.02) [0]
Wound drainage	1 (0.02) [1]
Wound treatment	1 (0.02) [0]
Anaemia	5 (0.09) [2]
Cervix carcinoma	1 (0.02) [0]
Hepatic cancer metastatic	1 (0.02) [0]
Metastases to bone	1 (0.02) [0]
Neoplasm	1 (0.02) [0]
Ovarian cancer	1 (0.02) [0]
Acute prerenal failure	1 (0.02)[0]
Haematuria	1 (0.02) [0]
Oliguria	1 (0.02) [0]
Renal failure	1 (0.02) [0]
Urinary retention	1 (0.02) [1]
Decubitus ulcer	1 (0.02) [0]
Dermatitis allergic	1 (0.02) [0]
Dermatitis contact	1 (0.02) [0]
Exanthem	1 (0.02) [0]

Skin bleeding	1 (0.02) [1]
Cholestasis	1 (0.02) [0]
Liver disorder	1 (0.02) [0]
Blood creatinine increased	1 (0.02) [1]
Hepatic enzyme increased	1 (0.02) [1]
Vertigo	1 (0.02) [0]
Inappropriate antidiuretic hormone secretion	1 (0.02) [0]
Hyponatraemia	1 (0.02) [0]
Serious Adverse Events (fatal) – On therapy, n (%) [n considered by the investigator to be related to study medication]	
	ITT Population N=5704
Subjects with any fatal SAE	8 (0.14) [0]
Respiratory failure	2 (0.04) [0]
Cerebral hemorrhage	1 (0.02) [0]
Intestinal infarction	1 (0.02) [0]
Cerebrovascular accident	1 (0.02) [0]
Pneumonia	1 (0.02) [0]
Hemorrhage	1 (0.02) [0]
Ovarian cancer	1 (0.02) [0]

Conclusion:

The results of this study indicate that in subjects undergoing major orthopedic surgery of the lower limbs, the incidence of symptomatic VTE following FX 2.5 mg given 6-12 hours postoperatively and for 4±1 weeks was similar in patients with or without indwelling catheters (0.9% and 1.1% respectively). During the treatment period, 1362 (23.9%) subjects experienced an AE with the most frequently reported being pyrexia and nausea, and 208 (3.65%) experienced an SAE with the most common being post procedural hematoma. A total of 8 subjects experienced a fatal serious adverse event during the treatment period.

Publications:

No Publication

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