TITLE: Module 1.8.2 European Union Risk Management Plan for Arixtra (fondaparinux)

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name):	Fondaparinux sodium
Pharmaco-therapeutic group (ATC Code):	B01AX05
Name of Marketing Authorisation Holder or Applicant:	Aspen Pharma Trading Limited 3016 Lake Drive Citywest Business Campus Dublin 24
Number of medicinal products to which this RMP refers:	One
Product(s) concerned (brand name(s)):	Arixtra™

Data lock point for this EU RMP:	06 December 2013
Version Number:	2.0
Date of final sign off:	31 August 2015

Administrative Information on the RMP

Part	Module/annex	Date last updated for submission	*Version number of RMP when last submitted/ or Not Applicable
PART II Safety Specification	SI Epidemiology of the indication and target population(s)	11 March 2014	1.9
	SII Non-clinical part of the safety specification	06 June 2011 Previous EU RMP template	1.8
	SIII Clinical trial exposure	06 June 2011 Previous EU RMP template	1.8
	SIV Populations not studied in clinical trials	06 June 2011 Previous EU RMP template	1.8
	SV Post-authorisation experience	31 August 2015	2.0
	SVI Additional EU requirements for the safety specification	11 March 2014	1.9
	SVII Identified and potential risks	11 March 2014	1.9
	SVIII Summary of the safety concerns	06 June 2011 Previous EU RMP template	1.8
PART III Pharmacovigilance Plan		31 August 2015	2.0
PART IV Plan for post-authorisation efficacy studies		NA	NA
PART V Risk Minimisation Measures		06 June 2011 Previous EU RMP template	1.8
PART VI Summary of RMP		31 August 2015	2.0
PART VII Annexes	ANNEX 2 Current or proposed SmPC/PIL	11 March 2014	1.9
	ANNEX 3 Worldwide marketing status by country	11 March 2014	1.9
	ANNEX 4 Synopsis of clinical trial programme	11 March 2014	1.9
	ANNEX 5 Synopsis of	11 March 2014	1.9

Part	Module/annex	Date last updated for submission	*Version number of RMP when last submitted/ or Not Applicable
	pharmacoepidemiological study programme		
	ANNEX 6 Protocols for proposed and on-going studies in Part III	31 August 2015	2.0
	ANNEX 7 Specific adverse event follow-up forms	11 March 2014	1.9
	ANNEX 8 Protocols for studies in Part IV	NA	NA
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	NA	NA
	ANNEX 10 Details of proposed additional risk minimisation activities	NA	NA
	ANNEX 11 Mock up examples	NA	NA
	ANNEX 12 Other supporting data	NA	NA

** A new RMP version number should be assigned each time any Parts/modules are updated*

QPPV name:	Thomas McConnon Aspen Pharma Trading Limited
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Overview of versions:

Document number	RMP Version number	Agreed within
2011N117506_00	Version 1.8	CHMP Opinion 17 Nov 2011
2014N1948776_00	Version 1.9	CHMP Opinion 26 Jun 2014

Current RMP versions under evaluation:

None

Invented name(s) in the European Economic Area (EEA)	ARIXTRA™
Authorisation procedure	Centralised
Brief description of the product	Fondaparinux sodium (fondaparinux) was the first selective Factor Xa inhibitor to be marketed. It is a synthetic pentasaccharide with antithrombotic activity, which is the result of antithrombin III (ATIII)-mediated selective inhibition of Factor Xa. By selectively binding to ATIII, fondaparinux potentiates (about 300 times) the innate neutralisation of Factor Xa by ATIII. Neutralisation of Factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.
Indication(s) in the EEA	Fondaparinux is currently approved in Europe and in the US as follows: • prevention of venous thromboembolic events (VTE) in various patient populations • treatment of deep vein thrombosis (DVT) and acute pulmonary embolism (PE) • treatment of unstable angina or /non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 mins) invasive management (PCI) is not indicated (EU only) • treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy (EU only) • treatment of acute symptomatic isolated spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis (EU only)
	Proposed indication: not applicable
Posology and route of administration in the EEA	Fondaparinux is to be administered by subcutaneous injection once daily as follows: • 1.5mg (EU only) and 2.5mg for VTE prophylaxis and treatment of superficial vein thrombosis • 5, 7.5, and 10mg for treatment of DVT

	and PE • 2.5mg for treatment of UA/NSTEMI and STEMI (first dose in STEMI patients should administered intravenously)
Pharmaceutical form(s) and strengths Current (if applicable) Proposed (if applicable)	Fondaparinux is supplied as a sterile, preservative-free injectable solution for subcutaneous and intravenous use, in a single dose prefilled syringe as follows: • Each syringe contains 1.5 mg of fondaparinux sodium in 0.3 ml solution for injection. The solution is a clear and colourless liquid with a pH between 5.0 and 8.0. • Each syringe contains 2.5 mg of fondaparinux sodium in 0.5 ml solution for injection. The solution is a clear and colourless liquid with a pH between 5.0 and 8.0. • Each syringe contains 5.0 mg of fondaparinux sodium in 0.4 ml solution for injection. The solution is clear and colourless to slightly yellow with a pH between 5.0 and 8.0. • Each syringe contains 7.5 mg of fondaparinux sodium in 0.6 ml solution for injection. The solution is clear and colourless to slightly yellow with a pH between 5.0 and 8.0. • Each syringe contains 10.0 mg of fondaparinux sodium in 0.8 ml solution for injection. The solution is clear and colourless to slightly yellow with a pH between 5.0 and 8.0.
Country and date of first authorisation worldwide	07 Dec 2001 (United States)
Country and date of first launch worldwide	08 Feb 2002 (United States)
Country and date of first authorisation in the EEA	Centrally approved in EEA on 21 Mar 2002
Is the product subject to additional monitoring in the EU?	No

Abbreviations

ACCP	American College of Chest Physicians
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndromes
AE	Adverse Event
APTL	Aspen Pharma Trading Limited
ARB	Angiotensin receptor blocker
ASA	Aspirin (acetylsalicylic acid)
ATIII	Anti-thrombin III
AUC	Area Under the Curve
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CrCl	Creatinine Clearance
CRP	C-reactive protein
CSD	Central Safety Department
DHCPL	Dear Healthcare Provider Letter
DUS	Duplex ultrasound
DVT	Deep-Vein Thrombosis
EEA	European Economic Area
EU	European Union
FDA	Food and Drug Administration
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
GSK	GlaxoSmithKline (previous MA holder)
HIT	Heparin induced thrombocytopenia
INR	International Normalized Ratio
IV	Intravenous
IVC	Inferior vena cava
LDL	Low-density lipoprotein
LMWH	Low Molecular Weight Heparin
MI	Myocardial Infarction
MOSLL	Major orthopaedic surgery of the lower limbs
NHS	National Heath Service
NICE	National Institute for Heath and Care Excellence
NSAID	Non Steroidal Anti-Inflammatory Drug
NSTEMI	Non ST-Elevation Myocardial Infarction
OASIS	Organization to Assess Strategies in Acute Ischemic Syndromes
OR	Odds ratio
OSM	Online Signal Management
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PF4	Platelet Factor 4
POST	Prospective Observational Superficial Thrombophlebitis
PRAC	Pharmacovigilance and Risk Assessment Committee
PSUR	Periodic Safety Update Report
QA	Quality Assurance

RMP	Risk Management Plan
r-tPA	Recombinant Tissue Plasminogen Activator
SAE	Serious Adverse Event
SC	Subcutaneous
SMQ	Standard MedDRA Query
SPC	Summary of Product Characteristics
STEMI	ST-Elevation Myocardial Infarction
SVT	Superficial-vein thrombosis
UA	Unstable Angina
UFH	Unfractionated Heparin
UK	United Kingdom
US	United States
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WHO	World Health Organisation

Trademark Information

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ARIXTRA

SI.1 Epidemiology of the disease

Venous Thromboembolism (VTE)

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is any thrombolytic event occurring within the venous system. DVT is a radiologically confirmed partial or total thrombotic occlusion of the deep venous system, typically of the leg (such as calf veins, femoral vein, or popliteal vein) or in the deep vein of the pelvis sufficient to produce symptoms of pain or swelling [McManus 2011]. PE is a blockage of the main artery of the lung that can develop from DVT that migrates to the lung. PE is associated with a high risk of death.

Incidence and prevalence (VTE)

Overall annual incidence per 100,000 ranged from 57 [Ho 2008] to 183 [Oger 2000] for VTE, 17 [Cheuk 2004] to 124 [Oger 2000] for DVT, and 4 [Cheuk 2004] to 69 [Silverstein 1998] for PE. VTE incidence in US, Europe, Canada, India, Australia, and China is briefly summarized below in Table 1. Rates varied across regions but were fairly consistent with the exception of China where incidence was notably lower (17 and 4 per 100,000 for DVT and PE, respectively.

Table 1 Incidence of VTE in the general population

Reference	Region, Data Collection Years, Design	Population, N Cases, Population Size	Incidence, per 100,000
Spencer, 2009	US 1999, 2001/3	Worcester, MA residents all ages with healthcare system encounters data from 12 area hospitals; N=1,576, population 477,800	VTE: 114 DVT: 95 PE: 34
Cushman, 2004	US 1987-97	Adults age ≥45 years followed for 7.6 years as part of ARIC and CHS cohorts; N=304, population 21,680	VTE: 161 DVT: 117 PE: 45
Tagalakis, 2013	Canada 2000-09	All residents of Quebec providence with health care records	VTE: 124 DVT: 78 PE: 45
Ho, 2008	Australia 2003-04	Residents all ages of metro Perth; N=137, population 151,923	VTE: 57 DVT: 35 PE: 21
Isma 2009	Sweden 1998-2006	Adults age>18y at a single hospital with objective diagnosis of DVT or PE; N=1,140, population 280,000	VTE: 66 DVT: 51 PE: 19
Naess, 2007	Norway 1995-2001	Adult residents age ≥20y in a geographically defined region, N=740 , population 94,194	VTE: 94 DVT: 61 PE: 33
Cimminiello, 2010	Italy	All patients age ≥40 years with	VTE:

Reference	Region, Data Collection Years, Design	Population, N Cases, Population Size	Incidence, per 100,000
	2001-04	DVT or PE event and treated with antithrombotic drugs within 90 days; N=774, population 372,000	Male: 96 Female: 117
Oger 2000	France 1998-99	All residents of a geographically defined district served by 3 hospitals; N=627, population 342,000	VTE: 183 DVT: 124 PE: 60
Cheuk, 2004	Hong Kong 2000-01	All patients with admission or discharge records from 44 hospitals in Hong Kong; N=2,830, population 1.1 mil	DVT: 17 PE: 4
Lee, 2009	India 1996-2005	All ages hospital admissions at single hospital; N=722, 438,667 admissions	VTE: 175

A study by Cohen et al. [Cohen, 2007] developed an epidemiological model to estimate the number of community- and hospital-acquired incident VTE cases in six EU countries (France, Germany, Italy, Spain, Sweden, and the UK) in 2004. The following number cases were projected for these countries:

Table 2 Projected patient numbers for VTE in the EU in 2004 [Cohen 2007]

Event	Number of Community-Acquired Cases, N (95%CI)	Number of Hospital-Acquired Cases, N (95%CI)	Total, N (95%CI)
Non-fatal DVT	200,482 (172k–226k)	265,233 (209k–332k)	465,715 (404k–538k)
Non-fatal PE	86,511 (73k–99k)	209,471 (153k–273k)	295,982 (242k–360k)
VTE-Related Deaths	108,535 (77k–178k)	261,477 (211k–325k)	370,012 (300k–483k)

Approximately 10% of patients with history of VTE will develop recurrent VTE within 6 months and about 30% of surviving patients develop recurrent VTE within 10 years. Independent predictors for recurrence include increasing age, obesity, malignancy with or without chemotherapy, and neurologic disease with extremity paresis [Heit, 2002]. In the Worcester Venous Thromboembolism Study, 1999-2003, 1,142 patents presented with isolated DVT and 549 with PE (with or without DVT). Among those with DVT, 5.1% had subsequent PE, 17.9% recurrent VTE and 29.6% died during three years of follow-up. Among those with PE, 5.9% had recurrent PE, 15% recurrent VTE and 35.3% died during three years of follow-up [Spencer 2008].

In the absence of prophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10 to 40% among medical or general surgical patients and 40 to 60% following major orthopaedic surgery. It is estimated that one-quarter to one-third of these thrombi involve the proximal deep veins which are more likely to produce symptoms and to result in PE [Geerts 2004]. However, as the clinical presentation of PE is quite variable many cases of PE go unrecognized. Autopsy studies continue to show that most cases of fatal PE are unrecognized and undiagnosed. In addition, studies of

postoperative patients or patients with DVT that screen for PE have also found that many patients with PE are asymptomatic and that the PE is often unrecognized [Ryu, 1998].

Demographics of the target population – age, sex, race/ethnic origin (VTE)

Incidence increased steadily with age across studies and was similar in men compared to women. Some studies reported a higher incidence of VTE among women during reproductive years, [Ho 2008] but rates were generally similar by sex in older age.

VTE is extremely rare in childhood; a study in the Netherlands (1997-8) focused on the pediatric population found VTE incidence to be between 1.1-1.4 per 100,000 in children ages 0-18 years [van Ommen 2001], and only 0.5 per 100,000 when excluding neonates [Cheuk 2004]. In the United States, between 1979 and 2001, 64,000 children [4.2/100,000 children/year] were diagnosed at hospital discharge with DVT and 13,000 [0.9/100,000 children/year] were diagnosed with PE based on data from the National Hospital Discharge Survey.

The total number of children with VTE [DVT and/or PE] was 75,000 [4.9/100,000 children/year (based on yearly census estimates) [Stein 2004].

The rates were higher during the neonatal period [DVT 8.7/100,000/year and PE 2.2/100,000/year] and during adolescence, especially in girls, [DVT 9.9/100,000/year and PE 2.0/100,000/year] compared to children age 2 to 14 years [DVT 2.1/100,000/year and PE 0.4/100,000/year]. Black children had approximately twice the rates as white children [Stein 2004]. An estimated 95% of VTEs in children are secondary to serious conditions such as cancer, trauma/surgery, congenital heart disease, and systemic lupus erythematosus [Monagle 2004].

Three studies in the US in adults reported incidence by ethnicity. In a large study of VTE in the state of California, White et al. [White 2005] found VTE incidence was highest among blacks (138 per 100,000) and lower among Hispanics and Asian/Pacific Islanders (61 and 29 per 100,000 respectively) compared to whites (103 per 100,000). When considering only idiopathic VTE, the incidence among blacks was only 11% higher than whites, which was not statistically significant. In a state-wide study of racial differences in PE in New Jersey, [Schneider 2006] PE incidence was 47% higher among blacks compared to whites (53.64 vs. 36.47 per 100,000), and among females it was 62% higher (61.53 vs. 37.96 per 100,000). An older study of Medicare claims also found PE incidence to be higher among blacks compared to whites [Kniffin 1994].

Risk factors for the disease (VTE)

Approximately 25% of VTE's are idiopathic without any identifiable underlying cause. Strong risk factors (OR >10) for VTE include fracture (hip or leg), hip or knee replacement, major general surgery, major trauma and spinal cord injury. Moderate risk factors (OR 2-9) include arthroscopic knee surgery, central venous lines, chemotherapy,

congestive heart or respiratory failure, hormone replacement therapy, malignancy, oral contraceptive therapy, paralytic stroke, pregnancy/postpartum, previous VTE, and thrombophilia. Weak risk factors (OR <2) for VTE include bed rest >3 days, immobility due to sitting, increasing age, obesity, and varicose veins [Anderson 2003].

Risk factors specifically for DVT include immobility, surgery (particularly orthopaedic), malignancy, pregnancy, older age, and inherited or acquired prothrombotic clotting disorders [McManus 2011].

Main treatment options (VTE)

Treatment options for VTE are dependent on disease phenotypes and severity of symptoms. For example, pharmacological interventions include a choice of low molecular weight heparin (LMWH) or fondaparinux to patients with confirmed proximal DVT or PE [NICE clinical guideline 144; guidance.nice.org.uk/cg144 NHS]. There are newer oral anticoagulant agents such as dabigatran, apixaban and rivaroxaban available, for which guidelines are being considered. In the VTE Swiss registry, the following VTE therapies were given, some differing significantly by age (*) [Spirk 2012]:

Table 3 VTE Therapy

Inpatient therapy, n (%)	800 (64.2)*
Compression therapy, n (%)	1'031 (82.7)*
IVC filter, n (%)	20 (1.6)
UFH or LMWH, n (%)	1'200 (96.2)
Vitamin K antagonist, n (%)	970 (77.8)
Planned duration of anticoagulation	
≤3 months, n (%)	198 (15.9)*
3–6 months, n (%)	483 (38.7)
6–12 months, n (%)	243 (19.5)
12 months or indefinitely, n (%)	323 (25.9)*

Under-utilization of VTE prophylaxis among hospitalized patients is a global problem [Cohen 2008]. Without thromboprophylaxis, sensitive radiolabelling studies reveal evidence of subclinical DVT occurring in up to 60% of patients undergoing orthopaedic surgery, 15–40% undergoing major general surgery, and is a complication in as many as 20% of patients on a general medical ward [Geerts 2008]. A literature review showed that more than half and up to 70% of high risk hospitalized patients did not receive prophylactic VTE treatment [Khoury 2011].

Mortality and morbidity (natural history) [VTE]

In-hospital or 28-day mortality ranged from 3% [Kniffin 1994] to 10% [Tagalakis 2013] for DVT, 10% [Naess 2007] to 24% [Cheuk 2004] for PE and 6% [Naess 2007] to 14% [Tagalakis 2013] for VTE. Long-term mortality (1 year to 3.5 years) ranged from 21% [Kniffin 1994][Naess 2007] to 32% [Anderson 1991] for DVT, 23% [Naess 2007] to

39% [Kniffin 1994] for PE, and 22% [Naess 2007] to 29% [Tagalakis 2013] for VTE. One study in India found a 50% mortality rate for PE although among a subset that included only confirmed PE cases, mortality was 14% [Lee 2009]. A prospective study of VTE in two community-based cohorts found mortality from idiopathic DVT or PE to be 5%, 7% for secondary non-cancer DVT or PE, and 25% for secondary cancer-related DVT or PE Cushman 2004].

VTE mortality was 17% in the pediatric population [van Ommen 2001]. Mortality was higher in blacks compared to whites [White 2005] [Schneider 2006]. In a study of PE mortality using the US National Center for Health Statistics Compressed Mortality File, it was estimated that nationwide age-adjusted death rates, per 100,000, by gender and race as follows: white male 3.72, black male 7.80, white female 3.22, black female 6.44 [Schneider 2006].

Superficial-vein thrombosis (SVT)

Incidence and prevalence (SVT)

Superficial-vein thrombosis is a common condition; however, its incidence remains to be determined. It is estimated that superficial-vein thrombosis occurs in 3-11% of the general population, which is approximately 2 fold higher than that of DVT or PE combined [Decousus, 2012]. The prevalence of superficial-vein thrombosis is likely underestimated because symptoms can be mild and patients may not present for medical attention. Information on the prevalence and incidence of SVT in the general population is limited.

A landmark study [Coon 1973] examined the frequency of SVT and VTE in a population-based longitudinal study in Michigan (Table 4) SVT was detected by physical examination in combination with self-reported symptoms and history. The overall cumulative prevalence of SVT was 0.5% among males and 0.9% among females. Among ages ≥70 years, the prevalence was 3.2% among both males and females. The incidence of first-time and any SVT events, per 100,000, increased with age ranging from 4 among ages 10-19 years to 333 among ages 70-79 years. Rates were generally higher among females. The authors noted in their discussion that the true frequency of SVT is likely much higher than recorded since many events are likely forgotten by subjects as a minor condition.

Table 4 Cumulative prevalence (%) adapted from Coon et al 1973

Age	SVT	Any varicose veins	Varicose veins 2+ or greater	Varicose ulcer active or healed
10-19y	M 0, F 0	M 0, F 0.1	M 0, F 0	M 0, F 0
20-29y	M 0, F 0.2	M 0.9, F 8.0	M 0.2, F 3.5	M 0, F 0
30-39y	M 0.4, F 0.7	M 6.7, F 26.4	M 3.9, F 14.8	M 0, F 0
40-49y	M 0.6, F 1.7	M 23.7, F 41.3	M 12.5, 24.7	M 0.2, F 0.2
50-59y	M 1.7, F1.6	M 36.3, F 53.4	M 20.0, F 36.9	M 0.3, F 1.2
60-69y	M 1.7, F 2.6	M 43.4, F 72.1	M 28.0, F 53.7	M 0.6, F 2.1
70+	M 3.2, F 3.2	M 56.8, F 76.8	M 36.8, F 58.1	M 0, F 0
Total	M 0.5, F 0.9	M 12.9, F 25.9	M 7.4, F 16.7	M 0.1, F 0.3

Table 5 Incidence of first-time and any SVT event per 100,000 by age and gender (adapted from Coon 1973)

Age	First-time SVT events	All SVT events
10-19y	M 4, F 0	M 4, F 0
20-29y	M 5, F 31	M 5, F 39
30-39y	M 13, F 51	M 20, F 79
40-49y	M 69, F 76	M 80, F 134
50-59y	M 45, F 59	M 110, F 147
60-69y	M 164, 120	M 156, F 446
70-79y	M 182, F 223	M 333, F 202
80-89y	M 0, F 0	M 0, F 0

In the US, in a large, multi-ethnic sample of 2,211 men and women in San Diego, California, [Criqui, 2003] the estimated prevalence of major manifestations of chronic venous disease, including superficial and deep functional disease, using four visible and three functional categories. SVT was assessed using duplex ultrasound of five regions of each leg- thigh, knee, calf, ankle, and foot, as well as interview questions regarding history of "a blood clot in a leg vein" and "phlebitis or inflamed vein in your leg."

Table 6 Prevalence (%) of visible and functional chronic venous disease by gender age and ethnicity (adapted from Criqui 2003)

	Visible Disease				Functional Disease		
	Normal	Spider veins	Varicose veins	Trophic changes	Normal	Superficial functional disease	Deep functional disease
Overall	19.0	51.6	23.3	6.2	72.1	19.0	9.0
Male	33.6	43.6	15.0	7.8	75.6	13.1	11.3
Female	11.0	55.9	27.7	5.3	70.1	22.2	7.8
<50y	33.0	47.9	16.9	2.3	81.8	11.2	6.9
50-59y	22.5	52.8	20.7	4.0	78.0	14.5	7.6
60-69y	12.4	52.8	26.0	8.8	66.1	23.5	10.4
70+y	7.4	52.5	29.9	10.2	61.3	27.3	11.3
White	14.3	54.8	24.0	6.9	69.7	20.0	10.3
Hispanic	18.9	50.0	26.3	4.7	71.0	22.8	6.2
Black	27.7	45.3	20.8	6.3	76.7	16.4	6.9
Asian	31.1	45.4	18.7	4.8	78.8	12.5	8.8

The overall prevalence of superficial events was 2.4% (male 1.5%, female 2.8%). SVT was nearly twice as prevalent in women compared to men. The prevalence of superficial events by race/ethnicity was as follows: non-Hispanic white 2.6%, Hispanic, 3.6%, African-American 0.9%, Asian 1.5%. Age-specific rates showed a prevalence of 2.1% in subjects <50 years of age, 2.5% in 50-59 year category, 2.2 in 60-69 year category and 2.7% in 70+ age category [Criqui 2003].

Three studies in Italy studied the frequency of SVT in relation to VTE. The first estimated the prevalence of SVT in a primary care setting among the 774 VTE cases to be 6.6%, and among the 7,740 non-VTE controls to be 4.5% Cimminiello2010]. In analyses adjusted for concurrent diseases and previous hospitalization, SVT was not associated with increased risk for VTE, though other studies have shown an association [Decousus 2012].

Another Italian study [Di Minno 2005] assessed the self-reported history of SVT among patients consulting their general practitioner for a health disorder. Participating general practitioners enrolled two patients per day for five consecutive days and interviewed patients on history of VTE risk factors including SVT. The overall age-adjusted prevalence of SVT was 4.9% among males and 10.8% among females. Age-specific prevalence was as follows: 18-45 years: 2.8% male, 4.2% female; 46-74 years: 6.2% males, 14.5% female; ≥75 years: 12.1% males, 23.8% females.

A third study [Tosetto 2003] from Italy randomly selected 15,055 residents of Vicenza aged 18-65 years and screened for history of VTE using a validated questionnaire that included history of SVT. In the population without any history of VTE, prior SVT was prevalent in 3.6% (n=546/14,939). Among subjects with history of VTE, history of SVT was prevalent in 20%.

Recent review [Decousus 2012] summarized the relationship between SVT and VTE. Studies have shown that 6-36% of patients with SVT exhibit DVT on systematic ultrasonography evaluation and up to 33% of SVT patients show concomitant PE on systemic lung scan evaluation. The authors suggest the coexistence of SVT and VTE might be explained by the migration of the SVT towards the deep venous system via the saphenofemoral junction, the sapheno-popliteal junction or a perforating vein.

It has been shown that SVT is a risk factor for the development and recurrence of DVT or PE [Leon 2005 (a), Decousus 2010, van Langevelde 2011]. In particular the MEGA study showed that among 4,956 consecutive patients with DVT or PE, the presence of SVT before onset of DVT and/or PE onset substantially increased the risk of recurrent DVT (OR: 6.3; 95%CI: 5.0-8.0) as well as PE (OR: 3.9; 95%CI: 3.0-5.1) [van Langevelde 2011].

In the French epidemiological POST study (N=844 superficial-vein thrombosis patients), concomitant DVT and/or symptomatic PE was present in 24.9% of patients [Decousus, 2010]. Proximal DVT was diagnosed in 9.7% and symptomatic PE in 3.9%. Extension of ST to perforating veins, recent hospitalization/ immobilization, auto-immune disease, age >=75 years, personal history of VTE, distance between the thrombus and sapheno-femoral junction ≤ 3 cm, involvement of at least 2 superficial veins, and no varicose veins and venous insufficiency were all found to be independent risk factors for concomitant VTE in patients with superficial-vein thrombosis.

Furthermore, patients with acute, isolated superficial-vein thrombosis (i.e. without concomitant DVT or PE at presentation) are at risk of symptomatic VTE even when receiving some form of active treatment [Quenet, 2003; Decousus, 2010; The STENOX Study Group, 2003; The VESALIO Investigators Group, 2005].

In the POST study, among the 586 isolated superficial-vein thrombosis patients, 8.3% experienced a symptomatic thromboembolic event at 3 months [DVT – 2.8%; PE – 0.5%; recurrence of superficial-vein thrombosis -1.9%; extension of superficial-vein thrombosis – 3.3%] despite simultaneous treatment with anticoagulants and compression stockings.

Male gender, history of cancer and a history of VTE were independent risk factors for the occurrence of VTE at 3 months [Decousus, 2010].

Demographics of the target population – age, sex, race/ethnic origin (SVT)

See incidence and prevalence section above.

Risk factors for the disease (SVT)

Many factors are common to both SVT and DVT [Leon 2005(a), Decousus 2010, Di Minno 2005] including age, previous thromboembolic episodes, pregnancy, oral contraceptives, hormone replacement therapy, prolonged flights, immobilization, recent surgery, trauma, obesity, sclerotherapy, auto-immune disease and thrombophilia. However, varicose veins, present in 80-90% of subjects with SVT, appear to be a major predisposing factor [Decousus 2012].

Main treatment options (SVT)

SVT diagnosis is based principally on clinical assessment, but the use of duplex ultrasound imaging (DUS) has enabled accurate detection of the extent and progress of the condition [Leon 2005(b)]. Treatment options available for SVT include ambulation, surgery, elastic stockings, anti-inflammatory agents and anticoagulants [Leon 2005(b), Wichers2005]. In the POST study, 91.5% of patients with isolated SVT received one or more anticoagulant drugs, mainly LMWH; 47.2% received topical NSAIDs and 8.2% oral NSAIDs. [Decousus 2010]. Recently, Fondaparinux once-daily 2.5mg was added to the treatment options or at a reduced dose of 1.5mg daily in special populations e.g. hepatically impaired patients.

Mortality and morbidity (natural history) [SVT]

SVT has long been regarded as a benign condition; however, several studies showed that SVT is associated with increased risk of VTE [Decousus 2012]. The 3-month mortality for SVT has been estimated to range from 0-1%.

Acute Coronary Syndromes (ACS)

Incidence and prevalence (ACS)

ACS refers to a spectrum of acute ischemic conditions including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). In the US an estimated number of 1,190 000 unique hospitalizations for ACS were documented in 2009; 694 000 were males, and 496 000

were females. Of the total, 829 000 were for MI alone, 357 000 were for UA alone, and 4000 hospitalizations received both diagnoses [Roger 2012].

The overall diagnosed event rate of ACS ranges from 0.4 per 1,000 per year in Japan to 6.9 per 1,000 per year in Germany in 2010. The diagnosed event rate of STEMI ranges from nearly 0.2 per 1,000 per year in Japan to 1.6 per 1,000 per year in Germany. Germany also has the highest diagnosed event rate of NSTEMI, 3.2 per 1,000 per year, followed by the United Kingdom at 2.1 and France at 2.0. The diagnosed event rate of UA in 2010 ranges from 0.2 per 1,000 per year in Japan to 2.1 per 1,000 per year in Germany [Cardium Study, 2012].

The percentage of ACS or MI cases with ST-segment elevation varies in different registries/databases and depends heavily on the age of patients included and the type of surveillance used. According to the National Registry of Myocardial Infarction 4 (NRMI-4), ~29% of patients with MI are patients with STEMI [Roe 2005]. The Global Registry of Acute Coronary Events (GRACE) study, which includes US patient populations, found that 38% of ACS patients have STEMI, whereas the second Euro Heart Survey on ACS (EHS-ACS-II) reported that ~47% of patients with ACS have STEMI [Mandelzweig 2006].

In addition, the percentage of ACS or MI cases with ST-segment elevation appears to be declining. In an analysis of 46 086 hospitalizations for ACS in the Kaiser Permanente Northern California study, the percentage of MI cases with ST-segment elevation decreased from 48.5% to 24% between 1999 and 2008 [Yeh 2010].

Demographics of the target population – age, sex, race/ethnic origin (ACS)

Baseline characteristics, intervention, and outcomes in UA/NSTEMI and STEMI patients based on final ACS diagnosis in the GRACE registry are summarised in Table 7. The GRACE registry is a multi-national registry of ACS patients from over 100 hospitals in 14 countries in Europe, North America, South America, Australia and New Zealand.

Table 7 Characteristics of UA/NSTEMI and STEMI Patients Based on Final ACS Diagnosis

	UA [n=4,397]	NSTEMI [n=2,893]	STEMI [n=3,419]
Patients characteristics			
Median age (yrs)	66	68	64
Age >65 yrs (%)	57	60	51
Men (%)	62	67	72
Medical history			

	UA [n=4,397]	NSTEMI [n=2,893]	STEMI [n=3,419]
Prior angina (%)	49	67	82
Prior MI (%)	41	33	19
Prior heart failure (%)	14	14	7
Diabetes (%)	25	27	21
Hypertension (%)	65	59	50
Hyperlipidaemia (%)	51	42	35
Current smoker/ history of smoking (%)	54	57	62
In hospital Procedures			
PCI (%)	18	28	40
CABG (%)	5	10	4
Select Pharmacologic treatments during hospital stay			
Glycoprotein IIb/IIIa inhibitors (%)	7	20	23
Calcium blockers (%)	38	29	15
Aspirin (%)	90	91	95
β-blockers (%)	74	78	81
ACE inhibitors (%)	50	55	66
Unfractionated heparin (%)	47	61	66
Hospital Outcome			
Death (%)	3	5	7

1. Data from GRACE registry [Steg, 2002]

The annual rate of first heart attacks increases with age is higher in males compared to females and also higher in subjects of black compared to white origin (Atherosclerosis Risk in Communities Surveillance: 1987-2004) [Roger 2011].

Risk factors for the disease (ACS)

The risk factors for ACS are well described including history of diabetes, hypertension, high lipid levels (cholesterol, LDL), smoking, obesity, limited or lack of physical activity, inflammatory markers such as CRP, prior cardiovascular events.

Main treatment options (ACS)

Temporal changes and improvements in the management of ACS patients, through both pharmacologic and intervention treatments, were found to be associated with significant reductions in the rates of cardiovascular-related outcomes, such as in-hospital death, new heart failure, and MI at 6 months; these improvements were more dramatic in STEMI patients [Fox, 2007].

Among STEMI patients between 1999 to 2005, the use of β-blockers, statins, ACE inhibitors/(ARBs), LMWH, thienopyridine, and glycoprotein IIb/IIIa antagonists increased by 11%, 48%, 22%, 20%, 49%, and 24%, respectively and the use of UFH and fibrinolytic therapy declined by nearly 20%. The rate of cardiac catheterization and PCI increased from 31% to 37%. The in-hospital death rates declined by 3.9%, cardiogenic shock by 2.4%, and in-hospital congestive heart failure or pulmonary edema decreased by 9.0%. The rate of MI diagnosed > 24 hours after hospital presentation and the rate of recurrent MI declined by 1.6%, and the 6-month MI rate decreased by 2.8% [Fox, 2007].

Among NSTEMI/UA patients between 1999 to 2005, the use of β-blockers, statins, ACE inhibitors/ARBs, LMWH, thienopyridine, and glycoprotein IIb/IIIa antagonist increased by 10%, 42%, 23%, 23%, 51%, and 11%, respectively, and the use of UFH and calcium channel blockers decreased by 19% and 12%. The rate of cardiac catheterization and PCI procedures increased nearly 20% from 1999 to 2005. The rate of in-hospital death and in-hospital congestive heart failure or pulmonary edema declined by 0.7% and 6.5% respectively. The rate of MI diagnosed > 24 hours after hospital presentation and the rate of recurrent MI decreased by 1.3%. The 6-month mortality rate declined by 1.6% [Fox, 2007].

Mortality and morbidity (natural history)

Worldwide cardiovascular diseases are the leading cause of death (29%) 32% of all death in women and 27% of all death in men. Ischemic heart disease accounting for 12% of all deaths (~7.2 mio) similarly in men and woman or 2.2 mio deaths in Europe [WHO 2004]. The information can be found broken down by country on the WHO website [WHO2004].

In the US, the frequency, morbidity and mortality of ACS can be found in the Heart and Stroke statistics publication, which is updated every year [Go 2013].

Analysis of data from the GRACE multinational observational cohort study of patients with ACS found evidence of a change in practice for both pharmacological and interventional treatments in patients with either STEMI or non–ST-segment– elevation ACS. These changes have been accompanied by significant decreases in the rates of in-hospital death, cardiogenic shock, and new MI among patients with non–ST-segment–

elevation ACS. The use of evidence-based therapies and PCI interventions increased in the STEMI population. This increase was matched with a statistically significant decrease in the rates of death, cardiogenic shock, and heart failure or pulmonary oedema [Fox 2007].

After adjustment for clinical differences and the severity of CAD by angiogram, 30-day mortality is similar in men and women [Berger 2009].

A clinical risk prediction tool, developed from GRACE data, for estimating the cumulative 6-month risk of death and the combined end-point of death or MI in patients with ACS found that nine factors independently predict death and the combined endpoint of death or MI. These factors include age; a previous medical history of congestive heart failure and/or peripheral vascular disease; systolic blood pressure, Killip class, initial serum creatinine concentration, positive initial cardiac markers, and cardiac arrest on presentation; and the number of leads with ST deviation by electrocardiography [Fox, 2006].

SI.2 Concomitant medication(s) in the target population

Medication use among VTE, SVT and ACS patients has been assessed using the CPRD (UK) during 2012 by drug class. The 20 most frequent concomitant medication classes in 2012 among persons diagnosed with VTE, SVT or ACS are presented in Table 8, Table 9 and Table 10. Overall, the most frequently prescribed concomitant medications in VTE and SVT subjects include non-opioid analgesics, proton pump inhibitors and statins and in ACS subjects statins, antiplatelet drugs and beta-adrenoceptor blocking agents.

Table 8 20 Most Common Concomitant Medications for a VTE Cohort (CPRD 2012)

Medication Class	Male N= 23362 % Exposed	Females N= 32606 % Exposed
Non-opioid analgesics	38.65	49.21
Proton pump inhibitors	34.33	39.53
Statins	40.9	31.88
Opioid analgesics	29.09	37.51
Broad-spectrum penicillins	23.38	26.84
Oral anticoagulants	29.63	20.62
Angiotensin-converting enzyme inhibitors	27.33	20.91
Antiplatelet drugs	25.39	20.39
Corticosteroids (for respiratory conditions)	17.73	22.17
Non-steroidal anti-inflammatory drugs	17.06	22.05
Calcium-channel blockers	20.5	18.73
Beta-adrenoceptor blocking drugs	21.06	18.21
Selective beta 2 agonists	16.03	20.42
Loop diuretics	14.42	17.01
Vitamin d	7.17	18.6

Medication Class	Male N= 23362 % Exposed	Females N= 32606 % Exposed
Osmotic laxatives	11.58	14.65
Selective serotonin re-uptake inhibitors	9.1	15.91
Glucocorticoid therapy	10.8	13.88
Topical corticosteroids	12.46	12.52
Macrolides	9.9	13.75

Table 9 20 Most Common Concomitant Medications for a SVT Cohort (CPRD 2012)

Medication Class	Male N= 8096 % Exposed	Females N= 3650 % Exposed
Non-opioid analgesics	34.25	45.87
Proton pump inhibitors	31.73	37.12
Statins	36.68	28.15
Opioid analgesics	23.51	32.18
Broad-spectrum penicillins	22.55	25.9
Non-steroidal anti-inflammatory drugs	20.33	25.58
Angiotensin-converting enzyme inhibitors	26.25	20.42
Antiplatelet drugs	25.04	20.08
Calcium-channel blockers	20.6	19.49
Corticosteroids (for respiratory conditions)	15.67	19.74
Beta-adrenoceptor blocking drugs	19.51	17.3
Selective beta 2 agonists	13.53	17.17
Topical corticosteroids	13.78	15.07
Thiazides and related diuretics	9.64	16.24
Vitamin d	4.99	16.85
Penicillinase-resistant penicillins	12.88	13.11
Loop diuretics	11.34	13.62
Glucocorticoid therapy	10.36	13.19
Topical nsaids and counter irritants	8.05	13.75
Macrolides	9.37	13.01

Table 10 20 Most Common Concomitant Medications for an ACS Cohort (CPRD 2012)

Medication Class	Male N= 53730 % Exposed	Females N= 26110 % Exposed
Statins	88.57	80.51
Antiplatelet drugs	82.6	78.06

Medication Class	Male N= 53730 % Exposed	Females N= 26110 % Exposed
Beta-adrenoceptor blocking drugs	67.42	60.74
Angiotensin-converting enzyme inhibitors	60.1	47.77
Proton pump inhibitors	46.18	55.11
Non-opioid analgesics	41.75	58.15
Nitrates	41.26	45.29
Hypertension and heart failure	39.91	37.17
Opioid analgesics	28.38	40.97
Calcium-channel blockers	28.9	32.89
Broad-spectrum penicillins	25.38	29.88
Loop diuretics	20.12	31.18
Corticosteroids (for respiratory conditions)	17.17	23.9
Selective beta 2 agonists	16.09	22.4
Angiotensin-ii receptor antagonists	16.18	20.84
Non-steroidal anti-inflammatory drugs	16.17	18.28
Management of myocardial infarction	16.42	14.79
Osmotic laxatives	12.77	19.68
Biguanides	15.7	12.5
Topical corticosteroids	12.14	13.31

SI.3 Important co-morbidities found in the target population

Patients with VTE or ACS frequently have co-morbid conditions many of which are often predisposing risk factors for the condition being treated. These risk factors are described above in Section SI.1, risk factors for VTE or ACS, respectively.

Among SVT patients, in addition to the predisposing risk factors, the most common comorbidities are concomitant DVT and PE. For example, among SVT patients, 6-53% have concomitant DVT, and suspected PE has been described in 0-10%. See section SI.1, risk factors for SVT.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The content of this module has been omitted due to the mature nature of the product and extensive clinical safety experience.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

This section is omitted in accordance with GVP Module 5 (Risk Management Systems), V.C.3.1.f. The content of this module has been omitted because the product meets the following criteria:

- The product was placed on the market 10 or more years, before the requirement for an RMP is established and
- The requirement for an RMP is not due to an application for a significant change to an existing marketing authorisation

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

This section is omitted in accordance with GVP Module 5 (Risk Management Systems), V.C.3.1.f. The content of this module has been omitted because the product meets the following criteria:

- The product was placed on the market 10 or more years, before the requirement for an RMP is established and
- The requirement for an RMP is not due to an application for a significant change to an existing marketing authorisation

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

No actions have been taken for safety reasons concerning withdrawal, revocation, rejection, suspension or failure to obtain a renewal of a Marketing Authorisation; neither have there been any dosage modifications, changes in target population, formulation changes, or clinical trial suspension since last EU RMP update.

Table 11 Cumulative list of actions taken by regulatory authorities and/or marketing authorisation holders for safety reasons

Safety concern 1: Adverse events reported in patients receiving fondaparinux in a manner not consistent with the marketing authorization was identified as an area of concern following a review of national pharmacovigilance data by AFSSAPS			
Country(ies)	Action taken	Comment	Date(s)
France	A Dear Healthcare Provider Letter (DHCPL) was distributed in France to inform physicians of the serious bleeding complications reported in association with the use of fondaparinux for unauthorised indications.	Further detail in PSUR 10 (UM2007/00250/00)	8 June 2007
Safety concern 2: OASIS 8 placed on 'full clinical hold' by the US FDA			
Country(ies)	Action taken	Comment	Date(s)
USA	A number of changes were made to the presentation of ACS clinical trial data in the fondaparinux investigator brochure. Since the application to register the ACS indication was still under review in the US, the FDA had requested these changes to further clarify that use in this indication was investigational. 'Clinical Hold' was lifted on 16 Sep 2009, and recruitment was initiated in the US.	Further information can be found in PSUR 15 (UM2010/00011/00)	13 May 2009

Safety concern 3: OASIS 8 urgent protocol amendment			
Country(ies)	Action taken	Comment	Date(s)
EU Trial sites	Updated practice guidelines were included in the study protocol to further ensure the safety of subjects, specifically during angiography and Percutaneous Coronary Intervention (PCI).	Further information can be found in PSUR 15 (UM2010/00011/00)	31 July 2009
Safety concern 4: Request from US FDA to update the US Prescribing Information			
Country(ies)	Action taken	Comment	Date(s)
USA	USPI updated to include warning that there is an increased risk for bleeding in paediatric patients. The USPI Boxed Warning for spinal/epidural hematomas was updated to indicate that there is an increased risk in patients with a history of spinal deformity or spinal surgery.	None	19 August 2009 13 November 2009

SV.2 Non-study post-authorisation exposure

SV.2.1 Method used to calculate exposure & cumulative exposure

Global Cumulative Exposure

Exposure estimates are based upon IMS Health sales data for the period 01 October 2001 to 30 September 2013. Approximately 112.3 million 2.5 mg and 1.5mg syringes and 51.5 million 5 mg, 7.5 mg, 10 mg and 12.5mg syringes were sold. According to the once-daily administration of fondaparinux, whatever the indication, the number of defined daily doses sold was about 163.7 million.

The average duration of therapy for prophylaxis with 1.5mg and 2.5 mg fondaparinux is approximately:

- 14 days in the European Union
- 15 days in the USA and
- 13 days in the rest of the world.

Therefore, to calculate patient exposure, 14 days of therapy will be used as has been done for the fondaparinux PSURs/PBRERs.

Similarly, exposure for curative (DVT/PE) treatment is based on a mean treatment duration of 7 days, as noted in the European summary of product characteristics.

In summary, based on sales figures from 01-October 2001 to 30-September-2013, it is estimated that approximately 8.0 million patients received prophylaxis therapy and 7.1 million patients received curative therapy worldwide. This brings the global cumulative exposure to 15.1 million patients.

Please note: IMS calculates exposure based on dosage assumptions. Therefore, indications which have the same doses (i.e. 2.5 mg for VTE prophylaxis s. Treatment of ACS or treatment of superficial vein thrombosis) cannot be differentiated.

Exposure by Indication in the EU

Since fondaparinux for the treatment of acute coronary syndrome (ACS) is limited strictly to use in hospital, IMS data cannot be used to accurately estimate use in this patient population. Therefore, hospital sales data from a number of key countries across the EU and emerging markets have been used to estimate market exposure for the ACS patient population. Key countries were considered those where GSK currently promotes fondaparinux and/or larger markets in which relevant sales information was available.

To estimate the market exposure for the treatment of ACS in Europe, the following assumptions have been made:

- The use of fondaparinux for the treatment of ACS in key countries across the EU is reflective of overall use.
- Available sales data represent approximately 95% of fondaparinux utilization in hospitals in Europe for treatment of ACS
    - The average treatment for ACS in Europe is estimated to be approximately 3.5 syringes per patient.
    - Approximately 8% of the fondaparinux hospital sales in Europe are estimated to be in ACS patients.

In summary, based on sales figures from 01 Oct 2012 to 30 Sep 2013, it is estimated that approximately 81,299 patients in Europe have received therapy with fondaparinux for the treatment of ACS.

In addition, fondaparinux is currently used for the treatment of ACS in a number of countries outside of Europe. To estimate market exposure for the treatment of ACS in these countries, the following assumptions have been made:

- The use of fondaparinux for the treatment of ACS in key countries outside of the EU is reflective of overall use in regions outside of Europe.
- Available sales data represent approximately 75% of fondaparinux utilization in hospitals outside of Europe for the treatment of ACS.

- The average treatment for ACS in these non-European countries is estimated to be approximately 3.3 syringes per patient.
- Approximately 83% of the fondaparinux hospital sales in these non-European countries are estimated to be in ACS patients.

In summary, based on sales figures from 01 Oct 2012 to 30 Sep 2013, it is estimated that approximately 509,835 patients in countries outside of Europe have received therapy with fondaparinux for the treatment of ACS.

This brings the cumulative global exposure to approximately 1,545,823 patients for the treatment of ACS.

To estimate market exposure for patients receiving fondaparinux for the treatment of superficial vein thrombosis (SVT), IMS sales data from key countries across the EU where fondaparinux is promoted and/or known to be utilized for the treatment of SVT (i.e., Germany, Greece, Slovenia, France). The following assumptions have been made:

- Use of fondaparinux outside of these countries for the treatment of SVT is considered marginal.
- The average treatment for SVT in these four countries is estimated to be 30 syringes.
- Approximately 10% of the fondaparinux retail sales in these European countries is estimated to be for the treatment of SVT

In summary, based on sales figures from 01 Oct 2012 to 30 Sep 2013 it is estimated that approximately 20,739 patients in Europe have received therapy with fondaparinux for the treatment of SVT.

This brings the cumulative exposure in Europe to approximately 54,077 patients for the treatment of SVT.

SV.2.2 Other Exposure

The method for calculating the exposure in Table 12, Table 13, and Table 14 is outlined below:

- Time period: July 2010 to September 2013
- Rx (prescriptions) are prescriptions written by General Practitioners in office- apart from Japan where hospital data are included.
- Prescriptions are shown as absolute numbers.
- Regions for this report include: EU (Germany, France, Spain, Italy, and UK*); Other (USA, Japan*, Japan Hospital*, Argentina)
    - *Note that data for Japan are only up to June 2013 as it is only updated semi-annually at quarter 2 and quarter 4. Data for the UK are also only up to June 2013.

- Source: IMS Health Prescribing Insights Data

Table 12 Exposure by age group and gender

Indication: All			
Age Group	Rx Absolute		
	Male	Female	Unknown
1-23 months	0	0	0
2-11 years	0	0	0
12-18 years	5,270	3,660	0
19-64 years	449,581	507,306	1,305
65-74 years	279,075	326,993	11,292
75-84 years	206,721	521,287	0
85 + years	44,872	111,510	0
Unknown	3,939	7,749	29,572

Table 13 Exposure by dose

Indication: All	
	Rx Absolute
≤ 2.5 mg	1,714,688
> 2.5 mg	735,582
Unknown	125,411

Table 14 Exposure by country

Indication: All	
	Rx Absolute
EU	1,786,425
Non-EU	723,707

SV.3 Post-authorisation use in populations not studied in clinical trials

Data are not available for the post-authorisation use in hepatic impairment, renal impairment, and pregnant or breast feeding women. See table above for data regarding paediatric patients (Table 12, Exposure by Age Group and Gender).

SV.4 Post-authorisation off-label use

Reports of off-label use are monitored as part of routine pharmacovigilance, and are described annually in the PSUR/PBRER. Post-authorisation off-label use with fondaparinux has been followed closely since it was first identified as a risk in 2007. Below are the reporting rates of post-authorisation off label use available since December 2008, when these were first calculated for the PSUR.

In order to identify cases reported in the setting of off-label use, spontaneous reports received for each PSUR/PBRER reporting period were systematically reviewed utilizing data coded in the MAH Safety Database and were further assessed utilizing the fondaparinux Global Data Sheet (i.e. country specific labeling was not taken into consideration). Reports were categorized as off-label when information related to the following was reported: use in unapproved indications, inappropriate indication/dose combination, or adverse event (AE) term representative of off-label use (e.g., Off-label use, Use beyond labeled duration, Incorrect drug administration duration, Incorrect dose administered).

As shown in Table 15 and Table 16 below, the majority of spontaneous reports classified as either on-label or off-label received during the respective PSUR/PBRER reporting periods was associated with haemorrhagic adverse events. In addition, the percentage of serious reports with a fatal outcome is consistent for cases classified as off-label vs. on-label.

MAH will continue to monitor reports of off-label use with fondaparinux as part of routine pharmacovigilance practices and discuss annually in the PSUR/PBRER.

Table 15 Summary of spontaneous reports received between 07 Dec 2008 and 06 Dec 2010 classified as haemorrhage or non-haemorrhage and on-label or off-label

	PSUR 14/15 (07 Dec 2008 to 06 Dec 2009)			PSUR 16 (07 Dec 2009 to 06 Dec 2010)		
Category	Number	Serious	Fatal	Number	Serious	Fatal
Off-Label Use Reporting rate	N=245 1/8,745[1]	63%	11%	N=232 1/11,129[2]	60%	10%
Non-haemorrhage	N=112	41%	4%	N=103	29%	8%
Haemorrhage	N=133	81%	16%	N=129	84%	12%
On-Label Use Reporting rate	N=657 1/3,261[1]	68%	7%	N=496 1/5,205[2]	70%	12%
Non-haemorrhage	N=262	53%	8%	N=201	56%	16%
Haemorrhage	N=395	79%	7%	N=295	80%	8%
Total	902	603	75	728	486	81

1. Reporting rate based on estimated global exposure 2,142,618 patients.
2. Reporting rate based on estimated global exposure 2,581,846 patients

Source: PSUR # 16 MAH document # 2010N111162_00

Table 16 Summary of spontaneous reports received between 07 Dec 2010 and 06 Dec 2013 classified as haemorrhage or non-haemorrhage and on-label or off-label

	PSUR 18[1] (07 Dec 2010 to 06 Dec 2011)			PSUR 20[4] (07 Dec 2011 to 06 Dec 2012)			PSUR 21[5] (07 Dec 2012 to 06 Dec 2013)		
Category	Number	Serious	Fatal	Number	Serious	Fatal	Number	Serious	Fatal
Off-Label Use Reporting rate	N=184 1/14,537[2]	60% (111/184)	12% (22/184)	N=154 1/15,255[3]	64% (99/154)	12% (19/154)	N=194 1/11,057[5]	63 % (122/194)	13% (25/194)
Non-haemorrhage	N=89	38% (34/89)	9% (8/89)	N=65	31% (20/65)	5% (3/65)	N=83	35% (29/83)	11% (9/83%)
Haemorrhage	N=95	81% (77/95)	15% (14/95)	N=89	89% (79/89)	18% (16/89)	N=111	84% (93/111)	14% (16/111)
On-Label Use Reporting rate	N=568 1/4,709[2]	67% (378/568)	11% (63/568)	N=435 1/5,401[3]	67% (290/435)	16% (69/435)	N=429 1/4,999[5]	30% (120 /429)	10% (41/429)
Non-haemorrhage	N=234	53% (124/234)	12% (29/234)	N=227	53% (121/227)	16% (37/227)	N=225	53% (120/225)	20% (41/225)
Haemorrhage	N=334	76% (254/334)	10% (34/334)	N=208	81% (169/208)	15% (32/208)	N=204	83% (176/204)	10% (21/204)
Total	728	490	84	589	389	88	623	418	87

1. PSUR#17 describes data received between 07 Dec 2010 and 06 Jun 2011 and was prepared to meet regulatory requirements in countries outside of the EU. Data in PSUR#17 is entirely included in PSUR#18. As such, it has been omitted from this table
2. Reporting rate based on estimated global exposure 2,674,745 patients
3. Reporting rate based on estimated global exposure 2,349,319 patients
4. PSUR#19 describes data received between 07 Dec 2011 and 06 Jun 2012 and was prepared to meet regulatory requirements in countries outside of the EU. Data in PSUR#19 is entirely included in PSUR#20. As such, it has been omitted from this table.
5. Reporting rate based on estimated global exposure of 2,144,979 patients

Source: PSUR # 18 MAH document Number 2011N126845, PBRER MAH document Number 2013N159316, PBRER MAH document Number 2013N184216

SV.5 Targeted Safety Study Exposure

Since the first approval of fondaparinux in 2001, six targeted safety studies have been conducted. Summary details of these studies are provided in Table 17 and Table 18

Table 17 Epidemiological study exposure

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person time (if appropriate)	Comment
WEUSRTP2284 OnPAAR Evaluation of Physician Adherence to ARIXTRA (fondaparinux sodium) Prescribing Information in the Treatment of Acute Coronary Syndrome (ACS)	Evaluate physician adherence to prescribing information for use of fondaparinux in patients with a diagnosis of ACS (UA/NSTEMI or STEMI). Primary endpoint: proportion of patients with ACS treated with fondaparinux, for whom the prescribing information during PCI was followed	ACS patients treated with fondaparinux that undergo PCI 6 countries: Canada, Germany, Greece, France, Poland, Sweden	April 2008-April 2009	1056 patients	Completed
WEUSRTP4388 Risk of hemorrhage in patients treated with ARIXTRA compared to LMWH	To assess the risk of haemorrhage associated with fondaparinux sodium compared to LMWHs in patients hospitalized and	Hip fracture and hip/knee replacement patients	January 2003 to September 2008	13,442 Fondaparinux n=1,559 LMWH n=11,883	Completed

Study title and study type (e.g. cohort or case/control)	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person time (if appropriate)	Comment
	receiving VTE prophylaxis treatment for major orthopaedic surgery of lower limbs (MOSLL).				
WWE115280: WEUSKOP5233 Arixtra Physician Adherence to the Prescribing Information in isolated superficial vein thrombosis (SVT) Patients	Primary outcome will be a measure of physician adherence.	Superficial vein thrombosis (SVT) Patients	October 2013-December 2014	371 patients	Completed

Table 18 Targeted Safety Studies (Non-epidemiology)

Study	Subject Population	No. Subjects Randomised	Treatment Groups	Fondaparinux Daily Dose	Treatment Duration
0701017 – PROPICE (non-MAH, investigator-initiated study)	Prevention of VTE following MOSLL in patients with renal insufficiency (CrCl 20-50mL/min)	442 treated	Fondaparinux (non-comparative)	1.5mg SC	5-35 days
AR1108888 (FUTURA; OASIS 8)	UA/NSTEMI undergoing PCI	2026	Standard dose UFH vs. low-dose UFH as adjunct to PCI, in patients receiving fondaparinux	2.5mg SC	≤8 days
ART108651 – SWITCH III (non-MAH, investigator-initiated study)	ACS patients undergoing PCI	100	Bivalirudin vs. Standard dose UFH as adjunct to PCI, in patients receiving fondaparinux	2.5mg SC	Prior to coronary catheterization

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for harm from overdose

Since fondaparinux is supplied in a fixed dose pre-filled syringe, potential for overdose is thought to be low.

SVI.2 Potential for transmission of infectious agents

Fondaparinux is a synthetic agent. Therefore, the potential for transmission of infectious agents has not been identified for fondaparinux. Fondaparinux is supplied in pre-filled, single-use syringes. Due to the automatic needle protection system associated with the syringe, the risk for transmission of infectious agents arising from accidental needlestick injuries is thought to be low.

SVI.3 Potential for misuse for illegal purposes

Due to its mechanism of action, the potential for illegal use or abuse potential of fondaparinux is not expected.

SVI.4 Potential for medication errors

SVI.4.1 Description of medication errors during the clinical trial programme

Given the length of time fondaparinux has been on the market and the extent of post-marketing patient exposure, reports of medication errors during the clinical trial program have not been included in the RMP.

SVI.4.2 Preventive measures for the final product(s) being marketed

Since fondaparinux is supplied in a fixed-dose, pre-filled syringe, potential for medication errors is thought to be low.

Prevention of error due to wrong medication

Clear information on trade name, active substance and indication are provided throughout the product labeling.

External packaging features a different colour for each dose (1.5 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg).

Prevention of error due to wrong dose (strength, form, concentration)

Different doses are used for VTE prophylaxis (1.5, 2.5mg), superficial-vein thrombosis treatment (2.5mg), and VTE treatment (5, 7.5, 10mg). The SPC provides clear instruction on proper dosage according to indication for use. Additionally, external packaging features a different colour for each dose (1.5 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg).

In general, the potential for physicians to use the incorrect dose based on VTE indications for use (e.g. use treatment dose for a prophylaxis patient) is thought to be low. However, given the fact that higher doses of fondaparinux (5mg, 7.5mg, and 10mg) are indicated for the treatment of VTE, there is the potential for prescribers to use these higher doses for the treatment of superficial-vein thrombosis. Proper dosing instructions for the treatment of superficial-vein thrombosis are clearly provided in the SPC Section 4.2.

Prevention of error due to wrong route of administration

Statements throughout the SPC and patient information leaflet provide clear instructions on dosing, including pictorial guidance.

Fondaparinux is administered by subcutaneous injection for all indications, with the exception of the first dose in patients with STEMI, which is given intravenously.

The potential for physicians to use the wrong route of administration (e.g. give fondaparinux IV for VTE prophylaxis), is thought to be low. The SPC directs healthcare providers to corresponding guidance related to the indication and dosing and administration as appropriate for the indication they are treating. However, as the AUCs after IV and SC administration are similar, the potential for overdose when administered once daily is low.

SVI.4.3 Effect of device failure

Although the fondaparinux pre-filled syringe is not considered a device for regulatory reporting purposes, all product complaints received by MAH are evaluated by Quality Assurance (QA) and appropriate investigations carried out. Corrective actions are put into place if a complaint is found to be substantiated following investigation. Additionally, regular trend analysis is performed on all complaints received and any trends or patterns indicating potential technical issues are investigated and actioned appropriately. If at any time a complaint or trend indicates the potential for impact on human safety or efficacy then the Central Safety Department (CSD) is notified and the issue is evaluated by a multidisciplinary team in order to determine the appropriate course of action (eg. batch recall).

All product complaints associated with adverse events are notified to CSD within the pre-specified timeframes and recorded on MAH's global safety database. Adverse events coded with the term 'drug ineffective' are reviewed by the CSD on a monthly basis through MAH's Signal Management system. These reports are then individually investigated; therefore a potential manufacturing issue could be identified. However, because not all manufacturing defects will be recognised as such on receipt, the CSD is also alert to other coding terms that may indicate lack of efficacy (such as pulmonary embolism, DVT, thrombosis, etc.) or product complaint that may potentially indicate a manufacturing issue and these are also reviewed. Suspected manufacturing defects identified by CSD are reported to QA for evaluation and investigation to determine the appropriate course of action (as outlined above). Regulatory authorities are notified promptly if significant safety issues are identified.

SVI.4.4 Reports of medication errors with the marketed product(s)

Medication errors are followed in PSURs/PBRERs for fondaparinux. Reports of medication errors describe various situations including off-label use, use of fondaparinux in patients subject to special warnings/precautions for use (i.e., patients with renal insufficiency, patients who weigh <50kg), treatment non-compliance, incorrect site of injection, incorrect timing of dose (i.e., prior to surgery), incorrect dose (based on incorrect patient weight)/ under-dosing, incorrect frequency (i.e., more than once per day), accidental exposure, use of expired medication, drug dispensing error, and/or drug prescribing error. Many of these reports do not provide information concerning specific adverse events. Additionally, many describe overdose including accidental overdose, intentional overdose, and prescribed overdose (due to incorrect dosing, renal status not taken into consideration, or incorrect dose/indication combination). Overdose, accidental or prescribed, may lead to an increased risk of bleeding events.

Overall, review of cases of medication errors presented in the fondaparinux PSURs/PBRERs is not suggestive of new important safety information. Cases of medication errors will continue to be monitored through normal proactive phamacovigilance and reported in future PSURs/PBRERs.

SVI.5 Potential for off-label use

In clinical practice the population that may warrant VTE prophylaxis is likely to be broader than those groups indicated in the SPC. There are many potential reasons why physicians will decide to use a medication for an off-label indication or in a manner not described in the product labeling. This may be due to the physician's own positive experiences or a colleagues experiences with using a medication in an off label fashion.

It may also be due to educational programs, professional conferences, published case reports or clinical trials, or even professional guidance. For example, the 2008 ACCP

Antithrombotic and Thrombolytic Therapy Guidelines, which are generally recognized internationally, described several non-approved uses of anti-thrombotic agents:

- Grade 1C (strong) recommendations for the use of fondaparinux for patients undergoing, major thoracic surgery, major open urologic procedures, or major vascular surgery who have additional thromboembolic risk factors [Geerts, 2008].
- Grade 2C (weaker indication) recommendation for the use of fondaparinux for the treatment of patients experiencing Heparin Induced Thrombocytopenia despite a lack of rigorous clinical trials to support the use of fondaparinux for this condition [Warkentin, 2008].

The ACCP guidelines were updated in 2012 (9th edition), and no longer include the above mentioned recommendations for fondaparinux [Guyatt, 2012]. However, since the 2008 guidelines were in place for approximately 4 years during the lifecycle of fondaparinux, these may have potentially contributed to its off-label use.

The ACCP 9th edition guidelines contain a weak recommendation (Grade 2C) for the use of lepirudin or fondaparinux in pregnant patients with acute or subacute HIT, *only* if danaparoid is not available [Linkins, 2012]. However, the authors of this chapter of the guidelines note that further studies evaluating the role of fondaparinux in the treatment of HIT are needed [Linkins, 2012].

In contrast, authors of a recent review of anticoagulants for HIT stated that "on the basis of emerging data showing efficacy and lower bleeding risks, our preference is to use fondaparinux, even though it is not FDA-approved, in patients with normal renal function" [Kelton, 2013].

Off-label use from professional guidelines is not unique to fondaparinux, but is seen with many antithrombotic agents. Low Molecular Weight Heparins (LMWH) are given a strong recommendation for use for the anticoagulation of patients who have atrial fibrillation for ≥ 48hours [Singer 2008]. Additionally, the French Society of Anaesthesia and Intensive Care (SFAR) guidelines provide the following guidance [Maghami-Pour 2005]:

- LMWH reduce the risk of asymptomatic VTE without increasing major bleeding when used during an immobilization + cast after fracture or lesion of ligaments of lower limb (ankle, tibial or peroneal fracture, foot): level 1 (based on randomised clinical trials or strong meta-analyses).
- Due to the low risk of VTE, due to the duration of the immobilization and thus the duration of the treatment to foresee (at least 45 days), LMWH use should be adapted according to the risk factors of the patient; they should be systematic after a fracture (B) (based on scientific assumption/consensus).

These are only a few examples of where professional guidelines may influence physicians to deviate from the indications as outlined in approved product labeling.

The indication statements in Section 4.1 of the SPC are considered to be clear and accurately reflect the phase III study populations.

There is a potential that fondaparinux may be used in primary PCI for patients with STEMI, which is not advised, based on fondaparinux not demonstrating any efficacy or safety advantage over control in OASIS 6. A recommendation against use in this patient population (any use before or during primary PCI) is included in the Warnings and Precautions section of the SPC. Additionally, the STEMI indication statement clearly only includes patients undergoing thrombolysis or no reperfusion.

With respect to the use of fondaparinux for the treatment of ACS, MAH conducted a post-authorisation safety study to evaluate physician adherence to the prescribing information. Results of this study (WEUSRTP2284, OnPAAR) revealed that, overall, the rate of adherence to the prescribing information for fondaparinux was high at all physician sites and in all patient groups (UA/NSTEMI, STEMI, and other ACS).

For the treatment of superficial-vein thrombosis, there is some potential for improper patient selection. In practice, superficial-vein thrombosis is often diagnosed by clinical examination (i.e., by sight and palpation). However duplex ultrasound is also required to confirm the diagnosis, determine the extent of the thrombus and rule out concomitant DVT. Therefore, if prescribers do not objectively rule out DVT, there is the potential for use of fondaparinux 2.5mg in superficial-vein thrombosis patients with unrecognized concomitant DVT. However, the appropriate treatment of asymptomatic DVT is not well established since clinical trials for the treatment of DVT have focused on symptomatic presentations. It is possible that such patients may require higher treatment doses of fondaparinux (i.e., 7.5mg adjusted for body weight). Therefore, there could potentially be an increase in reporting of terms representative of lack of effect (i.e., DVT, PE) due to the subsequent identification of pre-existing DVT or complications due to sub-therapeutic dosing. Proper dosing instructions for the treatment of superficial-vein thrombosis are clearly provided in Section 4.2 of the SPC. Additionally, language to reinforce use in the proper patient population (i.e. presence of superficial-vein thrombosis should be confirmed and concomitant DVT should be objectively excluded) is included in the Warnings and Precautions section of the SPC.

SVI.6 Specific paediatric issues

MAH excluded the patients < 18 years of age (<20 years for ACS studies) in the clinical study programmes.

One non-MAH study (ART113100) involving use of fondaparinux in children or adolescents was completed in 2009 to establish dosing and study the pharmacokinetics of fondaparinux in children greater than 1 year of age with deep vein thrombosis or heparin-induced thrombocytopenia. The study enrolled a total of 24 subjects. Ten subjects were >

1 to 5 years of age and seven subjects each were 6 to 12 and 13 to 18 years of age. Adverse events assessed as related to study medication were consistent with the current known safety profile of fondaparinux in adults and no new safety signals were observed in the study. In view of the limited safety data in a small population of paediatric subjects with confounding illnesses in this study, it is difficult to draw meaningful conclusions about the safety profile of fondaparinux in this population.

FondaKIDS II was a non-interventional, observational study that evaluated the long-term safety, dosing, and efficacy of fondaparinux in 35 children. Descriptive statistics were used to present findings. There were 18 males and 17 females with a mean age of 9.11 yrs (range: 1-17 years). The mean duration of treatment with fondaparinux was 371 days (median: 152 days; range: 2-1566 days). The mean dose of fondaparinux was 0.1 mg/kg/dose (median: 0.1 mg/kg/dose; range: 0.04-0.15 mg/kg/dose). Fourteen of 22 evaluable patients (63.6%) had complete resolution of their thrombus while 6/22 (27.3%) had partial resolution, and 2/22 (9.1%) had no change. Thus, 20/22 (90.9%) patients had either a complete or partial response while none had progression. The mean time to best outcome from initiation of fondaparinux was 171.5 days (median: 92.5 days; range: 11-839 days). Eleven patients needed a total of 16 dose adjustments to achieve therapeutic levels. Two patients (9.1%) had recurrent VTE: one was on fondaparinux at the time of recurrence and one was on warfarin. There were 3 major (intracranial hemorrhage occurred prior to initiation of fondaparinux subsequently, pulmonary hemorrhage, and subretinal hemorrhage) and 6 minor (2 with blood in stool, one with injection site, one CVC site, one tracheostomy bleed, one epistaxis) bleeding events. Importantly, only one of these events resulted in discontinuation of fondaparinux. One patient had an allergic reaction [Young 2013, Har Ko 2012].

The SPC Section 4.2 states that fondaparinux is not recommended in children below the age of 17 years.

A paediatric VTE treatment study is planned to satisfy a post marketing commitment to the US FDA.

SVI.6.1 Issues identified in paediatric investigation plans

There is no paediatric investigation plan for fondaparinux in the EU.

Table 19 Issues identified in paediatric investigation plans

Product Name and PIP : Not Applicable		
Issue (safety or long term efficacy)	Background	Relevance to indications covered in this RMP and how, if appropriate, it will be addressed.
Not applicable	Not applicable	Not applicable

SVI.6.2 Potential for paediatric off-label use

VTE is a paediatric concern. Among children, advances in care have resulted in increasing numbers of children requiring antithrombotic treatment [Monagle 2004; Goldenberg 2008]. However while VTE in children may not be considered rare, the incidence of VTE is lower among children than adults. For example, in the US the incidence of VTE rises exponentially from fewer than 5 cases/100,000 in persons <15 years to approximately 500 cases/100,000 at age 80 years [White 2003]. According to the American College of Chest Physician (ACCP) Guidelines for use of Antithrobotics in Neonates and Children [Monagle 2008], approximately 95% of VTEs in paediatrics occur secondary to conditions such as the presence of a central venous line (CVL), cancer, trauma/surgery, congenital heart disease and systemic lupus erythemastosus.

Paediatric recommendations for antithrombotic treatment have been extrapolated from adult recommendations because events are rare enough to hinder testing yet common enough to present management dilemmas [Monagle, 2004; Monagle, 2008]. The *Antithrombotic Therapy in Neonates and Children, ACCP Evidence Based Clinical Practice Guidelines 9th edition* do not suggest the use of fondaparinux in paediatric patients. The guidelines recommend that children with first VTE are treated with either UFH or LMWH (Monagle 2012). Given the low incidence of VTE in the paediatric population and the recommendations suggesting the use of heparin, off- label use with fondaparinux in the paediatric population should be limited.

ACS is an acquired disease of aging as coronary arteries become more atherosclerotic with prolonged smoking, hypertension, and diet/obesity [Kleiman 2005]. As such, ACS is thought to be rare in the paediatric population. This is supported by the results of a worldwide literature search carried out by MAH, which found only three case reports for teenagers (and none for younger children) for any country in the Medline database for years 2000 to 2005, and one additional case using the Google search engine. None of these had atherosclerotic arteries [Jang 2004; Maghami-Pour 2005; RuDusky 2002]. Due to the low incidence of ACS in the paediatric population, it is unlikely that there will be any substantial off-label use of fondaparinux in this age group for the treatment of ACS.

Superficial-vein thrombosis is a relatively poorly studied condition and there is very limited published data available in paediatrics. A literature review identified no publications regarding estimates of superficial-vein thrombosis among paediatric patients and only 1 case report in a 12-year-old girl. In addition, using an online query system [HCUP.net, a part of the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ)], the number of paediatric patients with a diagnosis of superficial-vein thrombosis (ICD9 451.0) during hospitalization was estimated using the Kids' Inpatient Database (KID). Among the estimated 6,578,069 paediatric discharges in 2006, a total of 122 children age 0-17 years had a discharge diagnosis of superficial-vein thrombosis. Considering the average age of patients with superficial-vein thrombosis is approximately 60 years and the lack of available data regarding superficial-vein thrombosis in paediatric patients, it is unlikely that there will be any substantial off-label use of fondaparinux in the paediatric population for the treatment of superficial-vein thrombosis.

SVI.7 Conclusions

Table 20 Safety concerns from this module

Safety concern	Comment
Identified Risk: Off-label use (VTE treatment and prophylaxis)	See Pharmacovigilance Plan (PART III)
Potential risk: Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis	See Pharmacovigilance Plan (PART III)
Potential risk: Use of fondaparinux 2.5mg in superficial-vein thrombosis patients with concomitant DVT	See Pharmacovigilance Plan (PART III)
Missing Information: Use in paediatric patients	See Pharmacovigilance Plan (PART III)

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Newly identified safety concerns (since this module was last submitted)

There have been no newly identified safety concerns since this module was last submitted.

SVII.2 Recent study reports with implications for safety concerns

There have been no recent study reports since the last EU RMP that have had a significant impact on existing safety concerns.

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

Identified Risks:

- Bleeding events
- Off-label use (VTE treatment and prevention)
- Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI(for the treatment of ACS)

Potential Risks:

- Heparin-induced thrombocytopenia
- Use of higher VTE treatment doses (5 mg, 7.5 mg, 10 mg) for the treatment of superficial-vein thrombosis
- Use of fondaparinux 2.5 mg in superficial-vein thrombosis patients with concomitant DVT

Identified Risk of Bleeding Events

Clinical Trial Data

The rates of bleeding are described for each indication below. It should be recalled that the studies supporting the different indications may have employed slightly different bleeding definitions; therefore caution is warranted when comparing incidences across the indications. However within specific indications (e.g. VTE prophylaxis in surgical patients, VTE treatment, treatment of ACS, treatment of superficial-vein thrombosis), the studies employed a common definition of bleeding.

In general the safety profile of fondaparinux is consistent with that expected for an anticoagulant and similar to active comparator. The only exception to this, is the incidence of bleeding in the UA/NSTEMI population where with fondaparinux 2.5mg the risk of major bleeding was approximately half that of enoxaparin 1mg/kg twice daily.

As might be expected the incidence of bleeding with fondaparinux in VTE prophylaxis tended to be higher in surgical patients, particularly those studies that employed pre-operative randomisation (i.e. in MOSLL and abdominal surgery). Further analysis of the incidence of major bleeding occurring after first active dose of fondaparinux (i.e. excluding peri-operative bleeding that occurred prior to initiation of active fondaparinux), the incidence of bleeding was reduced in both the MOSLL pre-operative and abdominal surgery studies. In addition, the timing of first administration post-operatively is also important; bleeding rates were reduced if administration commences at least 6 hours post-surgical closure. Consequently the SPC Section 4.2 recommends initiation of therapy commence at least 6 hours after surgical closure.

In the treatment of superficial-vein thrombosis where the duration of therapy was longer (i.e., 45 days) than for other indications (i.e., maximum of 31 days), the incidence of bleeding with fondaparinux 2.5mg once daily was similar to placebo.

VTE Prophylaxis in Orthopaedic Surgery

Pre-operative randomisation studies: The proportion [95% CI] of patients receiving fondaparinux (N=1971) experiencing a major bleeding event was 3.3% [2.6; 4.2] compared to 2.6% [2.0; 3.4] in the 40 mg once daily enoxaparin group (N=2050). The rates of any bleeding event were 7.3% [6.1; 8.5] and 5.9% [4.9; 7.0], respectively.

Post-operative randomisation studies: The proportion [95% CI] of fondaparinux patients (N=1645) experiencing a major bleeding event was 1.9% [1.3; 2.7] compared to 1.1% [0.7; 1.7] in the 30 mg twice daily enoxaparin group (N=1906). Rates of any bleeding event were 3.8% [2.9; 4.8] and 3.7% [2.9; 4.7], respectively.

Pooled MOSLL Studies: As the pre-operative randomisation studies necessitated fondaparinux patients receive a pre-operative dose of placebo to maintain the blind, the rates of bleeding in these studies include events occurring peri-operatively prior to initiation of active fondaparinux. Therefore the incidence of bleeding from the first active dose in the pooled fondaparinux dataset from both pre- and post- operative randomisation studies (N=3595) was evaluated. However, this was a non-comparative analysis as it is inappropriate to compare these rates to those for the first active enoxaparin which was initiated pre-operatively in half of the patients. In the pooled dataset the incidence of on-therapy major bleeding from first active injection of fondaparinux was 2.2% and for on-therapy any bleeding was 4.9%. If the initiation of fondaparinux occurred between 6-7 hours post therapy the incidence of major bleeding was 2.0%.

Extended prophylaxis in hip fracture: The proportion of fondaparinux patients (N=327) experiencing major bleeding events was 2.4% compared to 0.6% with placebo (N=329). The rates of any bleeding event were 4.0% and 1.2%, respectively.

VTE Prophylaxis in Abdominal Surgery

The proportion of fondaparinux patients (N=1433) experiencing major bleeding events was 3.4% compared to 2.4% with dalteparin (N=1425). The rates for any bleeding event were 5.6% and 4.0%, respectively. These slightly higher rates of bleeding in fondaparinux versus dalteparin patients were not statistically significant.

As this study also employed pre-operative randomisation the incidence of bleeding from first active fondaparinux dose was performed. The incidence of major bleeding and any bleeding was 2.9% and 5.0%, respectively. When fondaparinux was initiated at least 6 hours after surgical closure the incidence of major bleeding was 2.8%.

VTE Prophylaxis in Medically Ill Patients

The proportion of fondaparinux patients (N=425) experiencing major bleeding events was 0.2% compared to 0.2% with placebo (N=414). The rates for any bleeding event were 2.8% and 1.2%, respectively.

Treatment of UA/NSTEMI and STEMI Patients

UA/NSTEMI: The incidence of major bleeding at Day 9 with fondaparinux (N=9979) was 2.1% compared to 4.1% with enoxaparin (N=9969). Severe haemorrhage at Day 9 was 1.5%, and 2.6%, respectively. The differences in favour of fondaparinux were highly statistically significant ($p<0.001$).

STEMI: The incidence of severe haemorrhage at Day 9 with fondaparinux (N=5954) was 1.1% compared to 1.4% with control (placebo/UFH; N=5947). Major bleeding at Day 9 was 1.7%, and 2.1%, respectively.

Treatment of superficial-vein thrombosis

In the phase III study for treatment of superficial-vein thrombosis the proportion of patients receiving fondaparinux regimen (N=1499) who experienced major bleeding events was 0.1% compared to 0.1% for placebo (N=1488). Rates of any bleeding events were 1% (fondaparinux), and 0.9% (placebo), respectively. No evidence of a different time course of bleeding with fondaparinux during the 45 day treatment period was noted.

Treatment of VTE

In the pooled phase III studies for VTE treatment the proportion of patients receiving the curative fondaparinux regimen (N=2294) experiencing major bleeding events was 1.2 % compared to 1.2% for enoxaparin (N=1101) and 1.1% UFH treated patients (N=1092). Rates of any bleeding events were 4.3% (fondaparinux), 4.2% (enoxaparin), and 6.3% (UFH), respectively.

Bleeding in Low Body Weight Patients

In phase III studies conducted in VTE prophylaxis and treatment of UA/NSTEMI and STEMI utilizing fondaparinux 2.5mg SC once daily, the risk of major bleeding tended to be higher in low body weight patients (<50kg), and was most evident in the surgical population (Table 21). However, it is acknowledged that the number of patients in each of the low body weight categories is low and there may be an under estimation of risk in some studies.

The timing of initiation of fondaparinux therapy post-surgery is important particularly in vulnerable patients at risk of bleeding; consequently the SPC Section 4.2 states that the first dose in surgical patients warrants strict adherence in patients ≥75 years, and/or low body weight <50kg and/or with renal impairment (CrCl between 20-50ml/min).

In addition, factors that influence bleeding such as renal impairment and low body weight, as well as age may overlap. In the phase III MOSLL post-operative randomisation and abdominal surgery studies, approximately 47% of low body weight patients (<50kg) also had moderate-severe renal impairment (CrCl 20-50ml/min), whilst in other phase III VTE prophylaxis studies this overlap was as high as 72% (MOSLL pre-operative randomisation and extended prophylaxis in hip fracture) and 80% (medically ill). It is unclear whether this profile is reflective of the broader population encountered in clinical practice.

In the phase IV PROPICE study in patients with renal impairment (CrCl 20-50ml/min) undergoing VTE prophylaxis following MOSLL, 11.3% of the 442 patients studied had low body weight (<50kg). The median weight in the overall study population was 60kg.

Together, these data suggest that in the population likely to receive fondaparinux for VTE prophylaxis, moderate-severe renal impairment may be common in low body weight patients. Given that fondaparinux 1.5mg once daily is recommended for VTE prophylaxis in patients with renal impairment (CrCl 20-50ml/min), it is possible that many low body weight patients are already receiving a reduced dose.

In the UA/NSTEMI population there was some evidence of a higher risk of bleeding in low body weight patients with fondaparinux; however the risk of bleeding with fondaparinux was lower than enoxaparin which was a weight adjusted dose regimen (1mg/kg). In contrast in STEMI patients an increased risk of severe haemorrhage with low body weight was not evident. In both weight categories (<50kg and 50-100kg) the risk of haemorrhage with fondaparinux was similar to control (UFH/placebo) [see Table 21]. Therefore, based on the phase III ACS studies there is no compelling data to warrant a dose reduction in low body weight patients.

In the superficial-vein thrombosis treatment study, patients with low body weight (<50kg) were excluded. However, 2 patients with low body weight were treated with fondaparinux; neither reported any bleeding event during the treatment period. Additionally, the low number of major bleeding events (1 each in the fondaparinux and placebo group) precluded a detailed analysis by weight. The majority of bleeding events

occurred in patients with normal body weight (50-100kg) with an incidence similar in fondaparinux and placebo patients (see Table 21)

In summary, the risk-benefit analysis of fondaparinux 2.5mg in low body weight patients across the indications is considered positive. The SPC Section 4.4 provides warning of the risks in low body weight patients, particularly with respect to increased bleeding. In addition, the SPC Section 4.4 states that fondaparinux is not recommended for the treatment of superficial-vein thrombosis in low body weight patients (<50kg).

In the VTE treatment studies, no clear relationship between low body weight and bleeding was evident (see Table 22). However, in VTE treatment the fondaparinux dose was adjusted according to weight as recommended in the SPC.

Table 21 Incidence of the Bleeding by Weight - Phase III Studies with Fondaparinux 2.5mg – Safety Population

Population		
MOSLL	Fondaparinux n/N (%)	Enoxaparin n/N (%)[4]
Major Bleeding on therapy[1]		
Pre-operative studies	65/1971 (3.3%)	54/2050 (2.6%)
<50kg	7/109 (6.4%)	4/132 (3.0%)
≥50-<100kg	56/1739 (3.2%)	48/1783 (2.7%)
≥100kg	1/86 (1.2%)	2/87 (2.3%)
Post-operative studies	31/1645 (1.9%)	21/1906 (1.1%)
<50kg	0/21 (0%)	0/34 (0%)
≥50-<100kg	23/1310 (1.8%)	18/1541 (1.2%)
≥100kg	8/313 (2.6%)	3/328 (0.9%)
Extended prophylaxis hip fracture	Fondaparinux n/N (%)	Placebo n/N (%)
Major bleeding on-therapy[2]	8/327 (2.4%)	2/329 (0.6%)
<50kg	2/28 (7.1%)	0/25 (0%)
≥50-≤100kg	6/292 (2.1%)	2/301 (0.7%)
>100kg	0/5 (0%)	0/2 (0%)
Abdominal Surgery	Fondaparinux n/N (%)	Dalteparin n/N (%)
Major bleeding on therapy[1]	49/1433 (3.4%)	34/1425 (2.4%)
<50kg	3/57 (5.3%)	3/60 (5.0%)
≥50-<100kg	44/1280 (3.4%)	31/1265 (2.5%)
≥100kg	2/92 (2.2%)	0/97 (0%)
Medical Patients	Fondaparinux n/N (%)	Placebo n/N (%)
Any bleeding on therapy[1, 3]	11/425 (2.6%)	5/414 (1.2%)
<50kg	1/34 (2.9%)	1/38 (2.6%)
≥50-<100kg	9/371 (2.4%)	4/353 (1.1%)
≥100kg	1/14 (7.1%)	0/18 (0%)
UA/NSTEMI	Fondaparinux n/N (%)	Enoxaparin n/N (%)
Major Bleeding at Day 9	209/9979 (2.1%)	406/9969 (4.1%)
<50kg	6/150 (4.0%)	9/171 (5.3%)
≥50-≤100kg	197/9245 (2.1%)	369/9209 (4.0%)
>100kg	6/584 (1.0%)	28/589 (4.8%)
STEMI	Fondaparinux n/N (%)	Control (placebo/UFH) n/N (%)
Severe Haemorrhage at Day 9	64/5952 (1.1%)	82/5941 (1.4%)
<50kg	1/130 (0.8%)	1/98 (1.0%)
≥50kg – ≤ 100kg	62/5438 (1.1%)	78/5452 (1.4%)
>100kg	1/384 (0.3%)	3/391 (0.8%)
Superficial-vein thrombosis	Fondaparinux n/N (%)	Placebo n/N (%)
Any bleeding at Day 47, or + 4 days (whichever is longer)	15/1499 (1.0%)	14/1488 (0.5)
<50kg	0/2 (0%)	0/1 (0%)
≥50kg – ≤ 100kg	14/1312 (1.1%)	14/1304 (1.1%)
>100kg	1/183 (0.5%)	0/180 (0%)

1. Safety population included all randomised subjects who received at least 1 dose of study medication; subjects were analyzed according to the treatment actually received.
2. Note
1. on therapy was defined from first dose of double-blind medication to 2 days after the final dose.
2. on-therapy was defined from the first dose of double-blind medication to Day 25
3. due to the limited number of major bleeds in medical patients (1 in each group), subgroup analyses were performed on any confirmed (major or minor) bleeding
4. Enoxaparin N includes patients from phase II studies, note fondaparinux 2.5mg was not included in these phase II

Population		
MOSLL	Fondaparinux n/N (%)	Enoxaparin n/N (%)[4]
Major Bleeding on therapy[1]		
Pre-operative studies	65/1971 (3.3%)	54/2050 (2.6%)
<50kg	7/109 (6.4%)	4/132 (3.0%)
≥50-<100kg	56/1739 (3.2%)	48/1783 (2.7%)
≥100kg	1/86 (1.2%)	2/87 (2.3%)
Post-operative studies	31/1645 (1.9%)	21/1906 (1.1%)
<50kg	0/21 (0%)	0/34 (0%)
≥50-<100kg	23/1310 (1.8%)	18/1541 (1.2%)
≥100kg	8/313 (2.6%)	3/328 (0.9%)
Extended prophylaxis hip fracture	Fondaparinux n/N (%)	Placebo n/N (%)
Major bleeding on-therapy[2]	8/327 (2.4%)	2/329 (0.6%)
<50kg	2/28 (7.1%)	0/25 (0%)
≥50-≤100kg	6/292 (2.1%)	2/301 (0.7%)
>100kg	0/5 (0%)	0/2 (0%)
Abdominal Surgery	Fondaparinux n/N (%)	Dalteparin n/N (%)
Major bleeding on therapy[1]	49/1433 (3.4%)	34/1425 (2.4%)
<50kg	3/57 (5.3%)	3/60 (5.0%)
≥50-<100kg	44/1280 (3.4%)	31/1265 (2.5%)
≥100kg	2/92 (2.2%)	0/97 (0%)
Medical Patients	Fondaparinux n/N (%)	Placebo n/N (%)
Any bleeding on therapy[1, 3]	11/425 (2.6%)	5/414 (1.2%)
<50kg	1/34 (2.9%)	1/38 (2.6%)
≥50-<100kg	9/371 (2.4%)	4/353 (1.1%)
≥100kg	1/14 (7.1%)	0/18 (0%)

studies hence the slightly high N for enoxaparin

Table 22 Incidence of the Bleeding by Weight - Phase III Treatment Studies with Fondaparinux 7.5mg (weight adjustment 5.0mg<50kg and 10mg >100kg) – Safety Population

Major Bleeding during initial treatment[1]	Fondaparinux n/N (%)	Enoxaparin n/N (%)
DVT	12/1091 (1.1%)	13/1101 (1.2%)
<50kg	1/31 (3.2%)	0/24 (0%)
≥50-≤100kg	11/942 (1.2%)	12/967 (1.2%)
>100kg	0/118 (0%)	1/110 (0.9%)
	Fondaparinux n/N (%)	UFH n/N (%)
PE	14/1092 (1.3%)	12/1092 (1.1%)
<50kg	0/21 (0%)	1/25 (4.0%)
≥50-≤100kg	13/939 (1.4%)	10/932 (1.1%)
>100kg	1/130 (0.8%)	1/134 (0.7%)

1. Safety population included all randomised subjects who received at least 1 dose of study medication; subjects were analyzed according to the treatment actually received.
2. Note 1: during initial treatment was defined from first dose of double-blind medication and ended according calculated CrCl at the end of study drug treatment or, if missing, at baseline. This period ended 3 calendar days after the day when study drug was stopped if CrCl≥50 ml/min, 4 calendar days if 30≤CrCl<50 ml/min, and 9 calendar days if CrCl<30 ml/min or was missing.

Bleeding in the Elderly

In phase III studies the elderly (>65 years) and very elderly (>75years) population was well represented reflecting the demographics of the target population. For example in the medical patient and extended VTE prevention studies 80% of patients were >65 years and over 50% were >75 years, in the MOSLL VTE prevention studies 70% were >65years and 30% were >75 years and in remaining studies (VTE prevention in abdominal surgery, treatment of VTE and treatment of ACS) approximately 50% of patients were aged >65years and approximately 15% were >75years. In the superficial-vein thrombosis treatment study, the population was slightly younger than seen in previous phase III studies; approximately 32% were >65 years and approximately 8% were >75 years.

In MOSLL and abdominal surgery studies with pre-operative randomisation there was evidence of a higher risk of bleeding with increasing age with fondaparinux which was not evident in the post-operative MOSLL studies. In medical patients the risk of bleeding with fondaparinux was higher in the very elderly (≥75years) compared to younger patients (<75years).

In the UA/NSTEMI and STEMI phase III studies the incidence of bleeding increased with age in all treatment groups. In UA/NSTEMI patients the lower risk of major bleeding with fondaparinux vs. enoxaparin was consistent across age categories. In STEMI patients the incidence of severe haemorrhage was similar with fondaparinux and control across all age categories.

In the superficial-vein thrombosis phase III study the incidence and number of major bleeding events was low and precluded a detailed analysis by age. The incidence of any bleeding during the treatment period in fondaparinux patients was low and similar to that observed for placebo in patients in age categories <65 and 65-75. One bleeding event occurred in a fondaparinux patient aged >75 years (incidence 0.9%), however this rate was not higher than that observed in younger patients receiving fondaparinux (0.9% and 1.3% for <65 years and 65-75 years respectively).

In the phase III VTE treatment studies the incidence of major bleeding increased with age in all treatment groups, however there was no evidence to suggest that the risk of bleeding with fondaparinux relative to comparator differed by age.

Due to the consistency of the relative effect of fondaparinux versus control treatment across all age categories in the approved indications, the SPC states that no dose adjustment in the elderly is necessary. However, acknowledging that bleeding risk with fondaparinux therapy increases with age, Section 4.4 of the SPC recommends caution when fondaparinux is used in the elderly.

Bleeding in Renally Impaired Patients

<u>VTE prophylaxis</u>

In VTE prophylaxis studies with pre-randomisation (MOSLL and abdominal surgery) the risk of major bleeding tended to increase with decreasing renal function in all treatment groups. This observation was less evident in the post-operative randomisation studies. In medical patients bleeding with fondaparinux also increased with renal impairment, a similar relationship was also seen with the placebo group.

The SPC recommends a fondaparinux dose of 1.5mg once daily for patients requiring VTE prophylaxis with moderate to severe renal impairment (CrCl 20-50ml/min). The selection of this dose was based on PK modelling.

PROPICE, a phase IV study conducted in renally impaired (CrCl 20-50ml/min) patients requiring VTE prophylaxis following MOSLL surgery and treated with fondaparinux 1.5mg (n=442), was specifically designed to recruit patients encountered in real-world clinical practice. Unlike phase III studies with fondaparinux, PROPICE had few exclusion criteria. Consequently, the population studied in PROPICE was a fragile, elderly population at higher risk of bleeding and VTE.

As compared to the patient population with moderate-to-severe renal impairment in the phase III MOSLL studies, the PROPICE population had a higher proportion of males and patients undergoing knee replacement surgery with a much greater proportion of patients taking pre-operative aspirin and/or anti-platelet agents.

In PROPICE, the median age and weight of the population was 82 years and 60kg respectively, and 80% (n=353) of patients were female. The median creatinine clearance was 40ml/min (range 15.0-59.2 ml/min). Use of aspirin prior to surgery occurred in 26% (n=113) of patients. Approximately 27% (n=119) of patients had at least 1 risk factor for VTE and 78% (n=343) had at least 1 risk factor for bleeding.

In PROPICE, the definition of a major bleeding event was generally similar to the one used in the phase III MOSLL program. In PROPICE, the incidence of major bleeding at Day 10 was 4.5% (n=20). There were no fatal or critical organ bleeds or bleeds that led to discontinuation of fondaparinux. Two events led to surgical re-intervention, and the remaining events resulted in either a fall in haemoglobin (≥2g/dL) and/or led to a transfusion (≥ 2 units). One event occurred at a site other than the surgical site.

An analysis of risk factors for major bleeding by univariate analysis identified male gender, time between surgery and first dose < 8 hours, pre-operative use of antiplatelet therapy and American Society of Anaesthesiology category ≥ 3 as high risk characteristics.

In this population expected to be at high risk of VTE, there were 3 events of distal DVT up to Day 30 (incidence 0.7%). This relatively low incidence, specifically in a high risk population, supports a favourable risk-benefit profile for the 1.5mg dose of fondaparinux.

Treatment of ACS

For patients requiring treatment for UA/NSTEMI or STEMI the 2.5mg dose is recommended without dose reduction for renal impairment. The basis for this is discussed below.

In both phase III ACS studies, in all treatment groups, the incidence of bleeding increased with decreasing renal function (see Table 23 and Table 24). The tendency for an increased risk of major bleeding with decreasing renal function was more marked in UA/NSTEMI patients who received enoxaparin as compared to patients who received fondaparinux. The relative effect of fondaparinux on major bleeding or severe haemorrhage was consistent across all categories of CrCl. It should be noted that the number of patients was relatively low in the CrCl <30 ml/min subgroup and these results should be interpreted with caution.

The data supporting the fondaparinux 2.5mg SC once daily in the treatment of patients with UA/NSTEMI and STEMI with CrCl > 20ml/min is based on a benefit risk analysis. The risk of morbidity and mortality is greatly increased in patients with renal impairment particularly those with STEMI, and is much higher than the risk of bleeding with fondaparinux (see Table 23 and Table 24, respectively). Therefore, it is concluded that the fondaparinux 2.5mg dose is the appropriate dose in UA/NSTEMI and STEMI patients and that dose reduction in renal patients (CrCl > 20ml/min) is not necessary. Fondaparinux is not recommended in patients with CrCl <20ml/min.

Table 23 Primary Efficacy Outcomes in UA/NSTEMI and STEMI Patients by Creatinine Clearance Categories – All Randomised Patients

Endpoint/ Timepoint Creatinine Clearance	Number Events / Number Analyzed (%)	
UA/NSTEMI (OASIS 5)	Fondaparinux n/N (%)	Enoxaparin n/N (%)
Death/MI/RI at Day 9	577/10016 (5.8%)	571/9979 (5.7%)
< 20mL/min	2/41 (4.9%)	6/44 (13.6%)
≥ 20mL/min – < 30mL/min	20/241 (8.3%)	24/242 (9.9%)
≥ 30mL/min – < 50mL/min	127/1660 (7.7%)	139/1720 (8.1%)
≥ 50mL/min – < 80mL/min	265/4289 (6.2%)	238/4205 (5.7%)
≥ 80mL/min	163/3785 (4.3%)	164/3768 (4.4%)
Missing	2/41 (4.9%)	3/42 (7.1%)
STEMI (OASIS 6)	Fondaparinux n/N (%)	Control (UFH/placebo) n/N (%)
Death/MI/ at Day 30	568/5948 (9.5%)	659/5970 (11.0%)
< 20mL/min	11/24 (45.8%)	12/24 (50.0%)
≥ 20mL/min – < 30mL/min	35/109 (32.1%)	34/105 (32.4%)
≥ 30mL/min – < 50mL/min	162/812 (20.0%)	183/839 (21.8%)
≥ 50mL/min – < 80mL/min	227/2299 (9.9%)	256/2250 (11.4%)
≥ 80mL/min	133/2704 (4.9%)	174/2752 (6.3%)

Table 24 Incidence of Bleeding in UA/NSTEMI and STEMI Patients by Creatinine Clearance Categories – As Treated Patients*

Endpoint/ Timepoint Creatinine clearance	Number Events / Number Analyzed (%)	
UA/NSTEMI (OASIS 5)	Fondaparinux n/N (%)	Enoxaparin n/N (%)
Major Bleeding at Day 9	209//9979 (2.1%)	405/9969 (4.1%)
<20mL/min	2/40 (5.0%)	5/43 (11.6%)
≥20 - <30mL/min	4/240 (1.7%)	21/239 (8.8%)
≥30 - <50mL/min	54/1649 (3.3%)	107/1715 (6.2%)
≥50 - <80mL/min	103/4257 (2.4%)	193/4188 (4.6%)
≥80mL/min	46/3757 (1.2%)	79/3743 (2.1%)
Missing	0/36	1/41 (2.4%)
STEMI (OASIS 6)	Fondaparinux n/N (%)	Control (UFH/placebo) n/N (%)
Severe Haemorrhage at Day 9	64/5876 (1.1)	82/5871 (1.4)
<20mL/min	2/23 (8.7)	0/24
≥20mL/min – <30mL/min	2/106 (1.9)	5/105 (4.8)
≥30mL/min – <50mL/min	12/803 (1.5)	13/823 (1.6)
≥50mL/min – <80mL/min	29/2273 (1.3)	34/2217 (1.5)
≥80mL/min	19/2671 (0.7)	30/2702 (1.1)

1. * "As treated" population included all randomised subjects who received at least 1 dose of study medication; subjects were analyzed according to the treatment actually received.

Treatment of superficial-vein thrombosis

In the phase III study conducted with fondaparinux 2.5mg in patients with superficial-vein thrombosis, patients with severe renal impairment (creatinine clearance <30ml/min) were excluded.

The study employed fondaparinux 2.5mg once daily, without a dose reduction in patients with moderate renal impairment. The rationale for this at the time of study design was that the treatment of superficial-vein thrombosis was considered analogous to the treatment of ACS and VTE since all three conditions are associated with an established thrombus that warrants anticoagulant therapy. Therefore a dose reduction was not thought appropriate for the treatment of superficial-vein thrombosis because it may be less efficacious. In addition, the potential for bleeding with fondaparinux 2.5mg in these patients was assessed as acceptable because the superficial-vein thrombosis population is generally at a lower risk of bleeding as compared to surgical patients requiring VTE prophylaxis.

Although the superficial-vein thrombosis treatment study did not exclude patients with moderate renal impairment, only 4.3% of patients in the treatment population fell within this category. This is likely a consequence of the relatively younger age and lower rates

of co-morbidity of the population compared to that seen in previous phase III populations.

In this study the single major bleeding event (intra-ocular bleed) in fondaparinux patients occurred in a patient with moderate renal impairment (baseline CrCl was 49.9ml/min) resulting in an incidence of 1.5% [95%CI, 0.1%, 7.3%], there were no other bleeding events reported in these patients. No placebo patients with moderate renal impairment experienced a major bleeding event (incidence of 0% [95%CI, 0%, 5.6%]), and 1 patient reported a minor bleeding. The single major bleeding event (epistaxis) that occurred in placebo patients occurred in a patient with mild renal impairment (CrCl 50-80) with a baseline creatinine clearance of 62.4ml/min.

In patients with moderate renal impairment (CrCl <50ml/min), there were no events of death or symptomatic PE, DVT, superficial-vein thrombosis extension or superficial-vein thrombosis recurrence at Day 47 in fondaparinux patients, as compared to 7 events (10.9% [95% CI: 5.2%, 20.3%]) in placebo patients. This finding was highly statistically significant (p=0.005).

Although the benefit risk profile of fondaparinux in patients with moderate renal insufficiency receiving treatment for superficial-vein thrombosis appears positive, it is acknowledged that these conclusions are based on small numbers of patients and events. Due to the limited clinical experience and the uncertainty in quantifying the bleeding risk with fondaparinux 2.5mg in superficial-vein thrombosis patients with moderate renal impairment, particularly given the longer duration of therapy in this indication and the potential for higher exposures in this sub-group of patients, a dose reduction is considered appropriate. Based on PK considerations and by analogy to the dosing regimen recommended in VTE prophylaxis, the 1.5mg dose is recommended for the treatment of superficial-vein thrombosis patients with moderate to severe renal impairment (creatinine clearance 20-50ml/min).

VTE Treatment

In the VTE treatment programme, the risk of major bleeding tended to increase in patients with decreasing renal function in all treatment groups; however, bleeding risk with fondaparinux relative to comparator agents was similar. In this indication fondaparinux is not recommended in patients CrCl <30ml/min.

Bleeding with Concomitant Therapies

In the phase III VTE prophylaxis and treatment studies the use of concomitant anticoagulants (except warfarin per protocol in VTE treatment) was prohibited. Additionally, the concomitant use of antiplatelet agents and NSAIDs was discouraged. In those studies with concomitant use of NSAIDS in approximately 30% of patients (MOSLL pre-operative randomisation and abdominal surgery) there was no clear evidence of an increased risk of major bleeding with NSAID use in fondaparinux

patients. In the medically ill patients there were too few bleeding events to draw a conclusion about the effect of aspirin use in this population.

In the management of ACS, the use of antiplatelet agents and thrombolytics is critical, and the phase III studies provide extensive experience with concomitant aspirin (approximately 97% of patients) and clopidogrel (approximately 60%), as well as other commonly used agents (e.g. statins, angiotensin converting enzyme (ACE) inhibitors, beta-blockers, nitrates – all >70%). In OASIS 6 in STEMI patients 45% of patients received a thrombolyic agent. In both ACS studies the use of GPIIb/IIIa inhibitors was less common (approximately 17% of all patients) reflecting usage mainly as an adjunct in some but not all patients undergoing PCI.

The rates of bleeding in UA/NSTEMI and STEMI patients receiving anti-platelet or thrombolytic agents is summarised in Table 25, note the vast majority of patients receiving thienopyridine, GPIIb/IIIa inhibitor and thrombolytic were also likely receiving ASA (acetylsalicylic acid). In UA/NSTEMI patients the lower risk of major bleeding with fondaparinux relative to enoxaparin was evident in all sub-groups. The risk of bleeding in both treatment groups tended to be increased with concomitant GPIIb/IIIa inhibitors. In STEMI patients the risk of bleeding with fondaparinux or control was similar across all sub-groups of concomitant medication including thrombolytics.

In STEMI patients receiving a non-fibrin specific lytic, fondaparinux was not associated with a higher risk of severe haemorrhage compared to placebo. Consistent with this, in the smaller group of patients (420 fondaparinux-treated patients; 7.1% of total) who received a fibrin-specific lytic (alteplase, reteplase, or tenecteplase), fondaparinux was associated with a non-statistically significant lower risk of clinically-important bleeding events compared to control, which in this case was UFH.

There is additional phase II experience with fondaparinux used in conjunction with fibrin-specific lytic. In the PENTALYSE study, 241 STEMI patients treated with recombinant tissue plasminogen activator (r-tPA) and aspirin, also received fondaparinux 4mg, 8mg or 12mg SC (first dose administered IV) for up to 5 days or UFH for up to 72 hours. There was no excess risk of major bleeding in the 4mg (4.9%) subgroup as compared to UFH (4.7%). There was no statistically significant dose effect for the percentage of patients with major bleeding although there were higher rates of major bleeding in the fondaparinux 8mg (7.8%) and 12 mg (7.2%) groups.

The SPC Section 4.4 warns that fondaparinux should be used with caution in UA/NSTEMI and STEMI patients who are being treated concomitantly with other agents (specifically GPIIa/IIIa inhibitors and thrombolytics) that increase the risk of bleeding.

Data on use of fondaparinux with adjunctive UFH during PCI is discussed below under the sub-heading *Bleeding with Coronary Interventions.*

In the phase III study for the treatment of superficial-vein thrombosis, concomitant aspirin ≤325mg daily was permitted. Consequently 21.4% of patients received aspirin or other anti-platelet agents concomitantly with fondaparinux 2.5mg. Use of topical

NSAIDs was discouraged although permitted when symptoms necessitated use. Overall, 41.5% of fondaparinux patients received topical NSAIDs.

Due to the low incidence and number of major bleeding events, a detailed analysis of the impact of concomitant agents was not possible. However, an evaluation of any bleeding event during the treatment period for the subgroups who received aspirin or NSAIDs during the study did not suggest an increased risk of bleeding with these agents. The SPC Section 4.4 warns that fondaparinux should be used with caution in superficial-vein thrombosis patients who are being treated concomitantly with other agents that increase the risk of bleeding.

Table 25 Incidence of the Primary Safety Bleeding Endpoints in OASIS 5 and OASIS 6 by Concomitant Therapies Sub-Groups - As Treated* Population

	Number Events / Number Analyzed	
OASIS 5 (UA/NSTEMI)	Fondaparinux n/N (%)	Enoxaparin n/N (%)
Major Bleeding at Day 9	209//9978 (2.1%)	406/9967 (4.1%)
ASA	198/9738 (2.0%)	392/9718 (4.0%)
Thienopyridine	150/6744 (2.2%)	297/6705 (4.4%)
GPIIb/IIIa Inhibitors	70/1851 (3.8%)	121/1746 (6.9%)
OASIS 6 (STEMI)	Fondaparinux n/N (%)	Control (UFH/placebo) n/N (%)
Severe Haemorrhage at Day 9	64/5954 (1.1)	83/5947 (1.4)
ASA	55/5773 (1.0)	67/5747 (1.2)
Thienopyridine	29/3438 (0.8)	30/3472 (0.9)
GPIIb/IIIa Inhibitors	13/935 (1.4)	9/912 (1.0)
Thrombolytic agents	20/2173 (0.9)	40/2199 (1.8)

1. * "As treated" population included all randomized subjects who received at least 1 dose of study medication; subjects were analyzed according to the treatment actually received.

Bleeding by Gender or Race or Hepatic Impairment

Across all indications there was no evidence of an effect of gender on the bleeding observed with fondaparinux relative to comparator agents.

The phase III VTE prophylaxis and treatment study populations were predominately Caucasian (>90% and >94%, respectively) such that there were too few non-Caucasians to permit a reliable conclusion of the effect of race.

The phase III ACS population was predominately of European designation (80% for UA/NSTEMI and 63% for STEMI). Among the 4 largest ethnic cohorts included [European; Native Latin, Chinese, and South Asian], there was no indication that the relative risk of bleeding of fondaparinux as compared to control differed by ethnicity.

The phase III superficial-vein thrombosis population was almost completely white/Caucasian/European heritage (99%), therefore an analysis by race was not possible.

The high proportion of Caucasian patients in the phase III study populations of VTE prophylaxis and VTE treatment, as well as treatment of superficial-vein thrombosis is not considered a significant limitation for the following reasons: the studies did not specifically exclude non-Caucasians and so the populations are assumed to be representative of patients likely to be encountered in real-world practice and ii) the pharmacokinetics of fondaparinux do not appear to be affected by race/ethnicity.

Patients with hepatic disease were not specifically excluded from the fondaparinux clinical programme (except severe hepatic impairment in the treatment of superficial-vein thrombosis) and hepatic status of patients was not recorded. Therefore analysis of patients by hepatic status of patients recruited in the phase III clinical programme was not performed. The SPC Section 4.4 states that for the treatment of superficial-vein thrombosis fondaparinux is not recommended in patients with severe hepatic impairment.

Bleeding with Coronary Interventions

- **CABG Surgery:** In patients undergoing CABG surgery in OASIS 5 and OASIS 6, study drug was stopped 24 hours prior to surgery and restarted 48 hours after surgery, where possible. The choice of anticoagulant during CABG surgery was at the investigator's discretion, although high doses of UFH are typically used. While the experience of patients undergoing CABG in STEMI patients is limited (experience in almost 1000 UA/NSTEMI patients indicates that the Day 9 major bleeding rate in fondaparinux patients was comparable to that with enoxaparin group (9.7% and 9.8%, respectively). As might be expected bleeding in both treatment groups was higher in CABG than non-CABG patients. Due to the absence of significant safety concerns and the need to be able to provide guidance to physicians managing ACS patients who warrant CABG, the SPC Section 4.2 provides the same guidance for stopping/restarting fondaparinux as employed in the phase III studies as described above.
- **PCI:** Although there is substantial experience in the ACS studies with fondaparinux patients undergoing PCI, this was with IV fondaparinux as adjunct to the procedure. Fondaparinux is not recommended for use as the sole anticoagulant during PCI. Section 4.2 of the SPC specifically recommends that patients undergoing non-primary PCI whilst receiving fondaparinux therapy should be administered IV UFH per standard practice. Consideration should be given taking into account the patient's potential risk of bleeding, including the timing of PCI relative to the last dose of fondaparinux.

The concluded post-authorisation safety study (AR1108888/OASIS 8/FUTURA) evaluated the safety of fondaparinux in patients undergoing PCI with adjunctive UFH (N=2026). Two UFH regimens were studied with the low dose group having a median total dose of 50U/kg and the standard dose group having a median total dose of 85U/kg. The incidence of peri-PCI major bleeding was similar in the low dose UFH group compared to the standard dose UFH group (1.4% vs. 1.2%). The incidence of peri-PCI minor bleeding was lower in the low dose UFH group compared with the standard dose UFH group (0.7% vs. 1.7%) and this difference was statistically significant (p=0.042).

Epidemiology

Bleeding is a major complication of anticoagulant and fibrinolytic therapy. The risk of bleeding varies depending on the underlying disease, concomitant medications, the intensity and duration of treatment [Schulman, 2008].

In general, all anticoagulants have a certain risk for hemorrhagic complications due to their very mode of action. With all anticoagulants currently in use, the bleeding risk is dose-related [De Caterina , 2007]. Age >70 was found to be a risk factor for major bleeding with UFH, LMWHs, VKAs and probably all other anticoagulants. Recent surgery, trauma or invasive procedures also increase bleeding risk. Underlying disease contributing to a higher risk of bleeding include: hypertension, cerebrovascular disease, ischemic stroke, serious heart disease, cancer and renal failure.

Among ACS patients, baseline demographic and clinical characteristics were found to identify patients at higher risk of bleeds using data from GRACE (Global Registry of Acute Coronary Events). Advanced age, female gender, history of bleeding and renal insufficiency was found to be independently associated with a higher risk of bleeding in the 24,045 patients analysed. This association remained after controlling for the use of invasive procedures and hospital therapies.

Among major surgery patients, orthopaedic procedures are associated with the greatest risk for perioperative thrombosis, (40% to 60% risk for those not receiving prophylaxis) [Shorr, 2007]. In an analysis of 144,806 major orthopaedic surgery patients age 18 years and older that received prophylaxis from over 500 hospitals in the Premier Perspective Comparative Database between 1.1% and 1.9% of patients experienced a major bleed depending on treatment. Patients treated with dalteparin were least likely to experience a bleed whereas there was no difference in bleeding among those treated with enoxaparin, fondaparinux or UFH. In a similar analysis including 68,301 adults age 75 years undergoing orthopaedic surgery in the same database, major bleeds occurred in 2% to 3% of patients depending on treatment [Horblyuk 2008]. No statistically significant differences in major bleeding events were found among those treated with dalteparin, enoxaparin, fondaparinux or UFH.

Details of all identified and potential risk are provided in Table 26 below:

Table 26 Identified and Potential Risks

Important Identified Risk	Bleeding events
Frequency	Haemorrhagic adverse reactions (various sites including rare cases of intracranial/intracerebral and retroperitoneal bleedings) reported from all clinical studies are reported as a common reaction in the Global Datasheet defined as occurring in ≥ 1/100 to <1/10 subjects.

	See text above table for discussion of bleeding events from clinical trials.
Impact on the Individual Patient	Bleeding complications can range in severity from mild to severe and also have the potential to be life threatening. Bleeding complications can worsen with continued fondaparinux therapy.
Public Health Impact	There is no anticipated major public health concern.
Patient Characteristics Relevant to Risk	Fondaparinux must be used with caution in patients with concurrent conditions that increase the risk of haemorrhage, such as congenital or acquired bleeding disorders, active ulcerative gastrointestinal disease, recent intracranial haemorrhage, shortly after brain, spinal or ophthalmic surgery. Patient characteristics relevant to increased risk of bleeding for each indication are described below <u>All Indications</u> Patients with body weight less than 50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with decreased weight. The elderly population is at increased risk of bleeding. As renal function generally decreases with age, elderly patients may show reduced elimination and increased exposure of fondaparinux. The plasma clearance of fondaparinux decreases with the severity of renal impairment and is associated with an increased risk of haemorrhage. Patients with renal impairment, particularly those with a creatinine clearance of less than 30 ml/min are at increased risk of both major bleeding episodes and VTE. In patients with an elevation in prothrombin time, the use of fondaparinux should be considered with caution, because of an increased risk of bleeding due to a possible deficiency of coagulation factors in patients with severe hepatic impairment <u>Prevention and Treatment of VTE</u> Other medicinal products enhancing the risk of haemorrhage, with the exception of vitamin K antagonists used concomitantly for treatment of VTE, should not be administered with fondaparinux. If co-administration is essential, close monitoring of the patient is recommended. <u>Prevention of VTE following surgery</u>

	The timing of the first injection requires strict adherence. The first dose should be given no earlier than 6 hours following surgical closure, and only after haemostasis has been established. Administration before 6 hours has been associated with an increased risk of major bleeding. Patient groups at particular risk are those from 75 years of age, body weight of less than 50 kg, or renal impairment with creatinine clearance less than 50 ml/min. <u>Treatment of UA/NSTEMI and STEMI or Treatment of superficial-vein thrombosis</u> Fondaparinux should be used with caution in patients who are being treated concomitantly with other medicinal products that increase the risk of haemorrhage.
Duration of Treatment/Risk Period	Bleeding can occur at any time after treatment with fondaparinux is started.
Reversibility	There is no known antidote for fondaparinux. Bleeding complications should lead to treatment, discontinuation and search for the primary cause. Initiation of appropriate therapy which may include surgical haemostasis, blood replacements, fresh plasma transfusion and plasmaphoresis should be considered.
Preventability	Routine risk minimisation via labelling: Warnings and precautions for use of fondaparinux with respect to the risk of haemorrhage are described in the current labelling. Patients with conditions that enhance the risk of bleeding and populations at risk for bleeding as outlined above in 'Patient Characteristics Relevant to Risk' must be carefully evaluated and monitored if receiving fondaparinux.
Potential Mechanism	Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of Factor Xa. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development.
Evidence source and strength of evidence	Since fondaparinux acts on the coagulation pathway, the potential for bleeding is an expected adverse event. Clinical trial data and post marketing reports provide strong evidence for the link between fondaparinux and bleeding events.

MedDRA Term	Haemorrhages (SMQ) broad

Important Identified Risk	Off-label use (for use of fondaparinux in VTE treatment and prophylaxis)
Frequency	Off-label use of medications, including anti-coagulants, is common in medical practice. The global estimated reporting rate of spontaneous reports associated with off-label use has been steadily decreasing since this risk was first identified in 2007. It should be noted that spontaneous reporting rates do not reflect the true incidence rates of an adverse event for a variety of reasons including under-reporting of adverse events by health care professionals, which may be influenced by time on the market and familiarity with the drug.
Impact on the Individual Patient	The impact on the individual patient will vary depending on the characteristics of off-label use (i.e. use for unapproved indication, incorrect indication/dose combination, use beyond labelled duration) as well as individual patient risk factors for haemorrhage.
Public Health Impact	There is no anticipated public health concern.
Patient Characteristics Relevant to Risk	Not applicable
Duration of Treatment/Risk Period	Not applicable
Reversibility	Not applicable
Preventability	Routine risk minimisation via labelling: Indications for use are accurately reflected in the approved labelling. Additionally, MAH does not promote off-label use of its products. Following identification of a disproportionate number of reports of serious bleeding complications in association with unauthorised indications in France vs. Rest of World, MAH issued a Dear Health Care Provider letter in France in June 2007 in an effort to curtail inappropriate prescribing practices.
Potential Mechanism	Not applicable
Evidence source and strength of evidence	Spontaneous adverse event reports continue to highlight off-label use of fondaparinux with the majority of reports received from

	France. However, the estimated reporting rate of spontaneous adverse events associated with off-label use has steadily decreased over the last seven years both in France and globally.
MedDRA Term	Off label use

Important Identified Risk	Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI (for use of fondaparinux for treatment of ACS)
Frequency	Clinical trials have shown a low but increased risk of guiding catheter thrombus in patients treated solely with fondaparinux for anticoagulation during PCI compared to control. Incidences in non-primary PCI in UA/NSTEMI were 1.0% vs. 0.3% (fondaparinux vs. enoxaparin) and in primary PCI in STEMI were 1.2% vs. 0% (fondaparinux vs. control). In fondaparinux-treated UA/NSTEMI patients randomised to receive “standard dose” or “low dose” regimens of UFH during non-primary PCI, the incidences of catheter thrombus were 0.1% and 0.5%, respectively.
Impact on the Individual Patient	A catheter thrombosis can lead to replacement of PCI equipment (coronary guidewires, balloon catheter shaft, guide catheter) and/or intracoronary clot propagation and embolization and coronary thrombosis.
Public Health Impact	There is no anticipated major public health concern
Patient Characteristics Relevant to Risk	Not applicable
Duration of Treatment/Risk Period	A catheter thrombus can occur if fondaparinux is used as the only anticoagulant during PCI in patients with UA/NSTEMI or STEMI during the catheterization procedure.
Reversibility	A catheter thrombus cannot be reversed but the PCI equipment can be replaced.
Preventability	Routine risk minimisation via labelling: In STEMI patients undergoing primary PCI for reperfusion, the use of fondaparinux prior to and during PCI is not recommended. In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended, therefore UFH should be used according to

	standard practice.
Potential Mechanism	A definitive mechanism has not been identified. However, information available in the published literature suggest that (1) catheters are prothrombotic because of their propensity to activate fXII, thereby initiating the contact pathway of coagulation; (2) heparin attenuates this phenomenon, and (3) supplemental bivalirudin or low-dose heparin promotes the capacity of fondaparinux to inhibit catheter-induced clotting [Yau 2011.]
Evidence source and strength of evidence	Catheter thrombus is not well reported in the clinical setting. However, the clinical trial data provides evidence for the link between fondaparinux as the only anticoagulant during PCI in UA/NSTEMI and STEMI patients and the occurrence of catheter thrombus.
MedDRA Term	Catheter site related reaction, Thrombosis in device, Device occlusion

Important Potential Risk	Heparin induced thrombocytopenia (all indications)
Frequency	In the phase III studies for VTE prophylaxis and VTE treatment as well as superficial vein thrombosis there were no reports of HIT, while in the UA/NSTEMI study (OASIS 5) there were 3 SAEs of HIT occurring in fondaparinux patients by Day 30. Two of these had positive HIT tests and all 3 cases were confounded by the possible use of heparin during CABG. Rare spontaneous reports of HIT in patients treated with fondaparinux have been received (≥ 1/10,000, <1/1,000), although a causal association has not been established.
Impact on the Individual Patient	Heparin induced thrombocytopenia can result in a low platelet count and a pro-coagulable state which can lead to thrombosis.
Public Health Impact	There is no anticipated major public health concern.
Patient Characteristics Relevant to Risk	Fondaparinux should be used with caution in patients with a history of HIT.
Duration of Treatment/Risk Period	HIT could occur after one dose of fondaparinux.
Reversibility	HIT is not reversible. If HIT is suspected, fondaparinux must be discontinued and the patient should be treated as appropriate.

Preventability	Routine risk minimisation via labelling: Fondaparinux should be used with caution in patients with a history of HIT.
Potential Mechanism	Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT)-type II.
Evidence source and strength of evidence	Spontaneous adverse event reports have been reported rarely. To date a causal association between treatment with fondaparinux and the occurrence of HIT has not been established.
MedDRA Term	Heparin-induced thrombocytopenia, Heparin-induced thrombocytopenia test

Important Potential Risk	Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis (for use of fondaparinux for treatment of SVT)
Frequency	There is the potential for health care providers to use fondaparinux with higher doses that are not approved for treatment of superficial-vein thrombosis (5 mg, 7.5 mg and 10 mg). There is no data available on the frequency of this occurrence.
Impact on the Individual Patient	Patients receiving doses other than 2.5 mg for treatment of superficial-vein thrombosis could potentially lead to an increased risk of bleeding events.
Public Health Impact	There is no anticipated major public health concern.
Patient Characteristics Relevant to Risk	Not applicable.
Duration of Treatment/Risk Period	Risk period corresponds to time period that the patient is receiving the incorrect dose.
Reversibility	Not applicable
Preventability	Routine risk minimisation via labelling: Proper dosing instructions for the treatment of superficial-vein thrombosis are provided in the current labelling.
Potential Mechanism	Not applicable
Evidence source and strength of evidence	This is a potential risk which has not yet been substantiated via spontaneous adverse event reporting. A post marketing safety study is being conducted to evaluate health care providers'

	adherence to the prescribing information regarding use of fondaparinux for treatment of superficial vein thrombosis.
MedDRA Terms	Not applicable

Important Potential Risk	Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT (for use of fondaparinux for the treatment of SVT)
Frequency	There is the potential for health care providers to use fondaparinux for treatment of superficial-vein thrombosis in patients with concomitant DVT. There is no data available on the frequency of this occurrence.
Impact on the Individual Patient	If prescribers do not objectively rule out DVT, there is the potential for use of fondaparinux 2.5mg in superficial-vein thrombosis patients with unrecognized concomitant DVT. However, the appropriate treatment of asymptomatic DVT is not well established since clinical trials for the treatment of DVT have focused on symptomatic presentations. It is possible that such patients may require higher treatment doses of fondaparinux (i.e., 7.5mg adjusted for body weight). Therefore, there could potentially be an increase in reporting of terms representative of lack of effect (i.e., DVT, PE) due to the subsequent identification of pre-existing DVT or complications due to sub-therapeutic dosing.
Public Health Impact	There is no anticipated major public health concern.
Patient Characteristics Relevant to Risk	Concomitant DVT
Duration of Treatment/Risk Period	Risk period corresponds to time period that the patient is receiving incorrect treatment doses.
Reversibility	Not applicable.
Preventability	Routine risk minimisation via labelling: Proper dosing instructions for the treatment of superficial-vein thrombosis and warnings to reinforce use in the proper patient population (i.e. presence of superficial-vein thrombosis should be confirmed and concomitant DVT should be objectively excluded) are provided in the current labelling.
Potential Mechanism	Not applicable
Evidence source and	This is a potential risk which has not yet been substantiated via

strength of evidence	spontaneous adverse event reporting. A post marketing safety study is being conducted to evaluate health care providers' adherence to the prescribing information regarding use of fondaparinux for treatment of superficial vein thrombosis.
MedDRA Terms	Not applicable

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Effect of Food

Since fondaparinux, administered by subcutaneous injection, is rapidly and completely absorbed (absolute bioavailability is 100%), there is no potential for the ingestion of food to affect the pharmacokinetic profile of the drug. Similarly, there is no potential for the ingestion of food to affect the pharmacokinetic profile of fondaparinux after intravenous administration.

Potential for Drug Interactions

Fondaparinux is highly (at least 94%) and specifically bound to ATIII and does not bind significantly to other plasma proteins (including platelet Factor 4 [PF4]) or red blood cells. No drug interactions by protein-binding displacement are expected.

In an in vitro study in human liver microsomes, inhibition of CYP2A6 hydroxylation of coumarin by fondaparinux (200 μM i.e., 350 mg/L) was 17% to 28%. Inhibition of the other isozymes evaluated (CYPs 2A1, 2C9, 2C19, 2D6, 3A4, and 3E1) was 0% to 16%. Since fondaparinux does not markedly inhibit CYP450 enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4) in vitro, fondaparinux is not expected to significantly interact with other drugs in vivo by inhibition of metabolism mediated by these isozymes.

In drug-drug interaction studies performed with fondaparinux in healthy volunteers, the concomitant use of oral anticoagulants (warfarin), platelet inhibitors [acetylsalicylic acid (ASA)], non-steroidal anti-inflammatory drugs (NSAIDs) (piroxicam), digoxin, forced diuresis with or without furosemide, and recombinant factor VIIa did not affect the pharmacokinetics of fondaparinux. In addition, fondaparinux did not influence the pharmacodynamic profile of warfarin, ASA, piroxicam and digoxin, or the pharmacokinetic profile of digoxin at steady state.

SVII.4.2 Important identified and potential interactions

None

SVII.5 Pharmacological class effects

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

Major bleeding

Fondaparinux is a synthetic anti-thrombotic agent acting through indirect inhibition of factor Xa. Like all anti-thrombotic agents, it is associated with risk of bleeding due to its pharmacologic mechanism of action.

Table 27 Pharmacological class risks already included as important identified or potential risks

Risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class	Comment
Major Bleeding	The frequency of any bleeding (major + minor + other) with fondaparinux across the clinical trial programme for all indications ranges from approximately 3 to 7%. (see section SVII.3)		
	VTE prophylaxis in preoperative randomisation orthopaedic surgery: Fondaparinux 2.5mg SC OD Major bleeding: 3.3% Any bleeding: 7.3%	Enoxaparin Major bleeding: 2.6% Any bleeding: 5.9%	Phase III studies 63118 (Ephesus) and EFC2698 (Penthifra)
	VTE prophylaxis in postoperative randomisation orthopaedic surgery: Fondaparinux 2.5mg SC OD Major bleeding: 1.9% Any bleeding: 3.8%	Enoxaparin Major bleeding: 1.1% Any bleeding: 3.7%	Phase III studies EFC2442 (Pentathlon 2000) and 095-002 (Pentamaks)
	VTE prophylaxis in abdominal Surgery: Fondaparinux 2.5mg SC	Dalteparin Major bleeding: 2.4% Any bleeding: 4.0%	Phase III study ECF3557 (Pegasus)

Risk	Frequency in clinical trials of medicinal product	Frequency seen with other products in same pharmacological class	Comment
	OD Major bleeding: 3.4% Any bleeding: 5.6%		
	Treatment of UA/NSTEMI: Fondaparinux 2.5mg SC OD Major bleeding: 2.1% Severe haemorrhage: 1.5%	Enoxaparin Major bleeding: 4.1% Severe haemorrhage: 2.6%	Phase III study AR1103420 (OASIS 5)
	Treatment of STEMI: Fondaparinux 2.5mg SC OD Major bleeding: 1.7% Severe haemorrhage: 1.1%	Control (placebo/UFH) Major bleeding: 2.1% Severe haemorrhage: 1.4%	Phase III study AR2103413 (OASIS 6)
	Treatment of UA/NSTEMI undergoing PCI Fondaparinux 2.5mg SC +low dose UFH[1] Peri-PCI major bleeding: 1.4% Fondaparinux 2.5mg SC +standard dose UFH[2] Peri-PCI major bleeding: 1.2%	Enoxaparin Peri-PCI major bleeding: 3.4%	Phase III study AR1103420 (OASIS 5) Phase III/IV study AR1108888 (OASIS 8/ FUTURA)
	Treatment of VTE Fondaparinux 5, 7.5, 10mg SC OD Major bleeding: 1.2% Any bleeding: 4.3%	Enoxaparin Major bleeding: 1.2% Any bleeding: 4.2% UFH Major bleeding: 1.1% Any bleeding: 6.3%	Phase III studies EFC2441 (Matisse-DVT) and 63123 (Matisse-PE)

1. In FUTURA, for the low dose UFH regimen, all subjects received 50 U/kg bolus irrespective of planned GPIIb/IIIa use.
2. In FUTURA, the standard dose UFH regimen used was as follows: 1) No planned GPIIb/IIIa use: 85 U/kg bolus with additional bolus (2,000 U – 4,400U) if needed, to achieve a target ACT of 300 – 350 seconds (using the Hemochron device) or ACT of 250 – 300 seconds (using the HemoTec device), 2) Planned GPIIb/IIIa use: 60 U/kg bolus with additional bolus (2,000 U – 4,000U) if needed, to achieve target ACT of ≥200 seconds (using the Hemochron or HemoTec device). The median total dose in this group was 85U/kg.

SVII.5.2 Important pharmacological class effects not discussed above

None

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 28 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Bleeding events • Off label use (VTE treatment and prevention) • Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI (for the treatment of ACS)
Important potential risks	• Heparin induced thrombocytopenia • Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis • Use of fondaparinux 2.5mg in superficial-vein thrombosis patients with concomitant DVT
Missing information	• Use in paediatric patients

PART III: PHARMACOVIGILANCE PLAN

III.1 Safety concerns and overview of planned pharmacovigilance actions

Table 29 Safety concerns and overview of planned pharmacovigilance actions

Important Identified Risks:

Safety concern 1: Bleeding events		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	Continued monitoring and regular and systematic review of available safety data. To evaluate signals in a timely fashion.
	Additional pharmacovigilance: • The use of a targeted follow-up questionnaire for reports of haemorrhage.	To ensure consistency of data collected for spontaneous reports of haemorrhage with respect to risk factors for haemorrhage across all approved indications.

Safety concern 2: Off label Use (VTE treatment and prevention)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	Continued monitoring and regular and systematic review of available safety data. To evaluate signals in a timely fashion.
	Additional pharmacovigilance: • The use of a targeted follow-up questionnaire for reports of haemorrhage, which are issued regardless of treatment indication.	The targeted follow up questionnaires issued for spontaneous reports of haemorrhage are issued regardless of treatment indication. Therefore, information obtained will help to characterize risk factors for haemorrhage reported from off-

Safety concern 2: Off label Use (VTE treatment and prevention)		
		label use as well.

Safety concern 3: Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	Continued monitoring and regular and systematic review of available safety data. To evaluate signals in a timely fashion.
	Additional pharmacovigilance: • Use of targeted follow up questionnaire for spontaneous reports of catheter thrombosis	To ensure consistency of data collected for spontaneous reports of catheter thrombus in patients receiving fondaparinux for the treatment of ACS.

Important potential risks:

Safety concern 1: Heparin Induced Thrombocytopenia		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Although fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with HIT-type II, HIT is a concern with heparins/low molecular weight heparins and requires ongoing assessment for fondaparinux.	Routine pharmacovigilance	Continued monitoring and regular and systematic review of available safety data. To evaluate signals in a timely fashion.
	Additional pharmacovigilance: • The use of a targeted follow-up questionnaire for spontaneous reports of HIT	To ensure consistency of data collected for spontaneous reports of HIT

Safety concern 2: Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	Continued monitoring and regular and systematic review of available safety data. To evaluate signals in a timely fashion.
	Additional pharmacovigilance which includes: • Use of targeted follow-up questionnaire for spontaneous reports of haemorrhage • Conduct a drug utilization study regarding the use of fondaparinux for the treatment of superficial vein thrombosis (complete)	To ensure consistency of data collected for spontaneous reports of haemorrhage with respect to risk factors for haemorrhage across all approved indications To evaluate the physician adherence to the prescribing information regarding the use of fondaparinux for the treatment of superficial vein thrombosis

Safety concern 3: Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance	Continued monitoring and regular and systematic review of available safety data. To evaluate signals in a timely fashion.
	Additional pharmacovigilance which includes: • Conduct a drug-utilisation study regarding the use of fondaparinux for the treatment of superficial vein thrombosis (complete)	To evaluate the physician adherence to the prescribing information regarding the use of fondaparinux for the treatment of superficial vein thrombosis

Missing information:

Safety concern 1: Use of fondaparinux in paediatric patients		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Use of fondaparinux in paediatric patients	Routine pharmacovigilance	To identify safety data which add to the understanding of fondaparinux use in paediatric patients
	Additional pharmacovigilance: • Conduct a VTE treatment study in paediatric patients (planned- commitment to US FDA)	To further investigate the use of fondaparinux in paediatric patients

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

Table 30 Additional PV activities to assess the effectiveness of risk minimisation measures

Risk minimisation measure: Prescribing Information (routine risk minimisation via labelling)		
Component measured	Activity(ies)	Rationale
Physician adherence to prescribing information for the treatment of SVT	Conduct PASS study WWE115280: WEUSKOP5233 Arixtra Physician Adherence to the Prescribing Information in isolated superficial vein thrombosis (SVT) Patients	Primary outcome of this study was to measure the physician adherence to the prescribing information for the treatment of SVT

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

One study from the pharmacovigilance plan has been completed since the last update detailed in Table 32

Table 31 Other activities completed since last update of Pharmacovigilance Plan

Activity title: Comprehensive annual review of spontaneous reports of haemorrhage presented in the PSUR/PBRER (additional pharmacovigilance activity)	
Safety concern(s)	Identified risk of bleeding events

investigated	
Brief summary of results	Comprehensive evaluations of spontaneous reports of haemorrhage have been conducted annually since January 2008 and have been presented in the PSURs/PBRERs as part of additional pharmacovigilance measures. The presentation of case reports has been similar across each of the time periods covered by these evaluations; and the estimated reporting rate for spontaneous reports of haemorrhage has consistently decreased over time. Overall, neither the quantitative assessment of reporting rates nor the qualitative evaluation of cases identified any emerging concerns with regards to use of fondaparinux and no new risk factors for bleeding have been identified.
Implications	Comprehensive evaluations of spontaneous reports of haemorrhage will no longer be conducted on an annual basis; therefore this activity has been removed from the pharmacovigilance plan. All reports of haemorrhage, including reports of haemorrhage with fatal outcome, in patients treated with fondaparinux will continue to be closely monitored on an ongoing basis as part of MAH's routine proactive pharmacovigilance procedures. This was discussed in the PSUR/PBRER for the period 07 December 2011 to 06 December 2012, for which the PRAC recommendation indicated that the "PRAC considers by consensus that the risk-benefit balance of medicinal products containing the active substance fondaparinux sodium remains favourable and therefore recommends the maintenance of the marketing authorisations."
Activity title: Comprehensive annual review of spontaneous reports of off-label use presented in the PSUR/PBRER (additional pharmacovigilance activity)	
Safety concern(s) investigated	Identified risk of off-label use
Brief summary of results	Comprehensive evaluations of spontaneous reports in the setting of off-label use of fondaparinux have been conducted annually since January 2008 and have been presented in the PSURs/PBRERs as part of additional pharmacovigilance measures. The presentation of case reports has been similar across each of the time periods covered by these evaluations; and the estimated reporting rate for spontaneous reports of haemorrhage in the setting of off-label use has consistently decreased over time. The change in reporting rates may reflect introduction of generics into the market place or may be due to changes in reporting patterns. With this understanding, neither the quantitative assessment of reporting rates nor the qualitative evaluation of cases identified any emerging concerns with regards to use of fondaparinux and no new risk factors for bleeding in the setting of off-label use of fondaparinux have been identified.
Implications	Comprehensive evaluations of spontaneous reports in the setting of off-label use will no longer be conducted on an annual basis; therefore this activity has been removed from the pharmacovigilance plan.

	All reports of off-label use in patients treated with fondaparinux will continue to be closely monitored on an ongoing basis as part of MAH's routine proactive pharmacovigilance procedures. This was discussed in the PSUR/PBRER for the period 07 December 2011 to 06 December 2012, for which the PRAC recommendation indicated that the "PRAC considers by consensus that the risk-benefit balance of medicinal products containing the active substance fondaparinux sodium remains favourable and therefore recommends the maintenance of the marketing authorisations."

III.4 Details of outstanding additional pharmacovigilance activities

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

None

III.4.2 Mandatory additional Phamacovigilance Activity (being a Specific Obligation)

None

Non-interventional studies included in categories 1 and 2 are subject to the supervision exercised under Articles 107 (m)-(q) of Directive 2001/83.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

Table 32 Required Additional Pharmacovigilance Activities

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
		1.	
2	AR1116442 A study to evaluate the safety, efficacy and	1. Draft protocol submitted to FDA	17 December 2013

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
	pharmacokinetics of two doses of Arixtra (fondaparinux sodium) versus standard of care in treatment of venous thromboembolism in paediatric patients	2. Planned study start	2014
		3. Planned report complete	2018

III.4.4 Stated additional pharmacovigilance activities

There are no additional activities in scope.

III.5 Summary of the Pharmacovigilance Plan

III.5.1 On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Table 33 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
AR1116442 A study to evaluate the safety, efficacy and pharmacokinetics of two doses of Arixtra (fondaparinux sodium) versus standard of care in treatment of venous thromboembolism in paediatric patients Interventional Category 3	Primary efficacy endpoint is a composite of: - all recurrent VTE up to Day 90 and - VTE related mortality up to Day 90 Safety endpoints: - Major bleeding, clinically relevant non-major bleeding, and	Use of fondaparinux in paediatric patients	Planned start 2014	Planned report complete 2018

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	minor bleeding			

III.5.2 Completed studies from the Pharmacovigilance Plan

Table 34 Completed studies from the Pharmacovigilance Plan

Study Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (Completed)	Date of submission of final study report
AR1108888 (FUTURA; OASIS 8)	Standard dose UFH vs. low-dose UFH as adjunct to PCI, in UA/NSTEMI patients receiving fondaparinux	Safety of fondaparinux in patients undergoing PCI with adjunctive UFH	Complete	14 Jan 2011
WEUSRTP2284 (OnPAAR)	Evaluation of Physician Adherence to Arixtra (fondaparinux sodium) Prescribing Information in the Treatment of Acute Coronary Syndrome (ACS)	Primary endpoint: proportion of patients with ACS treated with fondaparinux, for whom the prescribing information during PCI was followed	Complete	18 Jul 2011
WEUSRTP4388 Risk of hemorrhage in patients treated with ARIXTRA compared to LMWH	To assess the risk of haemorrhage associated with fondaparinux sodium compared to LMWHs in patients hospitalized and receiving VTE prophylaxis treatment for major orthopaedic surgery of lower limbs (MOSLL).	Risk of haemorrhage	Complete	Q3 2010
WWE115280 WEUSKOP5233	Evaluation of Physician Adherence to Arixtra (fondaparinux sodium)	1. Use of higher VTE treatment doses (5mg,	Complete	04 Sep 2015 (planned)

Study Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (Completed)	Date of submission of final study report
Arixtra Physician Adherence to the Prescribing Information in isolated superficial vein thrombosis (SVT) Patients Type: Observational, retrospective, medical record abstraction study Category 3	Prescribing Information in the treatment of SVT of the lower limbs.	7.5mg, 10mg) for treatment of superficial-vein thrombosis		

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV.1 Applicability of efficacy to all patients in the target population

There are no plans for additional efficacy studies in the target populations. The efficacy profile of the product is applicable for the approved indications/populations.

IV.2 Tables of post-authorisation efficacy studies

Not applicable

PART V: RISK MINIMISATION MEASURES

V.1 Risk minimisation measures by safety concern

Table 35 Risk minimisation measures by safety concern

Identified Risks:

Safety concern 1	Identified Risk: Bleeding events
Objective(s) of the risk minimisation measures	Prescribing information clearly communicates risk of bleeding to both prescribers and patients.
Routine risk minimisation measures	Current text in SPC: *4.4 Special warnings and precautions for use* *Haemorrhage* *Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm^3), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.* *[For 1.5 and 2.5mg:]* *For prevention of VTE - Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). When required, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.* *For treatment of UA/NSTEMI and STEMI-* *Fondaparinux should be used with caution in patients who are being treated concomitantly with other agents that increase the risk of haemorrhage (such as GPIIb/IIIa inhibitors or thrombolytics).* *For treatment of superficial-vein thrombosis - Fondaparinux should be used with caution in patients who are being treated concomitantly with other medicinal products that increase the risk of haemorrhage.* *[For 5, 7.5 and 10mg:]* *Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). During treatment of VTE, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-*

Safety concern 1	Identified Risk: Bleeding events
	administration is essential, close monitoring is necessary. Recommendation to use UFH for anti-coagulation during non- primary PCI in patients treated with fondaparinux taking into account individual bleeding risk including timing since last dose of fondaparinux (as shown below): *4.2 Posology and method of administration* *Treatment of unstable angina/non- ST segment elevation myocardial infarction (UA/NSTEMI) :* *If a patient is to undergo percutaneous coronary intervention (PCI), unfractionated heparin (UFH) as per standard practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux (see section 4.4). The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the pivotal UA/NSTEMI clinical trial, treatment with fondaparinux was restarted no earlier than 2 hours after sheath removal.* Fondaparinux is contraindicated in patients with severe renal failure, as shown below: *4.3 Contraindications (1.5 and 2.5mg)* *- severe renal impairment defined by creatinine clearance < 20 ml/min.* *4.3 Contraindications (5, 7.5 and 10mg)* *- severe renal impairment defined by creatinine clearance < 30 ml/min.* Dosage adjustments in severe to moderate renal impairment (creatinine clearance 20-50 mL/min) as shown below: *4.2 Posology and method of administration* *Renal impairment -* *Prevention of VTE - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min).* *Treatment of UA/NSTEMI and STEMI - Fondaparinux should not be used in patients with creatinine clearance < 20 ml/min (see section 4.3). No dosage reduction is required for patients with creatinine clearance > 20 ml/min.* *Treatment of superficial-vein thrombosis - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min). The safety and efficacy of 1.5 mg has not been studied (see section 4.4.)*

Safety concern 1	Identified Risk: Bleeding events
	Comment: None
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	Objective and justification of why needed. None
	Proposed actions/components and rationale: Not applicable

Safety concern 2	Identified Risk: Off label Use (VTE treatment and prevention)
Objective(s) of the risk minimisation measures	Prescribing Information clearly and accurately reflects the indications for use
Routine risk minimisation measures	Current text in SmPC: *4.1 Therapeutic indications* *Prevention of Venous Thromboembolic Events (VTE) in adult patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.* *Prevention of Venous Thromboembolic Events (VTE) in adult patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery (see section 5.1).* *Prevention of Venous Thromboembolic Events (VTE) in adult medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.* *Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis (see sections 4.2 and 5.1).* *Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adultspatients for whom urgent (< 120 mins) invasive management (PCI) is not indicated (see sections 4.4 and 5.1).* *Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.* *Treatment of adults with acute Deep Vein Thrombosis (DVT) and treatment of acute Pulmonary Embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy.*
	Comment: None

Safety concern 2	Identified Risk: Off label Use (VTE treatment and prevention)
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	Objective and justification of why needed: None
	Proposed actions/components and rationale: Not applicable

Safety concern 3	Identified Risk: Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI
Objective(s) of the risk minimisation measures	Prescribing information clearly communicates that: • fondaparinux is not recommended for use in primary PCI • fondaparinux is not recommended for use as the sole anti-coagulation adjunct to non-primary PCI • it is recommended that UFH is used for anti-coagulation during non-primary PCI in patients treated with fondaparinux
Routine risk minimisation measures	Current text in SmPC: *4.4 Special warnings and precautions for use* *PCI and risk of guiding catheter thrombus* *In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended. Similarly, in UA/NSTEMI patients with life threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during PCI is not recommended. These are patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life-threatening arrhythmias or haemodynamic instability.* *In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended due to an increased risk of guiding catheter thrombus (see clinical studies section 5.1).Therefore adjunctive UFH should be used during non-primary PCI according to standard practice (see posology in section 4.2).*
	Comment: None
	Other routine risk minimisation measures: None
Additional risk minimisation measure(s)	Objective and justification of why needed. None
	Proposed actions/components and rationale Not Applicable

Potential Risks:

Safety concern 1	Potential Risk: Heparin Induced Thrombocytopenia
Objective(s) of the risk minimisation measures	Prescribing information appropriately describes thrombocytopenia and the risk of HIT-type II
Routine risk minimisation measures	Current text in SPC: *4.4 Special warnings and precautions for use* *Patients with Heparin Induced Thrombocytopenia* *Fondaparinux should be used with caution in patients with a history of HIT. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II. Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. However, rare spontaneous reports of HIT in patients treated with fondaparinux have been received. To date a causal association between treatment with fondaparinux and the occurrence of HIT has not been established.*
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. None
	Proposed actions/components and rationale Not applicable

Safety concern 2	Potential Risk: Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis
Objective(s) of the risk minimisation measures	Prescribing information clearly states proper dosing instructions for the treatment of superficial-vein thrombosis
Routine risk minimisation measures	*4.2 Posology and method of administration* *Treatment of superficial-vein thrombosis* *The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Patients eligible for fondaparinux 2.5 mg treatment should have acute, symptomatic, isolated, spontaneous superficial-vein thrombosis of the lower limbs, at least 5 cm long and documented by ultrasonographic investigation or other objective methods. Treatment should be initiated as soon as possible following diagnosis and after exclusion of concomitant DVT or superficial-vein thrombosis within 3 cm from the sapheno-femoral junction. Treatment should be continued for a minimum of 30 days and up to a maximum of 45 days in patients at high risk of thromboembolic complications (see sections 4.4 and 5.1). Patients could be recommended to self-inject the product when they are judged willing and able to do so. Physicians should provide clear*

Safety concern 2	Potential Risk: Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis
	instructions for self-injection. *Patients who are to undergo surgery or other invasive procedures. In superficial vein thrombosis patients who are to undergo surgery or other invasive procedures, fondaparinux, where possible, should not be given during the 24 hours before surgery. Fondaparinux may be restarted at least 6 hours post- operatively provided haemostasis has been achieved.*
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Not applicable
	Proposed actions/components and rationale Not applicable

Safety concern 3	Potential Risk: Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT
Objective(s) of the risk minimisation measures	Prescribing information clearly and accurately reflects indications for use. Warning/Precaution to reinforce proper patient population (i.e. presence of superficial-vein thrombosis should be confirmed and concomitant DVT should be objectively excluded prior to initiation of therapy)
Routine risk minimisation measures	*4.1 Therapeutic indications* *Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis (see sections 4.2 and 5.1).* *4.4 Special warnings and precautions for use* *Patients with superficial-vein thrombosis:* *Presence of superficial-vein thrombosis greater than 3 cm from the sapheno-femoral junction should be confirmed and concomitant DVT should be excluded by compression ultrasound or objective methods prior to initiating treatment of fondaparinux. There are no data regarding the use of fondaparinux 2.5 mg in superficial-vein thrombosis patients with concomitant DVT or with superficial-vein thrombosis within 3 cm of the sapheno-femoral junction (see section 4.2 and 5.1).* *The safety and efficacy of fondaparinux 2.5 mg has not been studied in the following groups: patients with superficial-vein thrombosis following sclerotherapy or resulting as a complication of an intravenous line, patients with history of superficial-vein thrombosis within the previous 3 months, patients with history of venous thromboembolic disease within the previous 6 months, or patients with active cancer (see section 4.2 and 5.1).*

Safety concern 3	Potential Risk: Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Not applicable
	Proposed actions/components and rationale Not applicable

Missing information:

Safety concern 1	Use in paediatric patients
Objective(s) of the risk minimisation measures	Prescribing Information clearly communicates that fondaparinux is not recommended for use in children below 17 years of age
Routine risk minimisation measures	*4.2 Posology and method of administration* *Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy.*
	Comment None
	Other routine risk minimisation measures None
Additional risk minimisation measure(s)	Objective and justification of why needed. Not applicable
	Proposed actions/components and rationale Not applicable

Table 36 Effectiveness of risk minimisation measures

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	This will be managed by routine pharmacovigilance to monitor any change in terms of severity or frequency of each risk. Study WWE115280 (WEUSKOP5233) will evaluate physician adherence to the prescribing information for the treatment of SVT.
Criteria for judging the success of the proposed risk minimisation measures	Ongoing monitoring and evaluation of AEs reported shows consistency with the known safety profile for fondaparinux. Adherence in prescribing to the product label.
Planned dates for assessment	With each PSUR/PBRER Completion of study WWE115280 (WEUSKOP5233)
Results of effectiveness measurement	The latest assessments will be provided at each update to the EU RMP as required. The results of study WWE115280 (WEUSKOP5233) suggest that the majority of physicians' adhere to fondaparinux prescribing information when treating patients with SVT across four European countries
Impact of risk minimisation	Preventability of the safety concerns.
Comment	Adverse events reported with fondaparinux to date have been consistent with the safety profile. Due to the limited sample size, interpretation of the data and comparisons between groups should be made with caution.

V.2 Risk minimisation measure failure (if applicable)

No risk minimisation measures have been judged to have failed.

V.2.1 Analysis of risk minimisation measure(s) failure

Not applicable

V.2.2 Revised proposal for risk minimisation

There is no revised proposal for risk minimisation activities.

V.3 Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IDENTIFIED RISKS		
Bleeding events	Guidance to prescriber about the appropriate administration in patients undergoing percutaneous coronary intervention (PCI) or in patients with renal impairment in section 4.2 of SPC Contraindications for use in severe renal impairment in section 4.3 of SPC Warning in section 4.4 of the SPC	No additional risk minimisation measures.
Off label Use (VTE treatment and prevention)	Therapeutic indications summarized in SPC section 4.1	No additional risk minimisation measures.
Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI	Warning in section 4.4 of the SPC	No additional risk minimisation measures.
POTENTIAL RISKS		
Heparin Induced Thrombocytopenia	Warning in section 4.4 of the SPC about possible Thrombocytopenia and the risk of HIT-type II	No additional risk minimisation measures.
Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis	Proper dosing instructions for the treatment of superficial-vein thrombosis are clearly provided in 4.2 of SPC	No additional risk minimisation measures.
Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT.	Indications for use are clearly and accurately reflected in Section 4.1 & warning statements in section 4.4 of the SPC	No additional risk minimisation measures.
MISSING INFORMATION		
Use in paediatric patients	Guidance to prescriber about the appropriate patient populations in	No additional risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	section 4.2 of SPC	

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

Summary of safety concerns	
Important identified risks	• Bleeding events • Off label use (VTE treatment and prevention) • Catheter thrombosis during PCI when fondaparinux is used as the sole anti-coagulant adjunct to PCI (for treatment of ACS)
Important potential risks	• Heparin induced thrombocytopenia • Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis • Use of fondaparinux 2.5mg in superficial-vein thrombosis patients with concomitant DVT
Missing information	• Use in paediatric patients

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
AR1116442 A study to evaluate the safety, efficacy and pharmacokinetics of two doses of Arixtra (fondaparinux sodium) versus standard of care	Primary efficacy endpoint is a composite of: - all recurrent VTE up to Day 90 and - VTE related mortality	Use of fondaparinux in paediatric patients	Planned start 2014	Planned report complete 2018

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
in treatment of venous thromboembolism in paediatric patients Interventional Category 3	up to Day 90 Safety endpoints: - Major bleeding, clinically relevant non-major bleeding and minor bleeding			

VI.1.3 Summary of post authorisation efficacy development plan

Not applicable

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
IDENTIFIED RISKS		
Bleeding events	Guidance to prescriber about the appropriate administration in patients undergoing percutaneous coronary intervention (PCI) or in patients with renal impairment in section 4.2 of SPC Contraindications for use in severe renal impairment in section 4.3 of SPC Warning in section 4.4 of the SPC	No additional risk minimisation measures.
Off label Use (VTE treatment and prevention)	Therapeutic indications summarized in SPC section 4.1	No additional risk minimisation measures.
Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI	Warning in section 4.4 of the SPC	No additional risk minimisation measures.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
POTENTIAL RISKS		
Heparin Induced Thrombocytopenia	Warning in section 4.4 of the SPC about possible Thrombocytopenia and the risk of HIT-type II	No additional risk minimisation measures.
Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis	Proper dosing instructions for the treatment of superficial-vein thrombosis are clearly provided in 4.2 of SPC	No additional risk minimisation measures.
Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT.	Indications for use are clearly and accurately reflected in Section 4.1 & warning statements in section 4.4 of the SPC	No additional risk minimisation measures.
MISSING INFORMATION		
Use in paediatric patients	Guidance to prescriber about the appropriate patient populations in section 4.2 of SPC	No additional risk minimisation measures

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

VTE - Venous thromboembolism

VTE is a condition when someone develops a blood clot in a vein. VTE covers two types of blood clots: deep vein thrombosis (DVT, a clot in a vein deep in the leg) and/or pulmonary embolism (PE, a clot that travels to the lungs). About 0.06-0.2% of people get this condition each year. It occurs in both men and women and is very rare in children. About 25% of VTE's cannot be linked to any identifiable underlying cause. Risk factors include fracture (hip or leg), hip or knee replacement, major general surgery, major trauma and spinal cord injury, chemotherapy, heart or lung failure, hormone replacement therapy, cancer, oral contraceptive therapy, stroke, pregnancy, immobility, increasing age, obesity, and varicose veins. The condition is serious and can be fatal in about 22-29% of cases.

SVT – Superficial vein thrombosis

Superficial-vein thrombosis, also called 'Superficial thrombophlebitis,' is an inflammation of a vein just under the skin, usually in the leg. A small blood clot also commonly forms in the vein, but is usually not serious. SVT is common but is usually

not serious. However, it has been shown that SVT is a risk factor for the development and recurrence of VTE. SVT occurs in about 3-11% of the general population. It occurs more often in women than men. Common risk factors include increasing age, previous blood clots, pregnancy, oral contraceptives, hormone replacement therapy, prolonged flights/immobilization, recent surgery, trauma, obesity, auto-immune disease. Most importantly, varicose veins (enlarged veins near the skin surface), occurring in 80-90% of people with SVT, appear to be a major risk factor.

ACS – Acute coronary syndrome

Worldwide cardiovascular diseases are the leading cause of death (29%) 32% of all death in women and 27% of all death in men. ACS is a form of heart disease called heart attack (myocardial infarction) responsible for 2.2 million deaths in Europe. In the US an estimated number of 1,190,000 hospitalizations for ACS occurred in 2009; 694,000 were males, and 496,000 were females. The risk factors for ACS include a history of diabetes, high blood pressure, high lipid levels (cholesterol, LDL), smoking, obesity, limited or lack of physical activity, prior heart disease. Improvements in the management of ACS patients through medicines and stents to keep heart arteries open were found to be linked with significant reduction in outcomes such as death and heart failure. Subjects at high risk of heart attack are commonly treated with medications to lower cholesterol levels (known as "statins").

VI.2.2 Summary of treatment benefits

Prevention and Treatment of Blood Clot (Venous Thromboembolic) Events

Arixtra was at least as effective as comparators in all of the studies that looked at the prevention of blood clot (venous thromboembolic [VTE]) events, treatment of blood clots in the deep veins of the legs (deep vein thrombosis [DVT]), and treatment of blood clots that travel to the lungs (pulmonary embolism [PE]).

Prevention of VTE:

- In patients treated with Arixtra, the overall rate of VTE was significantly less than in patients given dummy treatment (placebo) or enoxaparin (for patients undergoing leg surgery).
- The rate of VTE was similar to dalteparin for patients having belly surgery.

Treatment of DVT and PE:

- Treatment of DVT and PE with Arixtra was not less effective than treatment with enoxaparin or unfractionated heparin (UFH).

Treatment of Superficial Vein Thrombosis

Arixtra was more effective than placebo in reducing the overall occurrence of VTE or death in patients with blood clots in veins close to the surface of the skin of the legs

(superficial-vein thrombosis). About 1% of patients taking Arixtra and about 6% taking placebo had a VTE or died.

Treatment of Acute Coronary Syndromes (chest pain and heart attacks)

Chest pain (unstable angina [UA]) and heart attack (myocardial infarction without ST-segment elevation [NSTEMI])

- Arixtra was as effective as enoxaparin in preventing death, ongoing lack of blood flow to the heart (refractory ischemia), or heart attack.
- Around 6% of the patients in each group (Arixtra or enoxaparin) had one of the above events after nine days.

Heart attack (myocardial infarction with ST-segment elevation [STEMI])

- Arixtra was more effective in the prevention of death or a second heart attack after 30 days than placebo or unfractionated heparin (UFH).
- Arixtra also reduced the risk of death from any cause by 13% after 30 days compared to placebo or UFH.

VI.2.3 Unknowns relating to treatment benefits

Arixtra has been on the market for 12 years, therefore no further studies are needed to test the benefits in the approved indications. Based on the many years of experience with Arixtra use, the benefits to approved patient populations are well defined.

There is limited information on the use of Arixtra in children.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Bleeding events	Bleeding events (from various sites including rare cases of bleeding in the brain and bleeding in the space behind the lining of the belly area [abdomen]) are a common side effect that can occur in 1 in 100 to 1 in 10 people treated with Arixtra.	The Arixtra label contains warnings about the risk of bleeding. Arixtra should be used with caution in patients who have conditions that can increase the risk of bleeding (such as patients with bleeding disorders or those with active or recent bleeding, patients with severe liver problems). Patients with increased risk of bleeding (patients with low body weight, elderly, patients with kidney problems, patients on other medications that can increase risk of bleeding) must be carefully monitored if receiving Arixtra.
Off - label use (use of Arixtra for a condition or in a way that is not described in the product label)	Off-label use of medications is a common medical practice. A physician might prescribe Arixtra for a condition that it is not approved to treat. Adverse event reports received by MAH continue to show off-label use. In 2007, a higher than usual number of reports of bleeding events associated with off-label use were received from France.	The Arixtra label describes what the product should be used for and how it should be used.Reports of off-label use are monitored on an ongoing basis. Letters to Health Care Providers can be sent in an effort to limit off label use (MAH sent out such a letter in 2007 in France).
A clot in the tube used during a procedure to open a blood vessel in the heart (Catheter thrombosis during Percutaneous Coronary Intervention [PCI]) when Arixtra is used as the only medicine to prevent blood clots during this procedure.	Clinical trials have shown a low but increased risk of clots in the catheter tube in patients treated only with Arixtra to prevent blood clots during PCI compared to control group.	In patients with a certain type of heart attack called STEMI who are undergoing a procedure called primary PCI, the use of Arixtra prior to and during PCI is not recommended. In patients with chest pain (unstable angina) or heart attack (NSTEMI and STEMI) who need non-primary PCI, the use of

Risk	What is known	Preventability
		Arixtra as the only medicine to prevent blood clots during PCI is not recommended, therefore unfractionated heparin (another medicine used to prevent blood clots) should be used according to standard practice.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
A condition that results in a lower than normal number of blood cells that form blood clots (platelets) caused by a blood thinner called heparin (Heparin-induced thrombocytopenia [HIT])	Rare (more than 1 in 10, 000 but less than 1 in 1,000) reports of HIT in patients treated with Arixtra have been received; however, it is unknown if Arixtra causes HIT. Arixtra should be used with caution in patients who have had HIT in the past.
Use of high doses of Arixtra for the treatment of blood clots in veins just under the skin in the legs (superficial vein thrombosis)	Arixtra is used to treat superficial vein thrombosis at a dose of 2.5mg. There is a chance that health care providers might use higher doses of Arixtra (5mg, 7.5mg, or 10mg) to treat superficial vein thrombosis. This could lead to an increased risk of bleeding. This risk has not yet been confirmed by adverse event reports. A study is being done to see if health care providers are following the product label for the treatment of superficial vein thrombosis.
Use of 2.5 mg of Arixtra in patients with blood clots in veins just under the skin of the legs (superficial vein thrombosis) who also have blood clots in deep veins in the legs (deep vein thrombosis)	Arixtra is used to treat superficial vein thrombosis at a dose of 2.5 mg. Higher doses of Arixtra are required to treat deep vein thrombosis. There is the chance that health care providers might use 2.5 mg of Arixtra to treat superficial vein thrombosis in patients who also have a deep vein thrombosis that they do not know about. This could lead to a lack of effect for the treatment of the deep vein thrombosis. This risk has not yet been confirmed by adverse event reports. A study is being done to see if health care providers are following the product label for the treatment of superficial vein thrombosis.

Missing information

Risk	What is known
Use of Arixtra in children	There is limited information on the use of Arixtra in children. The Arixtra label states that its use is not recommended in children below the age of 17 years. A study of the use of Arixtra in children for the treatment of blood clot events (venous thromboembolic events) is

Risk	What is known
	planned.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Arixtra can be found in the Arixtra EPAR page

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
AR1116442 A study to evaluate the safety, efficacy and pharmacokinetics of two doses of Arixtra (fondaparinux sodium) versus standard of care in treatment of venous thromboembolism in paediatric patients Interventional Category 3	Primary efficacy endpoint is a composite of: - all recurrent VTE up to Day 90 and - VTE related mortality up to Day 90 Safety endpoints: - Major bleeding, clinically relevant non-major bleeding and minor bleeding	Use of fondaparinux children	Planned	2018

Studies which are a condition of the marketing authorisation

None of the above studies is a condition of the marketing authorisation.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 37 Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.9	11 March 2014	Identified risks: Bleeding events Off label use Potential risks: Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis Use of fondaparinux (2.5mg) in superficial-vein thrombosis patients with concomitant DVT. Missing Information: Use in paediatric patients	Identified Risks: Additional pharmacovigilance measures of comprehensive annual reviews of bleeding events and off-label use will no longer be conducted. These activities have been removed from the pharmacovigilance plan. Potential Risks: The planned submission date for the results of study WWE115280: WEUSKOP5233 Arixtra Physician Adherence to the Prescribing Information in isolated superficial vein thrombosis (SVT) Patients was updated to December 2014 Missing Information: A paediatric VTE treatment study required by the FDA was added to the pharmacovigilance plan. Additional comment: New EU RMP template implemented
2.0	31 August 2015	Effectiveness of risk minimisation measures Completion of study WWE115280: WEUSKOP5233 Arixtra Physician Adherence to the Prescribing Information in isolated superficial vein thrombosis (SVT) patients	No major risks identified in the results of study WWE115280: WEUSKOP5233 Arixtra Physician Adherence to the Prescribing Information in isolated superficial vein thrombosis (SVT) Patients. The majority of physicians adhere to the prescribing information when treating patients with SVT across 4 European countries.

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SVT Study Report: WE115280: WEUSKOP5233 Physician Adherence to Fondaparinux Prescribing Information for Patients with Superficial Vein Thrombosis (SVT) of the Lower Limbs. Dec 16, 2014

ANNEX 7. SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Aspen Pharma Trading Limited

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Arixtra (fondaparinux) and Catheterization-related Thrombosis

Patient/subject ID, DOB/initials:	Sex/weight (is patient obese if weight unknown):	ASPEN OCEANS CASE No:

Description of the Event:		
Indication for Cardiac Catheterization		
Unstable Angina (UA)	☐	
Non-ST Elevation Myocardial Infarction (NSTEMI)	☐	
ST Elevation Myocardial Infarction (STEMI)	☐	
Stable Coronary Artery Disease (CAD)	☐	
Did the observed thrombus occur during:	**Yes**	**No**
• Diagnostic Coronary Angiography?	☐	☐
• Primary Percutaneous Coronary Intervention (PCI)(initial reperfusion for STEMI)?	☐	☐
• Non-Primary PCI for STEMI (i.e. not initial reperfusion - includes PCI for recurrent ischemia/recurrent infarction, routine practice, rescue PCI for failed thrombolysis)?	☐	☐
• Elective or Urgent PCI for UA or NSTEMI?	☐	☐
• Elective PCI for stable CAD	☐	☐
For the procedure referred to above:		
Was fondaparinux administered within 48 hours prior to the procedure?	☐	☐
If yes, please provide the following:		
Date and time of last dose prior to procedure:		
Dose and route of fondaparinux prior to procedure:		
Duration of treatment prior to procedure:		
Date and time PCI started:		
Date and time of observed thrombus:		
Were anticoagulants (other than fondaparinux) administered within 24 hours prior to the procedure?	☐	☐
If yes, please specify (drug/dose/date/time):		
Were anticoagulants administered as adjunct to the procedure?	☐	☐
If yes, please specify the following:		
Drug/dose/date/time:		
Were anticoagulants administered *prior to* observed thrombus?	☐	☐
If yes, please specify (drug/dose/date/time):		
Were anticoagulants administered *after* observed thrombus?	☐	☐
If yes, please specify (drug/dose/date/time):		
Were any of the following anti-platelet therapies administered within 24 hours prior to the procedure AND prior to the observed thrombus:		
ASA (acetylsalicylic acid; aspirin)?	☐	☐
If yes, please specify dose/date/time:		
Thienopyridine (e.g. clopidogrel, ticlopidine)?	☐	☐
If yes, please specify dose/date/time:		
Glycoprotein IIb/IIIa inhibitor?	☐	☐
If yes, please specify drug/dose/date/time:		
Other (please specify):	☐	☐
If yes, please specify dose/date/time:		
Were additional antiplatelet therapies added after the observed thrombus?	☐	☐

[redacted]

If yes, please specify (drug/dose):		
Was fondaparinux administered after the procedure completed?	☐	☐
If yes, please provide date and time started/restarted and dose:		
Was the observed thrombus located (check all that apply):		
• In the coronary artery?	☐	☐
If yes, please specify: culprit vs. non-culprit vessel (circle one)		
If culprit vessel, could it have occurred from flushing forward of possible guiding/ angiography thrombus?	☐	☐
• In the guiding catheter or angiographic catheter?	☐	☐
If yes, please specify:		
Was there unexplained damping of the pressure trace during the procedure?	☐	☐
Was there clear evidence of thrombus flushed from within the catheter?	☐	☐
• On the hardware (e.g. balloon or guidewire)?	☐	☐
• In the femoral or radial access sheath?	☐	☐
• At the site of PCI?	☐	☐
Was there evidence of embolization from the guiding catheter?	☐	☐
If yes, specify coronary or non-coronary (circle one)		
Did the thrombus occur before any balloon inflation?	☐	☐
What were the direct consequences of the observed thrombus (mark all that apply)		
Prolonged procedure?	☐	☐
Prolonged hospitalization?	☐	☐
New thrombus in a coronary artery?	☐	☐
ECG evidence of MI?	☐	☐
Clinically significant elevation of Troponin and/or CPK? *If yes, please specify:*	☐	☐
Arrhythmia	☐	☐
Hemodynamic instability	☐	☐
Distal embolization in coronary artery	☐	☐
Peripheral embolization	☐	☐
Thrombotic stroke	☐	☐
Death	☐	☐
Other (please specify):	☐	☐
None	☐	☐
How was the observed thrombus treated?		
No treatment was necessary	☐	☐
New PCI +/- Stent	☐	☐
Additional anti-platelets?	☐	☐
If yes, please specify (drug/dose):		
Additional anti-coagulants?	☐	☐
If yes, please specify (drug/dose):		
Additional thrombolytics?	☐	☐
If yes, please specify (drug/dose):		
Clot extraction	☐	☐
Catheter removal and replacement	☐	☐
Does the patient have a history of:		
Known or suspected hypercoagulable state/syndrome?	☐	☐
Heparin-Induced Thrombocytopenia?	☐	☐

Version date	Reason for amendment	Version Number
Jan-2020	New template - Questionnaire content is unchanged	2.0
Mar-2014	N/A	1.0

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Targeted Follow-Up Questionnaire – HAEMORRHAGE

Patient/subject ID, DOB/initials:	Sex/weight (is patient obese if weight unknown):	ASPEN CASE No:

Patient History:

Patient weight: _____ kg or lb (please specify unit)

Was the patient receiving concomitant treatment at the time of the reported haemorrhage with any of the following:

- Unfractionated heparin? ☐Yes ☐ No
- LMWH (e.g. enoxaparin, dalteparin, tinzaparin)? ☐Yes ☐ No
- Vitamin K antagonist (e.g. warfarin, fluindione)? ☐Yes ☐ No
- GIIb/IIIa inhibitor (e.g. eptifibatide, abciximab, tirofiban)? ☐Yes ☐ No
- NSAID (e.g. ibuprofen, ketoprofen)? ☐Yes ☐ No
- Aspirin? ☐Yes ☐ No
- Platelet inhibitors (e.g. clopidogrel, ticlopidine) ☐Yes ☐ No
- Direct thrombin inhibitors (e.g. argatroban) ☐Yes ☐ No
- Herbal supplements (e.g., *Ginkgo biloba*) ☐Yes ☐ No
- Omega 3 fatty acid ethyl esters ☐Yes ☐ No

Did the patient experience / have a Past Medical History consistent with any of the following at or around the time of the reported haemorrhage:

- Recent trauma (i.e. fall, injury)? ☐Yes ☐ No
- Coagulopathy, congenital or acquired? ☐Yes ☐ No
- Thrombocytopenia or known platelet malfunction? ☐Yes ☐ No
- Liver problems? ☐Yes ☐ No
- Malabsorption syndromes/GI or nutritional problems? ☐Yes ☐ No
- Vitamin K deficiency? ☐Yes ☐ No
- Cancer? ☐Yes ☐ No
- Bone marrow suppression or failure? ☐Yes ☐ No

Description of Fondaparinux Use:

Indication for use of fondaparinux:

☐ VTE prevention following orthopaedic surgery
☐ VTE prevention following abdominal surgery
☐ VTE prevention for medical patients
☐ VTE treatment
☐ Treatment of superficial vein thrombosis
☐ Treatment of ACS
☐ Other indication (please specify): _____

Dates of first and last dose of fondaparinux? _____
Dose of fondaparinux: _____

[redacted]

Diagnostic Tests

Laboratory tests, including:

Serum Creatinine:

	Date	Value ☐ mg/dL ☐ umol/L	Normal Range
Baseline (control)			
Subsequent values (including value at time of event)			

Platelet Count:

	Date	Value	Normal Range
Baseline (control)			
Subsequent values (including value at time of event)			

Version date	Reason for amendment	Version Number
Jan-2020	New template - Questionnaire content is unchanged"	2.0
Mar-2014	N/A	1.0

[redacted]

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FONDAPARINUX SODIUM (ARIXTRA™) and HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Patient/subject ID, DOB/initials:	Age/Sex:	ASPEN CASE No:

History:

Was the patient previously treated with fondaparinux in the last year?
☐Yes ☐ No
If yes, please specify dose and dates of therapy: _____

Does the patient have a history of a bleeding or thrombotic disorder?
☐Yes ☐ No

Does the patient have a history of prior HIT or thrombocytopenia?
☐Yes ☐ No

Description of the Event:

Date of the first and last dose of fondaparinux? _____

Please specify the dose level and number of doses of fondaparinux that the patient took before developing HIT:
Dose: _____mg Number of doses: _____

Did the patient develop any new thrombotic complications (e.g., pulmonary embolism, deep vein thrombosis) after developing HIT?
☐Yes ☐ No
If yes, please specify: _____
If yes, was this complication a result of, or associated with, HIT? ☐*Yes* ☐ *No*

Is the patient currently being treated with, or has the patient been treated with heparin, heparinoids (any sulfated polysaccharide with anticoagulant activity similar to heparin, e.g., danaparoid sodium), or low molecular weight heparin, including heparin flush of IV line within 3-6 months prior to treatment with fondaparinux?
☐Yes ☐ No

If the patient is/was previously treated with heparin, heparinoids, or low molecular weight heparin, please provide the following:
Drug name: _____Dose: _____
Start/Stop Date of last treatment:_____

Did the patient receive a transfusion of blood products?
☐Yes ☐ No

If yes, please specify type and amount: _____

Did the blood products contain heparin/heparinoids/LMWH?
☐Yes ☐ No

[redacted]

Diagnostic Tests

Please provide, if available, laboratory tests, including:

Platelet Count:

	Date	Value	Normal Range
Baseline (control)			
Subsequent values			

Were **diagnostic tests for detecting HIT antibodies** performed?

☐Yes ☐ No

If yes, please provide the following:

Test performed	Date	Value	Normal Range

Version date	Reason for amendment	Version Number
Jan-2020	New template - Questionnaire content is unchanged"	2.0
Mar-2014	N/A	1.0

[redacted]

ANNEX 10. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

Not applicable

ANNEX 11. MOCK-UP OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

Not applicable