London, 29 August 2007
Product Name: **Arixtra**
EMEA/H/C/403/X/25

SCIENTIFIC DISCUSSION

I. SCIENTIFIC DISCUSSION

1.1 Introduction

This line extension pertains exclusively to the 2.5 mg strength, where the Applicant is seeking authorisation for a new intravenous route of administration in the treatment of patients with *ST segment elevation myocardial infarction (STEMI) Acute Coronary Syndrome (ACS) who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.*

The related application EMEA/H/C/403/II/24, presenting the results of the pivotal clinical trials to support the use of fondaparinux in the treatment of patients with Unstable Angina or non-ST segment elevation *myocardial infarction (UA/NSTEMI)* ACS and patients with STEMI ACS, has been reviewed in parallel. Under the proposed clinical dosing regimen, patients with ACS will routinely receive 2.5 mg fondaparinux once daily via the established subcutaneous route for up to 8 days. In addition, in patients with STEMI, the first 2.5 mg dose will be given by the intravenous route. Intravenous doses will be administered either by syringe via an existing intravenous access or as a rapid infusion over 1 to 2 minutes via a small volume (25 or 50 ml) 0.9% saline minibag.

This report will only cover the new intravenous route of administration. The clinical discussion pertaining to the new indication is reflected in the assessment report for the type II variation (EMEA/H/C/403/II/24).

1.2 Quality aspects

The existing 2.5mg pre-filled syringe, as used for the approved subcutaneous route of administration, is to be used for the intravenous (i.v.) route of administration. The product is to be administered by infusion via an existing i.v. line by direct access or an isotonic sodium chloride solution (0.9%) mini bag.
Compatibility studies were carried out in order to ascertain the suitability of the i.v. route of administration via mini bags. Four mini bags from three different suppliers (Perfuflex and Freeflex 50 ml from Fresenius Kabi, Bioperf 50 ml from Aguettant and Viaflex 25 ml from Baxter) were evaluated. One or two syringes were injected into the bag and the compatibility studies (assay, pH, colour, clarity and particulate matter) were performed over a period of 48 hours at ambient temperature.

The study results demonstrate the compatibility of the drug product with the mini bags tested. Degradation products were always below their respective detection limit.
It may be concluded that there are no compatibility problems between Arixtra solution for injection diluted with 0.9% sodium chloride, and the mini bags tested. Storing the product in mini bags over a 24 hours time period is acceptable.

1.3 Non-clinical aspects

To support the original indication, fondaparinux underwent a comprehensive number of non-clinical studies which were submitted as part of the initial Marketing Authorization. No new non-clinical studies were submitted for the current application.

Since the human systemic exposure is lower with 2.5 mg IV than with the already approved 7.5 mg SC no additional toxicity studies were deemed necessary in respect of systemic exposure.

Non-clinical data reveal no special risk for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

The previously submitted toxicological program sufficiently addresses the IV route and no additional data was considered necessary to allow toxicological characterization following IV administration. Therefore the application can be approved from a non-clinical point of view.

1.4 Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

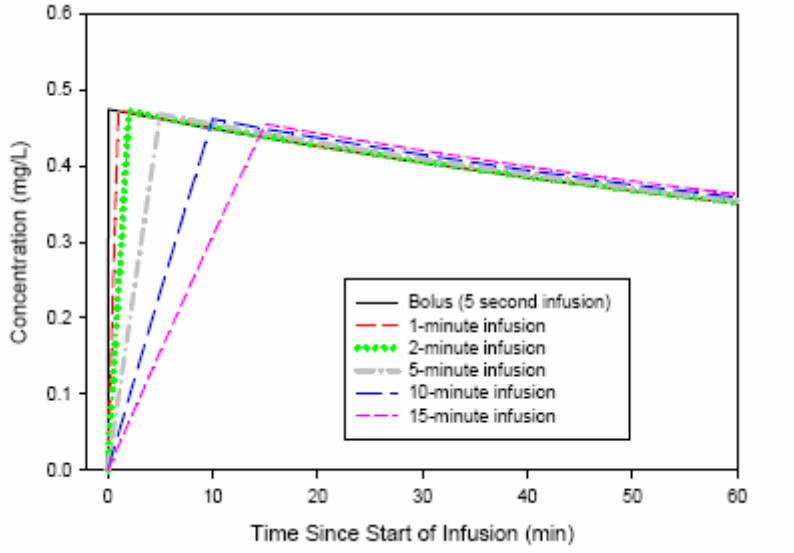
The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

No new pharmacokinetic data were submitted with this application. The clinical pharmacology and pharmacokinetics of fondaparinux were summarized previously in the original MAA (EMEA/H/C/403) for prophylaxis of VTE in patients undergoing major orthopaedic surgery of the lower limbs (MOSLL). The present application concerns intravenous administration of fondaparinux to rapidly achieve antithrombotic concentrations in patients with critical ischaemia. The pharmacokinetics following i.v. bolus and s.c. administration of fondaparinux have been characterised previously in healthy elderly subjects (Study 63106). Maximum concentrations of fondaparinux were achieved rapidly following i.v. bolus administration (with a median Tmax of 5 minutes, the first sampling time point) compared to s.c. administration (median Tmax 2 hours) with the mean Cmax following a 4 mg i.v. bolus dose approximately 1.8-fold higher than that observed following the 4 mg s.c. dose (0.86 mg/L vs 0.48 mg/L, respectively). Other pharmacokinetic parameters were similar for the two routes of administration. The mean AUC(0-inf) observed following the i.v. bolus dose was 10.0 mg*h/mL compared to 9.7 mg*h/L following the s.c. dose with mean elimination half-lives of 19.2 and 20.3 hours, respectively.

In *OASIS 6* (a randomised, double-blind, parallel-group, controlled trial comparing the safety and efficacy of 2.5mg fondaparinux versus a control of usual care (UFH or Placebo) in subjects with STEMI), i.v. bolus administration of fondaparinux was performed using the marketed 2.5 mg syringe via existing intravenous access, using an IN stopper with male luer lock. As an alternative method of administration, fondaparinux could be administered as a rapid i.v. infusion via a 0.9% saline mini-bag. In order to evaluate the impact of infusion duration on the plasma concentration-time profile for fondaparinux, pharmacokinetic simulations were performed.
As shown in Figure 2, predicted maximum concentrations (C_{max}) of fondaparinux were similar for i.v. infusion of 2.5 mg fondaparinux over 1, 2, 5, 10 and 15 minutes relative to an i.v. bolus dose.

Figure 2 Median Predicted Plasma Concentration-Time Profiles Following 2.5 mg Fondaparinux Sodium Administered via Rapid Intravenous Infusion and Intravenous Bolus



As all of these infusion rates achieve comparable predicted maximum concentrations of fondaparinux, it becomes clinically more important to consider the time required to achieve these maximum concentrations since the ultimate goal is to reach antithrombotic levels as soon as possible. It is therefore recommended as an alternative to i.v. bolus administration, that fondaparinux be administered as a rapid infusion over 1-2 minutes via a small volume (25 or 50 ml) 0.9% saline mini-bag. This is reflected in section 4.2 of the SPC.

Pharmacodynamics

No new data was submitted nor was it considered necessary.

Clinical efficacy

The clinical development program for fondaparinux in ACS included a total of 34,071 subjects who participated in 6 clinical studies. Four were phase II studies (PENTUA, PENTALYSE, ASPIRE and ACT 2445) and two were phase III studies (OASIS 5, conducted in unstable angina (UA) and non ST-segment elevation myocardial infarction (NSTEMI) and OASIS 6 in patients with ST-segment elevation myocardial infarction (STEMI) patients).

Study	Subject Population/No Subjects Randomized [1]	Treatment Groups	Fondaparinux Dose (once daily)	Treatment Duration
Phase II Studies				
PENTUA	UA/NSTEMI/1147	Fondaparinux vs Enoxaparin	2.5 mg, 4 mg, 8 mg, 12 mg s.c. after initial i.v. dose	3-7 days
PENTALYSE	STEMI/333	Fondaparinux vs UFH plus r-tPA in both arms	4 mg, 8 mg, 12 mg s.c. after initial i.v. dose	4-6 days
ASPIRE	PCI/350	Fondaparinux vs UFH	2.5 mg, 5 mg i.v.	Single dose
ACT2445	PTCA/71/71	Fondaparinux	12 mg i.v.	Single dose
Phase III Studies				
OASIS 5	UA/NSTEMI/20,078	Fondaparinux vs Enoxaparin	2.5 mg s.c.	≤8 days
OASIS 6	STEMI/12,092	Fondaparinux vs standard care	2.5 mg s.c. after initial i.v. dose	≤8 days

[1] 1147 subjects in *PENTUA* comprise 1138 who were randomized plus 9 treated subjects who were not randomized
UA unstable angina. NSTEMI non ST-elevation myocardial infarction. STEMI ST-elevation myocardial infarction
PCI/PTCA percutaneous coronary intervention.
UHF unfractionated heparin

PENTUA and *PENTALYSE* provided some evidence on which dose to select for further investigation in phase III. The other phase II studies, *ASPIRE* and *ACT2445* provided data primarily on the tolerability of an i.v. bolus of fondaparinux administered during coronary interventions (PTCA/PCI) and are discussed below in detail.
The two main phase III trials (*OASIS 5* and *OASIS 6*) were conducted in a total of over 32,000 patients. These studies are pivotal in providing the data to support the registration of fondaparinux for patients diagnosed with ACS and are discussed in the context of variation II/24.

Study ACT2445:
The ACT2445 was an open-label, uncontrolled study to assess the efficacy and safety of a single i.v. bolus injection of fondaparinux 12 mg administered prior to PTCA. The study enrolled male and post-menopausal females who had a history of stable or unstable angina, or of MI who had stenosis of ≥70% in at least one coronary artery selected for balloon angioplasty. Subjects with either an MI or UA symptoms within the previous 7 days were excluded. Seventy-one subjects were included in the study, but ten subjects had a stent implanted shortly after PTCA and received ticlopidine. These subjects were excluded from the per-protocol (PP) population.
The primary end point was the occurrence of abrupt vessel closure (AVC) during or after the

procedure as assessed by coronary angiography at 24 hours post-PTCA. The duration of AVC should be at least 10 minutes and not relieved by intracoronary or sublingual nitroglycerin and associated with ischemic pain and ECG changes. Success of treatment was defined as the Bayesian probability point of 95% (P) that the AVC rate (x) was less than 10%. [P ($x < 0.10$) = 0.971 if 2 AVC in 60 evaluable subjects.

Results
Two of the 61 evaluable subjects experienced the primary end point (AVC), giving a percentage of closure of 3.28% [0.04%, 11.35%], which was less than the preset 10% criteria for efficacy. The rate of AVC observed was within the range of previously reported rates with heparin. There were two non-fatal SAEs, both haemorrhagic events (hematoma and cerebral hemorrhage). Hemorrhagic events were reported in 17 subjects (23.9%), the majority of which were haematomas at the arterial injection site. The results from this pilot study were further evaluated in *ASPIRE*.

ASPIRE:
ASPIRE was a randomised blinded pilot trial of fondaparinux versus UFH in addition to standard therapy in a broad range of patients undergoing PCI. The objectives were to obtain experience in the use of fondaparinux as the primary anticoagulation strategy during PCI by evaluating the safety and efficacy of two dosages of fondaparinux compared with UFH. Two dosages of fondaparinux (2.5 mg and 5 mg i.v.) were used with UFH as the comparator. Randomisation was stratified by use of i.v. GP IIb/IIIa inhibitors. A single i.v. dose of investigational product was administered after randomisation and prior to the PCI procedure.

The study recruited 350 subjects scheduled for PCI at 22 centers in 3 countries. Subjects with active or potential bleeding complications or undergoing thrombolysis for STEMI within previous 24 hours were excluded. There were 118 subjects randomized to fondaparinux 2.5 mg, 115 to 5 mg and 117 to UFH, Fiftyeight percent of subjects received GP IIb/IIIa inhibitor. Treatment was administered by an independent unblinded coordinator.
The primary efficacy outcome was the first occurrence of any component of the composite of all-cause death, re-MI, urgent revascularization, or need for bailout GP IIb/IIIa inhibitor within 48 hours of randomization. The primary safety outcome was major or minor bleeding within 48 hours of randomization.
The sample size was based on the estimated event rate for the composite of major and minor bleeding in the UFH group. The estimated rate expected for the UFH group was 3%, which would provide 80% power to show a difference if the hazard ratio between the combined fondaparinux groups and the UFH group was 4.8.

Results
There was no statistically significant difference between the combined fondaparinux group (6.0%) and the UFH group (6.0%) in reducing the composite endpoint in subjects undergoing PCI (HR 1.02; 95% CI [0.41, 2.54]; p=0.97). The incidence of events was higher in the fondaparinux 5 mg group (7.8%) than in the fondaparinux 2.5 mg group (4.2%) and UFH group (6.0%).

Clinical safety

In *ASPIRE*, there were no significant differences in the incidence of major or minor bleedings between the combined fondaparinux group (6.4%) and the UFH group (7.7%), (HR 0.81, 95% CI [0.352, 1.840], p=0.61). The majority of the bleeding events in both the fondaparinux and UFH groups were minor and occurred mainly within the initial 48 hours of randomization in subjects receiving concomitant GP IIb/IIIa inhibitors. There were only four major bleeding events in fondaparinux subjects; all in subjects receiving concomitant GP IIb/IIIa inhibitors.

There was a non-significant trend towards a lower rate of bleeding in the fondaparinux 2.5 mg group (3.4%) compared with the higher fondaparinux 5 mg group (9.6%). There were two cardiovascular-related deaths, both in the fondaparinux 5 mg group; only one of these deaths occurred on-therapy. The incidence of SAEs to Day 30 was low and similar across the treatment groups.

The profile and incidence of AEs to Day 2 was similar across the treatment groups (fondaparinux 2.5 mg 31%, fondaparinux 5 mg 34% and UFH, 27% subjects. The most frequently reported AEs were puncture site haemorrhage, and angina pectoris With the exception of puncture site haemorrhage (fondaparinux 2.5 mg 3%, fondaparinux 5 mg 8% and UFH, 7% subjects), no other AE was reported by more than 5% subjects in any treatment group.

In the uncontrolled *ACT2445*, there were only three subjects with bleeding events on i.v. fondaparinux. All three bleeding events were at the sheath site and did not require any transfusions.

Nineteen subjects (26.8%) reported at least one AE. Most of the AEs reported were platelet bleeding and clotting disorders (13 subjects, 18.3%); predominantly haematomas (13 subjects, 18.3%) and one cerebral haemorrhage. Most of the haematomas were at the arterial injection site and were judges as mild.

Laboratory findings

There were no reports of thrombocytopenia in *PENTALYSE* and *ACT2445*, only one in the *PENTUA* study and three in *ASPIRE* in the fondaparinux 2.5 mg group and one report in the UFH group.

1.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Summary of Activities for each safety concern for fondaparinux (version number 1.2)

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks		
Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI	Routine pharmacovigilance which includes: 1. Review all spontaneous and literature reports of catheter thrombosis in patients with ACS treated with fondaparinux. 2. Develop targeted questionnaire to ensure consistency of data collected for spontaneous reports of catheter thrombosis Additional pharmacovigilance which includes: 1. Evaluate (post-approval) the appropriate use of fondaparinux in ACS patients who have to undergo PCI according to prescribing information.	Routine risk minimisation which includes: • Appropriate labelling: • Not recommending fondaparinux prior to or during primary PCI. • Recommendation against use of fondaparinux as sole anti-coagulation adjunct to non-primary PCI • Recommendation to use UFH for anti-coagulation during non-primary PCI in patients treated with fondaparinux

Potential Risks		
Risk of bleeding in non-primary PCI when UFH is used for anti-coagulation during the procedure in patients previously treated with fondaparinux	Routine pharmacovigilance Additional pharmacovigilance which includes: • Conduct PASS. • Evaluate (post-approval) the adherence to the prescribing guidance for recommended use of fondaparinux in ACS patients who have to undergo PCI.	Routine risk minimisation activities which includes: • Appropriate labelling: • 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

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.6 Overall conclusions, risk/benefit assessment and recommendation

According to the MAH, the two pivotal trials (*OASIS 5* and *OASIS 6*), have shown that fondaparinux is either as effective as, or superior to, current standard therapy in UA/NSTEMI and STEMI subjects. Importantly, in both studies fondaparinux was associated with a clinically relevant and statistically significant reduction in the risk of all cause mortality. Other than in STEMI subjects undergoing primary PCI, the relative efficacy of fondaparinux to control was seen across a range of key sub-groups indicating the applicability of these data to a broad range of subjects with ACS.

The MAH also claims that fondaparinux 2.5 mg was well tolerated in subjects with UA/NSTEMI and STEMI. Fondaparinux was generally associated with a lower risk of bleeding compared to enoxaparin (*OASIS 5*) or control (*OASIS 6*). Further, fondaparinux had comparable or slightly lower incidences of AEs, SAEs (total and drug-related), and AEs leading to withdrawal compared to enoxaparin (*OASIS 5*) or control (*OASIS 6*). Other than in STEMI subjects undergoing primary PCI, a satisfactory safety profile of fondaparinux to control was consistently seen across a range of important subgroups, indicating the applicability of these data to a broad range of subjects with ACS. Fondaparinux was also well tolerated in phase II studies at i.v. doses up to 12 mg and results from the supporting phase II studies are broadly in alignment with the phase III studies.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP agreed that the proposed activities described in section 3.5 adequately addressed these.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- the proposed pharmacovigilance activities were adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Arixtra in the 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, was favourable and therefore recommended the granting of the

marketing authorisation to the new intravenous route of administration for the 2.5 mg pre-filled syringe.