SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures which have been finalised before 1 November 2004. For scientific information on procedures after this date please refer to module 8B.

Introduction

Arixtra is indicated for the prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs (MOSLL) such as hip fracture surgery (HFS), major knee surgery (MKS) or hip replacement surgery (HRS).

The once-daily recommended dose is 2.5 mgadministered post-operatively by subcutaneous injection. In patients with impaired renal function, a 1.5 mg dose may be considered and in severe cases is recommended (see "Removal of the contraindication in severe renal impairment" section). The initial dose should be given 6 hours following surgical closure provided that haemostasis has been established. Timing of the first Arixtra injection requires strict adherence in special populations such as patients ≥75 years, and/or with body weight <50 kg and/or with moderate to severe (CL_{crea}: 20-50ml/min) renal impairment.
Treatment should be continued until the risk of venous thrombo-embolism has diminished, usually until the patient is ambulant, at least 5 to 9 days after surgery. In HFS patients, prophylactic treatment can be extended a further 24 days (see “Extended prophylaxis” section).
Arixtra should not be used in patients with very severe renal impairment (CL_{crea} < 20 ml/min).

The active substance is fondaparinux sodium, which is the sodium salt of a sulphated pentasaccharide molecule. In contrast to its animal sourced competitors unfractionated heparin (UFH) and low molecular weight heparin (LMWH), fondaparinux is manufactured totally by chemical synthesis.

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 neutralisation of Factor Xa by ATIII. Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated Factor II) and does not interact with platelet aggregation.
At the 2.5 mg dose, Arixtra does not affect routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalised Ratio (INR) tests in plasma, or bleeding time.
Fondaparinux does not bind to platelet factor 4 (PF4) and does not stimulate serotonin release in the presence of sera from patients with heparin-induced thrombocytopaenia.

Several other medicinal products have demonstrated efficacy for preventing acute VTE in post-surgical situations. Amongst these, the efficacy and safety of heparins (including unfractionated and low molecular weight heparins) have been the most documented.

Part II: Chemical, pharmaceutical and biological aspects

Composition

The medicinal product is presented as a solution for injection, 2.5mg/0.5ml or 1.5mg/0.3ml, in a prefilled syringe with an automatic needle protection system. The formulation consists of the active ingredient fondaparinux sodium dissolved in an isotonic solution of sodium chloride and water for injections (sodium hydroxide and hydrochloric acid are used as pH adjusters if needed).

The primary container is a single dose syringe consisting of a glass barrel with a stainless steel needle and a rubber needle shield, and closed with a plunger stopper.

Solutions with the same excipients but of different concentrations have been used during the clinical trials. A bioequivalence study comparing high and low concentrations has been carried out, and no significant difference has been observed.

Active substance

Fondaparinux sodium is a sulphated pentasaccharide obtained by total chemical synthesis. It is a white to almost white hygroscopic powderand is freely soluble in water, sodium chloride and sodium hydroxide solutions, and practically insoluble in ethanol. Fondaparinux sodium in the solid state is not light-sensitive.

The Applicant has confirmed that there is no TSE risk related to the manufacture of the active substance or the medicinal product.

Active Substance Specification

The specification includes relevant tests for identity assay, related impurities specific optical rotation, total viable microbial count, endotoxins, appearance of solution, pH, heavy metals, water content, residual solvents, etc. all performed by PhEur methods or by validated in-house methods where appropriate.

Data on 13 batches indicated satisfactory uniformity and compliance with the specification.

Stability:
In addition to short-term stress studies (including photostability studies), long-term data were generated from six batches at 25°C/60%RH, 30°C/60%RH and 40°C/75%RH for 24, 12 and 6 months of duration respectively. No significant degradation was seen at any of the conditions studied (25°C/60%RH, 30°C/60%RH and 40°C/75%RH). A retest period of two years was accepted at the time of the authorisation. The retest period has been extended from two to three years further to the assessment of a type I variation.

Other ingredients

The other ingredients of the formulation, hydrochloric acid, sodium hydroxide, and water for injections all comply with PhEur monographs. There are no ingredients of animal origin..

Product development and finished product

The aim of the development work has been to obtain an injectable sterile apyrogenic dosage form (for subcutaneous administration) of fondaparinux sodium.

The same manufacturing process as the commercial one, except for the terminal sterilisation step, has been used during clinical trials. The drug substance is readily dissolved in sodium chloride and water. Compatibility between the solution and the manufacturing equipment has been demonstrated. The documentation on product development is considered acceptable.

The manufacturing process with in-process controls was described in detail and a flow chart provided. Both strengths are manufactured using the same process; the only diference is the fill volume. The process comprises compounding, sterile filtration with nitrogen gas as a filtration aid, aseptic filling, stoppering, terminal sterilisation-inspection, packaging and labelling. Appropriate in-process controls are performed.

A total validation plan has been provided, describing the confirmatory validation studies for the manufacturing process and in-process control tests.

Product Specification

The product specification is essentially the same as the active substance specification, with additional tests for degradation products arising from the manufacturing process and storage over time. In addition, product-related tests include particulate matter, extractable volume and sterility.

Data on 14 batches indicate satisfactory uniformity and compliance with the specification.

The development of analytical methods applied to the finished product is fully described; reference is made, where possible, to PhEur methods.

Stability of the Product

Arixtra 2.5 mg/0.5 ml
Photostability studies have been carried out on two batches of the product. There is no evidence that the product is light sensitive and it can be concluded that the product is stable to intense light for 15 days.

The product was unaffected by drastic changes in temperature through temperature cycling studies.

At the time of initial submission, long term and accelerated studies under ICH conditions had been carried out on a large number of batches for up to 12 months. Updated stability data, up to 24 months from storage at 25°C/60%RH, and up to 24 months at 30°C/60%RH, were subsequently provided. A shelf life of two years was accepted. As a consequence of a type I variation, the shelf life was later extended to 3 years. The storage conditions as defined in the SPC remained the same.

Arixtra 1.5mg/03 ml
Photostability studies have been performed in accordance with ICH recommendations (1.2 million lux hours during 24 hours) on one drug product batch. The results are consistent with those for the higher strength and show that the drug product is not sensitive to light and no restrictions are needed in the storage conditions with respect to light.

Syringes have also been exposed to three cycles at 18°C/40°C (at least 48 h at each of the temperatures) and the results indicated that there was no change in the degradation profile or in the other parameters tested.
Three batches have been placed on stability studies under ICH conditions. The obtained results are in agreement with those for the higher strength. As suggested by the results of the stability studies and based on the fact that the only difference between the two strengths is the fill volume, the proposed shelf life for the lower strength product under the conditions specified in the SPC is acceptable. The stability studies for the applied lower strength will however continue for up to 36 months.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is notable for its complicated synthesis and the problems encountered in the detection and quantification of related impurities due to the low UV-absorbance of a carbohydrate molecule with no aromatic residues. Finished product manufacture has been evaluated in depth, particularly with regard to the validation of the process. Product stability has been established on the basis of a large amount of data and comprehensive statistical analysis. Following a list of questions put to the applicant and an assessment of the responses all important quality issues were resolved. The important quality characteristics of the active substance and product are well-defined and controlled, and the product is formulated, manufactured and controlled in a way that is characteristic of a solution for injection.

A number of minor quality issues were still outstanding at the time of the CPMP opinion, and the applicant provided a letter of commitments to resolve these within a given timeframe All but one have already been resolved and theMAH has planned to submit a type I variation by the end of 2003 to resolve the last commitment.

Part III: Toxico-pharmacological aspects

Pharmacodynamics

The primary pharmacological *in vitro* profile of fondaparinux consisted of investigations on ATIII affinity, effects on activity and generation of FXa, FIIa, FIXa and FVIIa activity, and effects on platelet aggregation and coagulation time (APTT and PT). Unfractionated heparin (UFH) was used as reference (comparison based on weight) in the studies except for the ATIII affinity experiments, while no comparison was made with LMWH. The studies were conducted with buffer systems (human ATIII) and with human plasma. On a weight basis and under the study conditions used, fondaparinux was more potent than UFH in the inhibition of FXa, FIXa and FVIIa and less potent in the inhibition of FIIa. Fondaparinux was equally or less potent than UFH in inhibiting the generation of the activated coagulation factors, and relatively less potent in aggregating platelets or prolonging coagulation time.

The short-term effect (≤ 5 min) of intravenously administered fondaparinux was studied in four pivotal experimental animal models for preventive venous antithrombotic activity (rat, mouse, rabbit), some in combination with experimental bleeding (rat and mouse). Fondaparinux inhibited thrombus formation dose-dependently up to a maximum lower than that seen with heparin (60-75 versus 100%). The reported potency (ED_{50}) varied (up to 50 fold) with the animal model used

In venous and arterial models of thrombosis where fondaparinux was active and where time-response relationships could be studied, there was a clear association between antithrombotic activity and AT III-mediated inhibition of factor Xa. Fondaparinux was 2-4 to 30 fold less potent than heparin on a weight basis, depending on the model used. In one of the venous models, LMWH (enoxaparin) was less potent than both fondaparinux and heparin. Significantly higher levels of anti-FXa activity were needed of fondaparinux efficacy compared with UFH.

Other data showed that fondaparinux had similar antithrombotic activity after IV and SC administration, if thrombosis was induced at time-points (5-90 min) of similar plasma anti-FXa activities.

The concomitant experimental bleeding data suggested both favourable and unfavourable efficacy/bleeding ratios for fondaparinux compared with UFH, depending on the experimental model used. Pig and the primate *Macaca mulatta* have been considered as useful preclinical models for the pharmacological evaluation of heparins. However, no evaluations were made in these species. Fondaparinux potentiated bleeding in combination with the platelet antiaggregatory drug clopidogrel or with dicumoxane. The antithrombotic activity and the bleeding complications of fondaparinux in man are discussed in the clinical section. The haemorrhagic effect of fondaparinux was neutralised by protamine sulphate in animals, but only at high, saturated and non-relevant exposure of fondaparinux. The potential for prothrombotic activity at treatment cessation was not investigated in animals.

The safety pharmacology studies addressing potential effects on CNS, fluid balance, GI tract, respiration, haematology, CV (+in vitro) and haemodynamic status, and the special studies investigating effects related to heparin-induced thrombocytopenia (HIT) antibodies and lipase induction, showed no untoward findings.

Pharmacokinetics

At lower SC exposures (up to about 0.5 mg/kg) fondaparinux showed high bioavailability, linear pharmacokinetics and was highly and almost completely bound to the target ATIII in plasma. At higher and ATIII-saturating exposure (0.4 to 10 mg/kg), the bioavailability decreased, the pharmacokinetics became non-linear, the plasma protein binding decreased and the clearance increased with the dose. The lack of dose-proportionality in the higher dose range was related to the

observed increase in clearance, which, in turn, was considered to be due to increased free fraction of fondaparinux, resulting from saturation of plasma protein (e.g. ATIII). The systemic exposure to fondaparinux in rat and monkey significantly increased following repeated administration, similarly to what was observed in man. At upper non-saturating exposure (0.4 mg/kg), drug-related radioactivity in rats receiving [^{35}S]-fondaparinux was detected in many specimensfondaparinux. The samples with the longest terminal half-lives were Harder's gland, liver, eye (vitreous humor), bone marrow and kidneys with 10-20 h, and cartilage with >40 h. Retention of drug-related radioactivity was considered to take place in kidney cortex and cartilage. Drug-related radioactivity was also detected in rat foetus and in breast milk. No radioactive metabolites could be detected in body fluids (blood and urine) or in *in vitro* tests for potential liver metabolism after exposure to [^{35}S]-fondaparinux when assayed with HPLC. Evidence of desulphation metabolism was detected in blood, urine, bile and hepatocytes by means of the detection of [^{35}S]-SO_4^{2-}ions. Urine secretion data in rat indicated some activity-reducing metabolism.
The elimination of fondaparinux from the circulation was significantly faster in rat, rabbit and monkey compared with man. The terminal half-life did not change with dose in the animals. Drug-related radioactivity was mainly excreted via urine, whereas the faecal excretion was low (rat) or negligible (monkey).

Toxicology

A large number of studies were performed in Sprague Dawley and Wistar rats and in *Cynomolgus* monkeys with maximal treatment duration of 3 months. The studies were generally adequately performed but inclusion of a comparator like a UFH or a LMWH would have been useful in the outcome assessment. At 10 mg/kg/day, the exposure ratios were approximately 5 (rat) and 16 (monkey), compared with the intended clinical exposure.

A single dose of fondaparinux was well tolerated in mouse, rat and monkey at doses up to 40 mg/kg. All repeated dose toxicity studies were performed with doses of 0.4, 2.0 and 10.0 mg/kg/day (approximately 12, 60 and 300 times the proposed therapeutic dose). Few non-haemorrhage related effects were observed. The true toxicity limits of fondaparinux are clearly beyond the chosen doses and probably differ for different animal species and treatment duration. Supporting arguments for dose selection were provided, including dose limiting effects such as adverse haemorrhagic events (AHE) (monkey) and saturable plasma protein binding (mainly rat). Thus, a significant increase in dose would be required to achieve a moderate increase in total exposure. This would lead to an increase of the free fraction that would be subject to a fast renal clearance.

Rat: Haemorrhagic, not fully dose-related changes were localised mainly to the injection sites and occasionally to the draining lymph nodes in the repeated dose toxicity studies. There were no major increases in other haemorrhagic adverse events. Reversible slight decreases in haemoglobin levels, reticulocytosis and an increase of urine urobilinogen, related to bleeding/haematoma-associated anaemia and erythropoiesis, were observed in some studies. Slight plasma electrolyte level variations were noted in the 2-week studies and also in the 3-month monkey study.

Monkey: The incidences of injection site haemorrhages and other trauma-related haemorrhagic events were increased in a dose-dependent manner. The reversibility of these findings after repeated administration of fondaparinux was assessed in one animal/sex from the control and high-dose groups in the 4-week study, which were followed after treatment. Histopathological treatment-related effects were not seen in the kidney, the major route of excretion, or in the liver. There were no, or only isolated increases in transaminase activity. Large or very large haematomas with or without associated resolutive inflammation were observed at handling sites, blood puncture sites and self-inflicted trauma sites in some treated animals at all doses. Such AHE were associated with a regenerative anaemia.

In the 3-month and in the 4-week monkey studies, the male animals displayed changes to genital organs which were related to degree of maturity or to health deterioration.

In the 3-month study, a dose-dependent increase in absolute (male) and relative (male and female) pituitary weights was noted, while the male monkeys had a decrease in T3 hormone at the end of the

study. However, the observed variation was within the physiological range as compared to the 2- and 4-week control monkeys.

No analysis specific for bone tissue (e.g. serum bone specific alkaline phosphatase) or morphometric analysis was used, but conventional total alkaline phosphatase and bone histology revealed no negative effects on bone in the rat and monkey.

Impurities During the impurity qualification, an increased incidence of retinal atrophy was observed in the treated rats in two 2-week studies. This was not considered to be due to impurities, but explained as a direct phototoxic-effect produced by excessive exposure of incandescent light during the infusion procedure, when, to favour vasodilatation, light was used to warm the animal. This warming procedure was performed only at the site where the atrophies were found and yielded energies that were within the reported levels that may induce retinal atrophy.
From a toxicological point of view, all impurities are considered qualified.

Reproductive and development toxicity All reproduction toxicity studies were performed with doses up to 10 mg/kg. In the rabbit studies, at the high-dose level, an exposure ratio of 12.6 was achieved compared to the human. Fondaparinux did not show any major effects on mating performance and fertility, gestation and parturition, lactation, new-born viability and growth, F1 behaviour and reproduction and F2 foetal development. An increased dose-dependent preimplantation loss was observed in both rabbit studies. This was explained to be within the physiological range when comparing in-house and external historical data. Such data should be interpreted with caution and concurrent control animals are considered more relevant. Moreover, a pharmacological effect could not be excluded since one action of sulphated polysaccharides is to inhibit cellular adhesion, as described in a number of publications. The clinical relevance of this finding was not clear, but was a cause for concern. The inadequate exposure of the animals (half-life of fondaparinux in human is 17 hours as compared to the 1-2 hours in rabbit) further strengthened this concern. However, data were re-calculated by the Applicant and does with high or low numbers of corpora lutea were excluded, as seems reasonable, since literature supports an increased loss in this population. This resulted in a non dose-related response in preimplantation losses. Further, the Applicant submitted convincing arguments that no effect of fondaparinux was likely on cell adhesion–and has agreed to add information regarding a limited exposure in the SPC, section 4.6.

Genotoxicity The mutagenic potential was evaluated in a battery of tests including bacterial reverse gene mutation (Ames) tests, mouse lymphoma gene mutation tests, mammalian *in vitro* DNA repair test, human lymphocytes chromosome aberration tests and one *in vivo* rat micronucleus test. Fondaparinux was not mutagenic or clastogenic.

Carcinogenicity No studies were performed since the intended treatment duration in humans is less than one month. The chemical structure of fondaparinux does not indicate a possible carcinogenic potential.

Local tolerance testing was performed during all single, repeated and reproduction toxicity studies. As expected, injection site haemorrhages, occasionally associated with an inflammatory infiltration, were noted.

Immunotoxicity Fondaparinux did not induce any active or passive anaphylactic signs in guinea pigs or rats. No relevant effects were seen on rat bone marrow cellularity or monkey T4, T8, NK and B peripheral blood lymphocyte counts, peripheral blood lymphoblast transformation tests with PHA, Con A and PWM, peripheral NK cells cytotoxicity test, mixed lymphocyte reaction and total plasma IgGs and IgMs levels.

Ecotoxicity/Environmental Risk Assessment A brief evaluation on the risk of use, excretion and disposal of fondaparinux has been conducted. No significant environmental effect is expected.

Discussion on toxico-pharmacological aspects

Preclinical data reveal no special risk for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Animal studies are insufficient with respect to effects on toxicity to reproduction because of limited exposure.
This information is reflected in the approved Summary of Product Characteristics

Part IV: Clinical aspects

Clinical pharmacology

Pharmacodynamics

Fondaparinux binds to human ATIII resulting in a 1:1 molar complex with a Kd of 58 nM. Plasma concentrations of 4 to 8 mg/l should saturate physiological concentrations of ATIII (2-4 μM). Circulating anti-Xa activity was proportional to fondaparinux dose after single or repeated q.d. s.c. dosing in healthy subjects and after repeated q.d. s.c.dosing (0.75 to 8 mg) in patients undergoing major orthopaedic surgery.

Fondaparinux has no ATIII-mediated anti-IIa activity except at concentrations beyond ATIII saturation, nor does it show significant anti-IIa activity through heparin cofactor II (HCII) activation. No circulating anti-IIa activity was detected after 0.7-18 mg s.c. or 2-16 mg i.v. Inhibition of thrombin generation is mediated by the anti-Xa activity. Indirect evidence of *in vivo* inhibition of thrombin generation was obtained by assessing thrombin-antithrombin complexes, prothrombin fragments 1+2 and D-dimers in healthy volunteers, and in different patient groups.
The reduction of thrombin generation also reduces the pro-coagulative feedback exerted by thrombin. This probably contributes to the minor inhibitory effects of fondaparinux on factor IXa and on factor X activation observed.

Fondaparinux does not alter prothrombin time and only slightly prolongs aPTT (maximal mean prolongation 20%) after 0.35-30 mg s.c., and 2-20 mg i.v. The aPTT was doubled only at plasma concentrations above 73 mg/l, whereas it is doubled at 2.5 mg/l UFH. Activated clotting time (ACT) has been measured only in patients undergoing PTCA after fondaparinux 12 mg IV. Inconsistent ACT increases were observed 2 and 48 hours after dosing, but not at 24 hours. These changes were much smaller than after UFH in this indication.

Unlike UFH, fondaparinux does not interact with ADP or collagen-induced platelet aggregation at concentrations up to 150 mg/l, and does not bind PF4 or stimulate platelet serotonin release in the presence of sera from heparin-induced thrombocytopenia (HIT) patients. This argues against a potential to induce HIT, which results from heparin binding to PF4 followed by antibody interactions and platelet activation. Fondaparinux showed no *ex vivo* effect on platelet aggregation induced by ADP, thrombin, collagen, or arachidonic acid, and did not change *in vivo* platelet counts after single and repeated dosing. Fondaparinux does not prolong bleeding time up to daily doses of 18 mg s.c. or 20 mg i.v.

Single or repeated doses of fondaparinux did not affect the ATIII level, but a decrease in ATIII was observed in patients undergoing total hip replacement (THR). The decrease was not different between the fondaparinux and enoxaparin treated patients.

One issue that was raised during the assessment was whether there is a risk that the fondaparinux concentrations exceed the binding capacity of ATIII in the postoperative phase. The mean ATIII reductions seen postoperatively after orthopaedic surgery were 10-15% and they were independent of treatment (fondaparinux or enoxaparin). It can be calculated that variations in ATIII levels within a wide range affect concentrations of bound fondaparinux only to a small extent. The changes of unbound fondaparinux with varying ATIII levels can be expected to be relatively larger. The concentrations of free fondaparinux that can be expected with the recommended dose, even with very low ATIII levels, are of no major safety concern according to the preclinical and clinical experience.

The small and transient aPTT prolongation after 10 mg sc fondaparinux was not affected by the co-administration of aspirin (single oral 975 mg dose). The lack of interaction with warfarin on PT and aPTT was documented by a single cross-over study involving 12 subjects. Whether a pharmacodynamic interaction between fondaparinux and vitamin K antagonists could result in an unexpected bleeding tendency was discussed. Based on clinical experience and on what is known about the pharmacodynamic interactions it was concluded that the expected bleeding tendency should not be significantly different with the combination fondaparinux/warfarin from what is seen with heparin/warfarin.

Pharmacokinetics

The human pharmacokinetics was evaluated in 27 clinical trials, including 6 Phase I studies in healthy subjects, 5 studies in special populations, 5 studies assessing specific drug interactions, and 8 studies in patients for the current indication. Generally, the pharmacokinetics of fondaparinux were well characterised. The plasma and urine fondaparinux concentrations in humans were assessed by validated biological assays (bioassays). These methods utilised the ATIII-mediated factor-Xa inhibitory activity of the drug with spectrophotometric detection of a specific factor-Xa substrate. Pharmacokinetic parameters were obtained following non-compartmental and compartmental (population) analysis.

Fondaparinux was rapidly absorbed following s.c injection (2.5mg) and C_{max} of 0.34 ± 0.04 mg/l was reached after 1.7 ± 0.4h in young healthy volunteers. The mean absolute bioavailability estimate was 107% (90% CI: 102%, 112%). The volume of distribution was approximately 8.2 ± 1.1l after s.c injections of 2.5mg. Fondaparinux is highly bound to ATIII (97.0-98.6%) and *in vitro* studies have shown that the binding becomes saturated at concentrations above 2 mg/l. The fondaparinux concentration-time profile is described by a bi-exponential decline. The terminal half-life estimates varied between 13 and 21h and the CL/F ranged from 5.1 – 7.9 ml/min, with renal excretion being the major elimination pathway. The renal CL exceeds the filtration CL and, thus, it is postulated that fondaparinux is actively secreted in the kidney. In healthy volunteers, steady-state was reached after 3-4 days, which is consistent with the half-life estimation. The accumulation ratio at steady-state was 1.3. The exposure is decreased non-proportionally at higher doses, due to saturation of protein binding, but the total concentrations are fairly linear within the therapeutic range. However, there are indications of saturability *in vivo* at lower concentrations than shown in *in vitro* studies.

Similar pharmacokinetic characteristics were observed for the healthy elderly and the patient populations. The inter-patient variability in CL/F and in V/F in the target population was 30-40% and 20%, respectively. The influence of various covariates was assessed in the population analysis and only weight was subsequently included in the final model as linearly increasing CL/F by approximately 9.3%/10kg. The lower plasma clearance leading to higher plasma levels with decreasing body weight was associated with a trend to higher major bleeding rates in patients less than 50 kg. Although highly correlated with total CL, renal function was not detected as significantly explaining the inter-patient variability in drug levels. The influence of important covariates was evaluated on post-hoc estimates but the predictive capacity of the population model seems limited.
Explanation was given in the August 2001 answers.
In a single dose study, impaired renal function resulted in a considerable reduction in CL/F (5-fold reduction in severe renal impairment), no change in distribution volume and, consequently, prolonged half-life. In Phase III trials, average CL/F was 1.3-1.6 fold lower in patients with mild renal impairment and 1.6-2.3 fold lower in patients with moderate renal impairment, compared with patients with normal renal function. Arixtra is contraindicated in patients with very severe renal impairment (CL_{crea}< 20 ml/min) and the use of a lower dose is recommended in patients with severe renal impairment (CL_{crea} between 20 and 30 ml/min) and may be considered in patients with moderate renal impairment (CL_{crea} between 30 and 50 ml/min). No pharmacokinetic evaluation was performed with respect to hepatic impairment, since the contribution of hepatic elimination to the overall elimination was assumed to be limited, which is acceptable. Studies in elderly patients showed an expected correlation between age and CL/F most likely explained by reduced renal function in the elderly.

Taking demographic differences into account, the pharmacokinetic profiles were similar in men and women.

The relation between plasma concentrations (C_{max}) and VTE or major bleedings (MB) was evaluated in DRI2643 (dose range 0.75mg to 8mg). Patients with MB tended to have higher mean C_{maxss} plasma concentration than patients without events, and patients with VTE tended to have lower mean C_{maxss} plasma concentration than patients without events, confirming the dose-response data.

There was a consistent trend to higher MB rate with increasing degree of renal impairment, with increasing age, and with decreasing body weight. It was demonstrated that the incidence of MB was higher in patients receiving the first post-operative dose early (<6 h after surgical closure) and that incidence of MB could be reduced by giving the first dose ≥6 h after dose. The difference was especially evident in the "fragile" population (age ≥75 years and/or weight < 50 kg and/or Clcr <50 ml/min).

Interaction studies:
From *in vitro* studies in human microsomes using relevant fondaparinux concentrations, it was concluded that fondaparinux did not significantly inhibit any drug metabolising CYP-isoenzyme. Single dose warfarin and aspirin and steady-state piroxicam and digoxin did not influence the fondaparinux pharmacokinetics at steady-state. The effect of forced diuresis on fondaparinux elimination was limited. However, the Arixtra dose (10 mg) in the interaction studies was higher than the dose recommended for the present indication. Arixtra neither influenced the INR activity of warfarin, nor the bleeding time under acetyl salicylic acid or piroxicam treatment. Bleeding risk is increased with concomitant administration of Arixtra and agents that may enhance the risk of hemorrhage.

If prophylactic treatment is to be continued with heparin or LMWH, the first injection should, as a general rule, be given one day after the last Arixtra injection. If follow up treatment with a Vitamin K antagonist is required, treatment with fondaparinux should be continued until the target INR value has been reached.

Bioequivalence studies:

A bioequivalence study was performed between the marketing formulation fondaparinux injection, 2.5 mg/0.5 ml (Ref 2B2) and the clinical formulation of 2.5mg/0.25 ml. The two formulations were considered bioequivalent.

Discussion on pharmacokinetic aspects
The pharmacokinetics of fondaparinux haves been well characterised. A main concern during the assessment was the posology in patients with renal impairment. The initial recommendation from the MAH for strong adherence to the dosing schedule in patients with renal impairment was accepted, whereas fondaparinux was contraindicated in patients with severe impairment (Clcr <30 ml/min). The dosing recommendations for renally impaired patients have subsequently been revised following the adoption of a line extension to introduce a lower 1.5 mg dose (see "Removal of the contraindication in patients with severe renal impairment").

Clinical efficacy in MOSLL

The clinical trials were performed according to GCP standards and agreed international ethical principles.

Dose response studies

The two dose-ranging studies of prophylaxis in orthopaedic surgery are summarised in Table 1.

Table 1

Title, Country of co-ordinating centre,	**Type of surgery**	**Doses given of fondaparinux Comparator**

Number of centres and of Randomized patients		Efficacy assessment
DRI2643 Canada, 70 centres N=950	Total hip replacement (THR) Double blind Assessor blind	0.75, 1.5, 3, 6, 8 mg s.c. started 6 ± 2 h postoperatively Comparator: Enoxaparin 30mg x 2 Venography day 5-10
95001 USA 19 centres N=318	Total knee replacement (TKR) Open Assessor blind	0.75, 1.5, 3, 6, 8 mg s.c. started 6 ± 2 h postoperatively noncontrolled Venography day 5-10

The number of patients with DVT found at the venographic assessment is given in tables 2 and 3.

Table 2 -Number (%) of Patients with any DVT, any Proximal DVT, and Distal only DVT During the Treatment Period in DRI2643

DVT		FONDAPARINUX					Enoxaparin
		0.75 mg (N = 102)	1.5 mg (N = 101)	3.0 mg (N = 101)	6.0 mg (N = 44)	8.0 mg (N = 22)	(N = 150)
Any DVT	n (%)	11 (10.8)	6 (5.9)	2 (2.0)	2 (4.5)	0 (0.0)	14 (9.3)
Any proximal DVT	n (%)	3 (2.9)	5 (5.0)	1 (1.0)	1 (2.3)	0 (0.0)	5 (3.3)
Distal only DVT	n (%)	8 (7.8)	1 (1.0)	1 (1.0)	1 (2.3)	0 (0.0)	9 (6.0)

Table 3 - Number (%) of Patients with any DVT, any Proximal DVT, and Distal only DVT During the Treatment Period in 95001

DVT		FONDAPARINUX				
		0.75 mg o.d. (N = 22)	1.5 mg o.d. (N = 44)	3.0 mg o.d. (N = 44)	6.0 mg o.d. (N = 18)	8.0 mg o.d. (N = 13)
Any DVT	n (%)	13 (59.1)	15 (34.1)	6 (13.6)	2 (11.1)	2 (15.4)
Any proximal DVT	n (%)	1 (4.5)	2 (4.5)	0 (0.0)	1 (5.6)	0 (0.0)
Distal only DVT	n (%)	12 (54.5)	13 (29.5)	6 (13.6)	1 (5.6)	2 (15.4)

The number of MB is given in Table 4. An adjudication committee blindly classified the bleeding reports. The definition of MB was essentially the same as used in the phase III studies. Due to increased bleeding the study arms of 6 and 8 mg were discontinued prematurely.

Table 4 - Number (%) of Patients Experiencing a Bleeding Event and/or With Bleeding-Related Criteria During the Treatment Period by fondaparinux Dose - Dose-Ranging Studies (DRI2643 and 95001)

Patients With		FONDAPARINUX				
		0.75 mg	1.5 mg	3 mg	6 mg	8 mg
All Dose Ranging Studies		**(N = 238)**	**(N = 279)**	**(N = 265)**	**(N = 121)**	**(N = 86)**
Bleeding event	Major bleeding	1 (0.4%)	2 (0.7%)	11 (4.2%)	18 (14.9%)	12 (14.0%)
	Minor bleeding only	4 (1.7%)	7 (2.5%)	12 (4.5%)	7 (5.8%)	3 (3.5%)
	Any bleeding	5 (2.1%)	9 (3.2%)	23 (8.7%)	25 (20.7%)	15 (17.4%)
Bleeding-related criteria	Re-operation due to bleeding	0 (0.0%)	0 (0.0%)	2 (0.8%)	3 (2.5%)	3 (3.5%)
	Transfused patients	97 (40.8%)	117 (41.9%)	127 (47.9%)	66 (54.5%)	53 (61.6%)

The results demonstrated a dose-response relation for DVT as well as for bleeding events. Based on the evaluation of the dose-response curves, the dose (2.5 mg) chosen for further evaluation in the phase III studies was considered reasonable.

Main studies (phase III = therapeutic confirmatory trials)

Four pivotal phase III studies were designed to show superior efficacy of fondaparinux over enoxaparin for prophylaxis in patients undergoing MOSLL.

The four main studies are summarised in Table 6.

Table 6. Pivotal studies in MOSLL

Title	Type of surgery	Comparator, Timing of randomisation	Number of patients randomised fondaparinux/enoxaparin
63118 Ephesus	Total hip replacement (THR)	Enoxap. 40 mgx1 Preoperative	1155/1154
EFC2442 Pentathlon 2000	Total hip replacement (THR)	Enoxap. 30 mgx2 Postoperative	1138/1137
EFC2698 Penthifra	Hip fracture surgery (HFS)	Enoxap. 40 mgx1 Preoperative	849/862
095-002 Pentamaks	Major knee surgery (MKS)	Enoxap. 30 mgx2 Postoperative	526/523

All studies were standardised for inclusion/exclusion criteria, dosing schedules (apart from the two different enoxaparin regimens used, see below), dose of fondaparinux (2.5 mg o.d., s.c), duration of treatment (5-9 days), efficacy end-point definitions and safety end-point definitions.

Enoxaparin was administered according to 2 different regimens, the once-daily 40 mg regimen authorised in the European countries, and the twice-daily 30 mg regimen authorised in North America.

The base-line characteristics of the patients in the different treatment groups were well matched. The population studied can be regarded as representative of the typical clinical population in the indications applied for with respect to age, concomitant diseases and other demographic factors including known risk-factors for VTE. Some of the exclusion criteria are listed below

- age less than 18 years
- serum creatinine level over 180 µmol/l (2.0 mg/dl)
- known bleeding tendency
- recent stroke
- thrombocytopenia or a history of thrombocytopenia (<100 x 10^9/l)
- more than 24 hours delay between trauma and hospital admission (this exclusion criteria refers to Penthifra only)

According to the study protocol every patient was to undergo a bilateral venography between day 5 (day 1=the day of surgery) and the end of the treatment period (by day 11), if a suspected symptomatic VTE was not confirmed first. An independent committee made a blinded assessment of all venographies and other objective tests.

The overall ratio of evaluable patients, i.e. randomised patients that had undergone surgery, treatment and an evaluable venogram was 73% with a slight variation between studies (69-79%). The fraction of patients who had a venography performed can be considered to be acceptable in all the phase III studies.

The primary efficacy endpoint was the rate of adjudicated VTE up to day 11, defined as symptomatic/asymptomatic DVT and/or pulmonary embolism (PE) documented by objective tests. The variables constituting the primary efficacy endpoint can be divided into asymptomatic proximal DVT, asymptomatic distal DVT and symptomatic VTE.

The results for the primary efficacy endpoint are presented in Table 7.

Table 7. Primary efficacy endpoint (incidence of asymptomatic/symptomatic DVT and/or PE).

Study, surgery	FONDAPARINUX	ENOXAPARIN	95% CI for diff. (%)
Ephesus, THR	37/908 (4.1%)	85/919 (9.2%)	-8.1;-2.7;
Pentathlon 2000, THR	48/787 (6.1%)	66/797 (8.3%)	-5.5;0.6
Penthifra, HFS	52/626 (8.3%)	119/624 (19.1%)	-15.3;-6.6
Pentamaks, MKS	45/361 (12.5%)	101/363 (27.8%)	-22.3;-9.3;

The majority of end-point events were distal asymptomatic DVT. The rate of proximal DVT (thrombosis engaging the venous segments above the trifurcation of the calf) up to day 11 was significantly reduced in the fondaparinux group in the Ephesus and Penthifra studies and there was a clear trend for a reduced rate also in the Pentamaks study. In the Pentathlon 2000 study, however, there was no difference in the rates of proximal thrombi between the two treatment groups. The rates of proximal DVT are given in Table 8.

Table 8. The incidence of all proximal DVT.

Study, surgery	FONDAPARINUX	ENOXAPARIN	95% CI for diff. in %
Ephesus, THR	6/922 (0.7%)	23/927 (2.5%)	-3.7;-0.5
Pentathlon 2000, THR	14/816 (1.7%)	10/830 (1.2%)	-1.0;2.6
Penthifra, HFS	6/650 (0.9%)	28/646 (4.3%)	-6.1;-1.3;
Pentamaks, MKS	9/368 (2.4%)	20/372 (5.4%)	-7.6;0.4

It can be concluded that fondaparinux 2.5 mg is more effective than the enoxaparin dosage regimens used for the prevention of venographic DVT in the early phase after lower limb orthopaedic surgery.

The incidence of symptomatic VTE until day 11 was low and did not significantly differ between the treatment groups, with 22 (0.6%) and 15 (0.4%) cases in the pooled fondaparinux and enoxaparin treated groups, respectively. There was a trend for an increased accumulated rate of symptomatic VTE by day 49 in the fondaparinux group as compared with the enoxaparin group [63/3603 (1.7%) vs.

45/3608 (1.2%)]. Thus, no apparent reduction of symptomatic VTE by fondaparinux treatment corresponding to the reduction of asymtomatic DVT could be seen.

The CPMP accepted that a reasonable explanation for the nominal difference regarding incidence of symptomatic VTE was the following: About 6.2 % of the evaluable patients in the fondaparinux group received curative treatment after the primary endpoint evaluation (phlebography) as compared with 11.9 % in the enoxaparin group. This type of difference would be expected in a situation when the compared products have different activity for prevention of DVT and when the large majority of endpoint events consists of venographically diagnosed, asymptomatic DVT, which, nevertheless, trigger curative treatment in a large proportion of patients. The bias introduced by leaving a larger fraction of patients at some continuing risk for VTE in the fondaparinux group without anticoagulant therapy for the remainder of the study period would also be expected to result in a somewhat higher incidence of symptomatic VTE in the fondaparinux group after the venographic evaluation.

For patients treated with fondaparinux or enoxaparin but not evaluable concerning the primary efficacy end-point (no venography performed), the incidences of symptomatic VTE between day 12 and day 49 did not differ between treatment groups (fondaparinux 1.3%, enoxaparin 1.0%).

The composite endpoint chosen is somewhat different from the endpoint recommended in the "Points to consider" document (CPMP/EWP/707/98) that includes all-cause mortality. However, the endpoint was chosen in accordance with scientific advice given by the CPMP in 1997. The overall conclusions regarding efficacy and safety remained unchanged after a reanalysis made retrospectively and including all-cause mortality.
An ITT analysis (a "best case scenario") including all patients that went through surgery and had any study medication administered gave additional support for the conclusions made on the overall efficacy of fondaparinux.

Clinical safety in MOSLL

Bleeding
Most bleedings occurred at the surgical sites. No fatal, CNS or retroperitoneal bleedings were reported in the fondaparinux 2.5 mg group.

In the two dose-ranging studies there was a significant dose response for MB as well as for all bleeding events and the percentage of transfused patients.

An adjudication committee blindly classified the bleeding reports in all the phase III studies. Only studies from the same randomisation type were pooled for integrated analyses since intraoperative bleeding was included only in the studies with preoperative randomisation. The frequencies of bleedings are given in Table 9.

Table 9. Number (%) of patients (Fondaparinux/ Enoxaparin) experiencing Bleedings up to day 11.

Preoperative randomisation*			
Study, surgery	**N**	**Major Bleedings**	**Minor bleedings only**
Ephesus, THR	1140/1133	47(4.1%)/32(2.8%)	44(3.9%)/38(3.4%)
Penthifra, HFS	831/842	18(2.2%)/19(2.3%)	34(4.1%)/18(2.1%)
Pooled Results	1971/1975	65(3.3%)/51(2.6%)	78(4.0%)/56(2.8%)

* enoxaparin European dosing regimen = 40 mg q.d

Postoperative randomisation*			
Study, surgery	**N**	**Major Bleedings**	**Minor bleedings only**
Pentathlon 2000, THR	1128/1129	20(1.8%)/11(1.0%)	17(1.5%)/24(2.1%)
Pentamaks, MKS	517/517	11(2.1%)/1(0.2%)	14(2.7%)/19(3.7%)
Pooled Results	1645/1646	31(1.9%)/12(0.7%)	31(1.9%)/43(2.6%)

* enoxaparin North- American dosing regimen = 30 mg bid

An overall tendency, although not significant, for higher major bleeding rates in the fondaparinux groups can be seen. Only a fraction of all minor bleedings can be expected to have been reported.

The percentage of patients that had a decrease in haemoglobin concentrations ≥ 2 g/dl during the treatment period was higher in the fondaparinux treated group as compared with the enoxaparin group, both in studies with preoperative randomisation (22.0% vs.16.0%) and postoperative randomisation (55.5% vs. 49.6%). The rates of bleedings related to some of the base-line covariates are given in Table 10.

Table 10. Number (%) of Patients Experiencing Major Bleeding Events From First Fondaparinux Injection up to Day 11 by Baseline Covariates - All fondaparinux 2.5 mg Treated Patients in Orthopaedic Surgery Studies

	fondaparinux 2.5 mg (N = 3595
Type of surgery	
Total Hip Replacement	51/2249 (2.3%)
Hip Fracture	18/829 (2.2%)
Total Knee Replacement	11/517 (2.1%)
Gender	
Male	34/1429 (2.4%)
Female	46/2166 (2.1%)
Age (years)	
Missing	0/4 (0.0%)
<65	23/1253 (1.8%)
[65-75[	24/1111 (2.2%)
≥75	33/1227 (2.7%)
Weight (kg) [n (%)]	
Missing	1/37 (2.7%)
<50	7/130 (5.4%)
[50,100[	63/3030 (2.1%)
≥100	9/398 (2.3%)
Creatinine clearance (mL/min) [n (%)]	
Missing	1/155 (0.6%)
<30	4/83 (4.8%)
[30,50[	19/504 (3.8%)
[50,80[	31/1288 (2.4%)
≥80	25/1565 (1.6%)
Timing of first post-operative active injection (hours)	
Missing	2/28 (7.1%)
<4	5/106 (4.7%)
[4, 5]	14/489 (2.9%)
[5, 6]	16/742 (2.2%)
[6, 7]	28/1403 (2.0%)
[7, 8]	13/609 (2.1%)
[8, 9]	0/107 (0.0%)
[9,10]	0/23 (0.0%)
>10	2/88 (2.3%)

NOTE: includes studies Pentathlon 2000, Ephesus, Penthifra and Pentamaks

[a] Per covariate, only non missing observations were taken into account

The rate of MB was inversely related to renal function and a tendency for an inverse relation was also seen with body weight. It tended to increase with age. For all patients treated with fondaparinux 2.5 mg in the phase III studies the incidence of MB was 2.8 % in a "fragile" population (age ≥75 years and/or weight < 50 kg and/or Clcr <50 ml/min) as compared to 1.9% for "non-fragile" patients.

More bleedings were seen in patients that got the first fondaparinux injection soon after surgery (< 6 hours). Again, this tendency was more pronounced in patients of increased age, with low body-weight and with impaired renal function. Strict adherence to the recommended timing of the first Arixtra injection reduced the risk of MB among the "fragile" patients to the same level as "normal" patients. For patients treated according to the finally proposed regimen (first dose ≥ 6 hours following surgical closure in all types of major orthopedic surgeries of the lower limbs), the incidences of MB were 2.8% and 2.6% in the fondaparinux and enoxaparin 40 mg groups, respectively and this was reflected in the SPC section 5.1.

Concerning race no conclusions were possible due to the low number of non-Caucasians included. There was no effect of surgery type or of type of anaesthesia on MB rates.

Other adverse events and serious adverse events/deaths

The mortality rates were low and did not differ between the treatment groups (Table 11).

Table 11. Number of deaths during treatment (until day 11) and study (until day 49) periods.

	Deaths until day 11		Deaths until day 49	
	fondaparinux	Enoxaparin	fondaparinux	Enoxaparin
Preoperative randomisation	11/1971	18/2051	40/1971	46/2051
Postoperative randomisation	4/1645	3/1906	8/1645	7/1906
Deaths due to bleeding, all studies	0	1	0	2
Deaths due to PE, all studies	2	3	11	11

Apart from the deaths caused by bleeding or PE, none of the deaths was suspected to be associated with the treatment by the investigators. The higher mortality rates in the studies with preoperative randomisation are due to the higher mortality in the HFS study (Penthifra), including elderly, acutely ill patients.
Concerning other adverse events such as surgical site reactions, myocardial infarctions, cardiac failure, cerebrovascular disorders, no differences between treatment groups were seen in the 4 phase III studies. The rate and spectrum of reported adverse events not related to bleeding did not deviate from what could be expected. No specific suspected drug-related other adverse events were reported.

Laboratory findings

In the clinical studies the percentages of patients experiencing a decrease in platelet count to < 100 x 10^9/l were not related to fondaparinux dose and were similar to those observed in the enoxaparin group.
In the orthopaedic surgery studies a slightly higher rate of patients developed positive ELISA tests in the preoperatively than the postoperatively randomised studied. No differences were seen between the treatment groups. The higher number of positive tests associated with positive serotonin release tests in the preoperatively randomised studies cannot be explained. The development of a positive test did not appear to be predictive of thrombocytopenia or of thrombotic event.
No thrombocytopenias with suspected immunoallergic pathophysiology (HIT, type II) were documented in the clinical development program.
Taking in to account that

- fondaparinux lacks PF4 binding capacity
- fondaparinux did not elicit any ^{14}C-serotonin release in the presence of sera from HIT patients and platelets from healthy subjects

the risk of thrombocytopenia of immunoallergic origin (HIT type II) induced by fondaparinux can be expected to be low from available documentation. However, until further experience is gained, a warning has been included in the SPC that fondaparinux should not be used in patients with a history of HIT type II.
Thrombocytopenia cases will be carefully monitored and reported by the Marketing Authorisation Holder in the Periodic Safety Update Reports.

A transitory increase in transaminases is observed during treatment with heparins. In the DVT treatment study (DRI2440) no significant mean increase in AST or ALT was observed under

fondaparinux in contrast to dalteparin, with consistent observations of larger percentage of patients experiencing increases above the ULN. No increases were seen after fondaparinux in patients undergoing PTCA or hemodialysis (studies ACT2445, 63113).
There was no difference in transaminase levels between fondaparinux and placebo in the phase I studies and no dose response in the phase II studies. As compared with the enoxaparin treated group in the pooled patient material in orthopaedic surgery the mean increase in AST, ALT levels was significantly less pronounced among the fondaparinux-treated patients and significantly fewer patients experienced elevations above ULN or 3xULN. The increases seen in the fondaparinux treated patients may be related to surgery and physiological reactions in the post-operative phase rather than to fondaparinux.

Safety in special populations

The rate of MB was inversely related to renal function and a tendency for an inverse relation was also seen with body weight. The rate of MB tended to be increased with age.

The safety in "fragile" patients (elderly, low body weight, impaired renal function) was a concern. Bleeding tendency in these patients may to a large extent be explained by co-morbid factors, but it remains that, with the proposed posology, there will, inevitably, be accumulation of fondaparinux and exposure considerably in excess of that seen in patients with normal excretory capacity.
By the strict adherence to the recommended timing of the first Arixtra injection, as emphasised by the applicant, the risk for MB may be reduced.
Renal failure should be expected to be associated with prolonged exposure to higher plasma concentrations of fondaparinux apart from the haemostatic disturbances caused by the kidney failure *per se*. Fondaparinux concentrations are significantly increased in severe renal impairment (CL_{cr}: <30ml/min), but also in moderate impairment (CL_{cr}: 30-50ml/min).

The pharmacokinetics in patients with severe renal impairment have not been sufficiently characterised as severe renal impairment was an exclusion criterion in the Phase III studies: therefore fondaparinux is contraindicated in this population (this contraindicaton has been addressed in a subsequent type II variation – see "Removal of the contraindication in patients with severe renal impairment"). In patients with moderate renal impairment caution should be used when administering Arixtra. It is emphasized in the SPC that the first Arixtra administration should not be given earlier than 6 hours following surgical closure. The injection should not be given unless haemostasis has been established.

As shown in the Figure 1, the influence of the timing of the first dose on the risk of MB is most apparent in a "fragile" population defined as patients >75 years old, <50 kg and/or CL_{cr} <50 ml/min.
It can be concluded that within the fragile population, adherence to the timing of the first post-operative dose is of most importance with respect to major bleeding risk. Consistently, all major bleedings among the 83 fondaparinux 2.5 mg patients with severe renal failure (CLcr <30 ml/min) (protocol violators) occurred among patients whose first post-operative dose was <6 hrs following surgical closure (4/36).

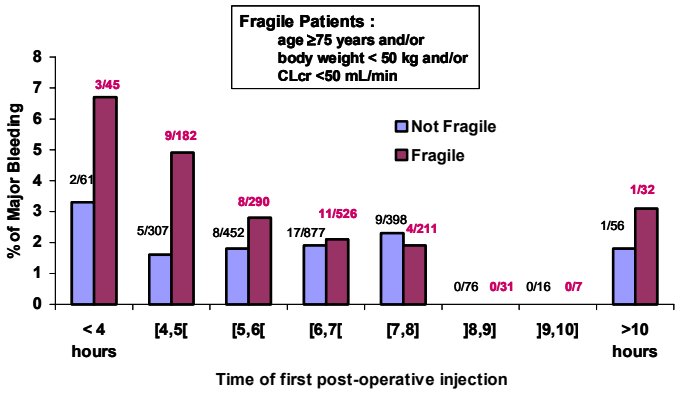


Figure 1. Major Bleeding from First Active Dose by Time of First Active Post-operative Dose and Fragileness -All Fondaparinux 2.5 mg Treated Patients

Overall conclusions, benefit/risk assessment and recommendation for the use of Arixtra in patients undergoing MOSLL

Quality

The important quality characteristics of the active substance and product are well-defined and controlled, and the product is formulated, manufactured and controlled in a way that is characteristic of a solution for injection. The specifications and batch analytical results indicate a consistent product and these in turn should guarantee a uniform clinical performance from batch to batch.
There are no unresolved quality issues that have a negative impact on the benefit/risk balance.

A number of minor quality points were still outstanding at the time of the CPMP opinion, and the applicant provided a letter of undertaking to resolve them within a given timeframe. To date, all but one have been resolved.

Preclinical pharmacology and toxicology

Overall, the toxicology programme was adequate to support the development of the product in the sought therapeutic indication. There were no data generated by exposure in pregnant animals and this information is included in the SPC.

Pharmacokinetics

The pharmacokinetics were well characterised and supportive of the claimed posology. The elimination of fondaparinux is highly dependent on the renal function, which is reflected in the SPC as contraindication of fondaparinux in patients with very severe renal impairment (CLcrea < 20 ml /min).

Efficacy

Approximately 94% of the patients treated with fondaparinux, 2.5 mg/day, in the orthopaedic surgery studies completed treatment according to the protocol. The completion rate was the same as in the pooled control group.

As expected with the study design employed, the actually demonstrated benefit on thromboembolic events is mainly restricted to a decrease in the incidence of venographic thromboses (proximal and distal).

There is scientific evidence beyond reasonable doubt that there is a direct relationship between the different clinical manifestations of venous thromboembolic disease. A relationship between distal, proximal and nonfatal/fatal PE is accepted and it is considered that there is little relevance of an endpoint consisting of only symptomatic DVT in the early post-operative phase. The composite endpoint recommended in the CPMP Points to Consider document also implies an acceptance of this concept. Therefore an indication text including ”prevention of VTE” was considered acceptable.

The dose, dose regimen and duration of treatment have been substantiated both in the general population and in the fragile patients groups (low body weight, elderly, moderate and severe renal failure). The information is reflected in the Summary of Product Characteristics.

Guidance for patients that need prolonged prophylaxis (beyond 9 days) was discussed in depth by the CPMP. Prolonged prophylaxis, beyond 9 days after surgery, was not tested in the pivotal trials of MOSLL hitherto assessed. Thus, a benefit/risk assessment for such prolonged treatment with fondaparinux could not be made at the time of the initial MA. Therefore, guidance on how to switch to prophylaxis with heparin, LMW-heparin or to treatment with a vitamin K antagonist (VKA) in case follow-up therapy was deemed necessary beyond the peri-operative period was included in the Summary of Product Characteristics. This guidance has subsequently been deleted further to the assessment of the Penthifra Plus study data (see "prolonged prophylaxis" section) ., .

Fondaparinux did not affect the prothrombin time in healthy volunteers also given warfarin (study 63108). Warfarin did not affect the pharmacokinetics of fondaparinux. In study DRI2440 (dose ranging DVT treatment study) over 300 patients have been treated concomitantly with fondaparinux (doses 5, 7.5 or 10 mg) and oral anticoagulants. As compared with dalteparin and oral anticoagulants, the same time of combined treatment was required to reach therapeutic INR values. There was no increased bleeding tendency in the fondaparinux group as compared to the dalteparin group. In conclusion there is no suggestion that fondaparinux when combined with oral anticoagulants should lead to a higher and unexpected bleeding frequency in comparison with heparin or LMWH. The information is included in the Summary of Product Characteristics.

Safety

The three main areas of concern discussed by the CPMP were the bleeding risk (particularly in fragile populations), the potential for interaction with other medicinal products used in prolonged prophylaxis, and the occurrence of thrombocytopenia.

These points have been addressed with appropriate additional analyses of the phase II and phase III extensive studies submitted. The SPC has been amended as necessary with contraindication of the use of Arixtra in very severe renal failure patients and introducing the necessary warning and precaution for use in other populations. The assessment of the pharmacokinetic, interaction and dose response studies, as well as a specific pooled analysis of all patients treated with other medicinal products for prolonged prophylaxis during the Phase III program has provided reassurance that there are no obvious indications of an unexpected synergistic effect on bleeding tendency following the combined treatment of fondaparinux and oral anticoagulants.

The same incidence of thrombocytopenia was observed in the two treatment groups across the phase III studies. Taking into account that no documented cases of immunoallergic thrombocytopenia have been reported across the whole clinical experience accrued so far with Arixtra, and considering that fondaparinux lacks PF4 binding capacity, the risk of thrombocytopenia of immunoallergic origin (HIT type II) induced by fondaparinux can be expected to be low. However, the CPMP recommended as follow-up measure that until further experience is gathered, thrombocytopenia cases be carefully monitored and reported by the Marketing Authorisation Holder in the Periodic Safety Update Reports.

Benefit/risk assessment

The Applicant has provided substantial evidence documenting the efficacy and safety of fondaparinux when used as directed in the Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.

Appropriate contra-indication in patients with very severe renal failure, recommendation for the duration of treatment as well as clarifications and undertaking of follow-up on the cases of thrombocytopenia which might occur during treatment with fondaparinux were subjects of in-depth discussion with the applicant in the course of an oral explanation with the CPMP.

Outstanding issues relevant to the complex manufacturing and quality control process of fondaparinux have been extensively addressed in the information and clarifications provided by the applicant. A number of minor quality points will be further addressed by the applicant after Marketing Authorisation is granted, with the generation of additional analytical data.

The over-all benefit/risk balance for Arixtra, used as recommended in the SPC, is considered to be favourable.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Arixtra in Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery was favourable and therefore recommended the granting of the marketing authorisation.

EXTENDED PROPHYLAXIS IN HIP FRACTURE SURGERY

Rationale

The request for extended prophylaxis is based on the results of the Penthifra Plus study (EFC4582) in patients undergoing Hip Fracture Surgery (HFS). No similar studies appear to have been performed in HFS prior to this pivotal study but long term prophylaxis experience was reported with LMWH in HRS. Indeed, since 1996 at least 6 placebo-controlled studies with LMWHs have demonstrated a reduction of venographically detected DVT approximately 1 month after elective HRS if prolonged prophylaxis (additional prophylaxis for approximately 3 weeks after the first post-operative week) is utilised. In summary, the results from these 6 studies demonstrate a reduction of DVT (venographically detected and symptomatic) from 22.5% in the pooled placebo group to 8.5% in the LMWH group. Proximal DVTs are also reduced from 11.2 to 3.0% and symptomatic VTE from 4.4 to 1.4% in the placebo and LMWH groups, respectively. Nevertheless, prolonged prophylaxis with LMWH has not been generally accepted for routine use in patients undergoing HRS. The labelling in several countries does, however, allow prolonged prophylaxis in patients deemed to suffer from an increased thrombotic risk.

Penthifra plus Trial Design

A multicentre, international, randomised, double-blind, placebo-controlled trial of fondaparinux 2.5 mg qd for 21±2 days following an initial open-label prophylaxis of 7±1 days, for the prophylaxis of VTE in patients undergoing HFS. Patients without evidence of symptomatic VTE or disqualifying bleeding during the initial week of prophylaxis and without study *exclusion criteria* could be randomised into the double-blind study.

The *primary efficacy outcome* was the rate of VTE (defined as DVT detected by mandatory bilateral venography, or documented symptomatic DVT, or fatal/non-fatal PE) during the randomised, double-blind extended prophylaxis period. The mandatory venography was to be performed at the end of the extended prophylaxis period (Day 21±2). The same composite efficacy and safety endpoints and adjudication ("Hamilton") used in all confirmatory studies of the original marketing authorisation application (MAA) were chosen, facilitating cross-study comparisons. The evaluable population for the primary efficacy analysis was defined as all treated patients with a VTE assessment up to Day 24 included. Patients were to be analysed in the group to which they were randomised. In order to explore possible effects of a missing VTE assessment on the interpretation of the efficacy results, the same sensitivity analyses (best case, realistic case and worst case) as those included in the original MAA were specified in the protocol. The safety population was the 'as treated' population, with a patient being considered in the fondaparinux group as soon as (s)he received at least one dose after randomisation. The main safety analysis considered all events observed up to Day 25, i.e., 2 additional days after the end of treatment.

A *sample size* of 210 patients per group was estimated assuming a rate of VTE after 3 weeks of extended thromboprophylaxis of 11.5%, a risk reduction of 50%, an expected incidence of VTE in the placebo group of 23% and a power of 85%. Assuming 10% of patients would not enter the double-blind period and 30% would be non-evaluable for primary efficacy, the target number of patients in the pre-randomised period was 670 in order to reach a total of 600 randomised patients (300/group).

Results

A total of 737 patients were enrolled, 81 (11%) of which were not subsequently randomised into the extended prophylaxis study. The most common reasons for subsequent non-randomisation were: 39 (S)AEs (serious adverse event) or efficacy failure [including 5 investigator-identified DVT/PE, 8 bleedings and 34 (S)AE], and 42 neither efficacy failure nor (S)AE [including 11 withdrawn informed consents and 31 other exclusion criteria/reasons]. The exposure of patients to fondaparinux before randomisation was 7.0 ± 0.8 days (mean ± SD). Thus, 656 patients were randomised to either fondaparinux or placebo. By Day 21 ± 2 (end of randomised double-blind period) 428 patients (65.2%) were included in the primary efficacy analysis. The 'as treated' population and the evaluable population for efficacy were evenly distributed between the 2 treatment groups.

The *demographic characteristics* of patients are consistent with those of the peri-operative HFS study (EFC2698) in the original MAA. As expected for patients randomised into HFS studies they tended to be older, lighter, female, and the incidence of impaired kidney function tended to be higher than in patients randomised into the studies of other types of MOSLL.

Efficacy

There was a highly significant reduction of the primary efficacy endpoint in the fondaparinux treatment arm as compared to the placebo group (Table 1).

Table 1 - Summary of efficacy results and subsequent curative treatment - Patients [n/N (%)] evaluable for the relevant endpoint

Efficacy Endpoint	Fondaparinux 2.5 mg qd	Placebo	p-Value
VTE (Primary efficacy analysis)	3/208 (1.4)	77/220 (35.0)	4×10^{-22}
DVT	3/208 (1.4)	74/218 (33.9)	4×10^{-21}
Proximal DVT	2/221 (0.9)	35/222 (15.8)	3×10^{-9}
Symptomatic VTE	1/326 (0.3) (1 proximal DVT)	9/330 (2.7) (1 fatal PE, 2 non-fatal PE, 5 proximal DVT, 1 distal DVT)	0.021
Patients with curative treatment (primary efficacy population)	5/208 (2.4)	50/220 (22.7)	5×10^{-11}

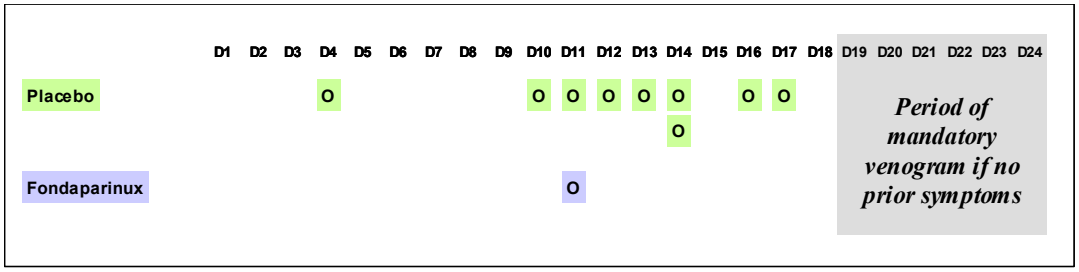
The VTE rate observed in the fondaparinux treatment group was low (1.4%), lower than that observed in study EFC2698 (8.3%) following peri-operative prophylaxis with fondaparinux in the same patient population. In this respect, the MAH suggests that prolonged prophylaxis not only prevents the development of new thrombi, but also may provide an environment that allows lysis of thrombi existing at the end of the peri-operative prophylaxis period. When the overall HFS population was subgrouped according to whether or not the patient received a hip replacement (either partial or total prosthesis) the observed VTE rates [fondaparinux: 1/56 (1.8%) vs. placebo: 25/70 (35.7%)] were consistent with the overall study results. The results of all 3 pre-specified sensitivity analyses of the primary analysis were also consistent and statistically significant (best case: RRR = 96%; 95%CI [88%; 100%]; realistic case: RRR = 60%; 95%CI [45%; 73%]; worst case: RRR = 35%; 95%CI [21%; 47%]).

The *secondary efficacy* analyses were consistent with the primary analysis; there was a statistically significant reduction in the rate of symptomatic VTE and a significant reduction of the combined endpoint of proximal DVT and/or PE (fondaparinux: 2/221 vs. placebo: 38/224).

Table 1 also shows that considerably fewer patients received curative treatment than those classified as having VTE (50 vs. 77 in the placebo group). Further to a request from CPMP, the MAH provided data showing that, unexpectedly, antithrombotic therapy was initiated by the investigators in only a small minority (3%) of the patients without any centrally adjudicated VTE. Even more unexpectedly, antithrombotic treatment was not initiated by the investigators in 12/37 patients with proximal DVT and in 22/40 with distal DVT (according to central reading). This point is addressed in the discussion.

The symptomatic events observed in the placebo group tended to present a week or more after randomisation, suggesting that it might take some time for symptomatic VTE to develop (Figure 1).

Figure 1 -Day of symptomatic VTE after randomisation



The trend for a delay in the occurrence of symptomatic VTE in the placebo group contributes to the impression of a considerable efficacy of fondaparinux prophylaxis in the early post-operative phase. A consistent trend for effect of fondaparinux was observed in several patient subgroups. The very low number of VTE in fondaparinux-treated patients does not allow identification of covariates by treatment interactions. However, in the placebo group gender, age, and increased kidney dysfunction appear to be associated with an increased VTE risk - age and female gender have previously been reported as VTE risk factors in HS, but not RI. The relationship of VTE risk with RI may be related to age and/or may be a marker of underlying concomitant morbidities that are actually responsible for the increased risk**.** Generally, ill patients are prone both to VTE and RI and thus, conclusions on a direct causal relationship between RI and VTE are difficult to draw. Hence, the observed increased thrombotic tendency has to be weighed against the well known increased bleeding risk in a benefit/risk evaluation of antithrombotic prophylaxis in RI patients.

Safety
The number of patients who discontinued study drug by reason is given in table 2.

Table 2 - Number (%) of patients who discontinued study drug prematurely by primary reason for discontinuation - All treated patients (as randomised groups)

Premature Treatment Discontinuation/Reason for Stopping	Fondaparinux (N=326)	Placebo (N=330)
Patients who discontinued study drug prematurely	40 (12.3%)	46 (13.9%)
Reason(s) for discontinuation[a]		
Lack of efficacy	2 (0.6%)	12 (3.6%)
DVT[a]	1 (0.3%)	9 (2.7%)
PE[a]	1 (0.3%)	3 (0.9%)
AE/SAE[b]	20 (6.1%)	14 (4.2%)
Bleeding AE/SAE	5 (1.5%)	1 (0.3%)
Repeated surgery	1 (0.3%)	3 (0.9%)
Suspicion of drug-induced decrease of platelet count	0 (0.0%)	0 (0.0%)
Other AE/SAE	14 (4.3%)	10 (3.0%)
Subject withdrawn consent	12 (3.7%)	16 (4.8%)
Other reason	6 (1.8%)	4 (1.2%)

NOTE: Patients are considered in the treatment group in which they were randomised.

[a] According to the Investigator's judgment.

[b] Including AEs recorded before the first double-blind study drug injection (based on the data collected in the 'end of treatment' form).

There were numerical increases in *bleedings* (Table 3) and bleeding-related criteria (i.e., transfusion, decrease in haemoglobin plasma level) under fondaparinux as compared to placebo treatment. The numerical difference in major bleedings (MB) was not statistically significant and was due to an increase in bleeding index (BI) ≥2 (i.e., a need for transfusion and/or a decrease in haemoglobin level). All of the MB occurred at the surgical site.

Table 3 - % of patients with adjudicated bleeding events during EFC2698 and EFC4582 by adjudication criterion -'As treated' patients

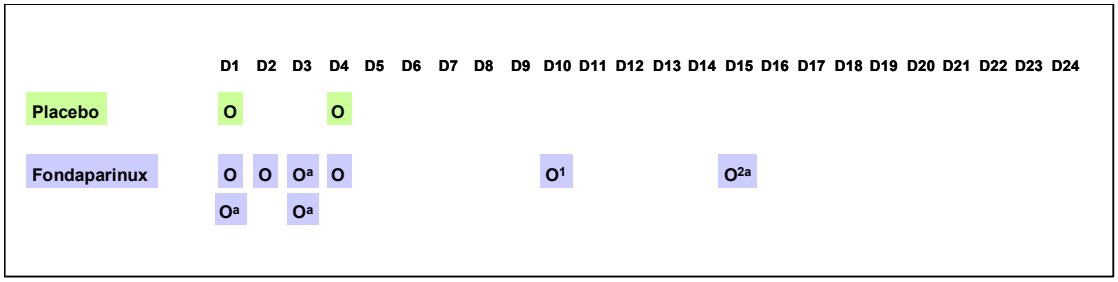
	Peri-Operative Prophylaxis EFC2698 (Penthifra)[a]		Extended Prophylaxis EFC4582 (Penthifra Plus)[b]	
Patients With	**Fondaparinux 2.5 mg qd (N=831)**	**Enoxaparin 40 mg qd (N=842)**	**Fondaparinux 2.5 mg qd (N=327)**	**Placebo (N=329)**
Major bleeding	18 (2.2%)	19 (2.3%)	8 (2.4%)	2 (0.6%)
Fatal bleeding	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Non-fatal critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding	18 (2.2%)	18 (2.1%)	8 (2.4%)	2 (0.6%)
At surgical site leading to re-operation	3 (0.4%)	2 (0.2%)	2 (0.6%)	2 (0.6%)
Only bleeding index (BI) ≥2	15 (1.8%)	16 (1.9%)	6 (1.8%)	0 (0.0%)
Minor bleeding only	34 (4.1%)	18 (2.1%)	5 (1.5%)	2 (0.6%)
Any bleeding	52 (6.3%)	37 (4.4%)	13 (4.0%)	4 (1.2%)

[a] From first double-blind injection up to Day 11 (Day 1 is the day of surgery).

[b] From first double-blind injection up to Day 25 (Day 1 is the day of first double-blind injection).

There was a temporal trend for MB, with bleedings more frequently observed immediately after randomisation (Figure 2), although 5 (4 fondaparinux vs 1 placebo) of the 10 MB reported after randomisation started before randomisation.

Figure 2 - Day of MB from the first study drug administration in EFC4582 'as treated' patients



[a] : patients with MB started before randomization and worsening after randomization
[1] : Patient 22050019 : MB only related to BI≥2 which only led to study drug temporary discontinuation for 48 hours
[2] : Patient 10020004 : MB started before randomization which led to re-operation on D15 after randomization

Because of the overall low number of MB, particularly in the placebo group, it was not possible to evaluate either the patient characteristics that might correlate with increased bleeding risk or the interaction of fondaparinux with any concomitant diseases or treatments (Table 4). Nevertheless, the tendency for increased MB rates with decreasing body weight and renal function are consistent with those observed during peri-operative prophylaxis in the original MAA. The safety concerns for patients with RI remain and must be carefully considered (see Removal of contraindication in severe renal impairment).

Table 4 - Number (%) [95% CI] of patients with MB by selected covariate - 'as treated' population

	Fondaparinux 2.5 mg qd (N=327)	Placebo (N=329)
Gender		
Male	2/92 (2.2) ; [0.3;7.6]	1/98 (1.0) ; [0.0;5.6]
Female	6/235 (2.6) ; [0.9;5.5]	1/231 (0.4) ; [0.0;2.4]
Age (years)		
<65	1/52 (1.9) ; [0.0;10.3]	1/56 (1.8) ; [0.0;9.6]
[65 – 75[	1/71 (1.4) ; [0.0;7.6]	1/58 (1.7) ; [0.0;9.2]
≥75	6/204 (2.9) ; [1.1;6.3]	0/215 (0.0) ; [0.0;1.7]
Weight (Kg)		
<50	2/28 (7.1) ; [0.9;23.5]	0/25 (0.0) ; [0.0;13.7]
[50 – 100]	6/292 (2.1) ; [0.8;4.4]	2/301 (0.7) ; [0.1;2.4]
>100	0/5 (0.0) ; [0.0;52.2]	0/2 (0.0) ; [0.0;84.2]
Creatinine clearance (ml/min)		
<30	1/28 (3.6); [0.1;18.3]	0/25 (0.0) ; [0.0;13.7]
30 – 50	3/104 (2.9); [0.6;8.2]	0/84 (0.0) ; [0.0;4.3]
50 – 80	3/125 (2.4); [0.5;6.9]	1/131 (0.8) ; [0.0;4.2]
≥80	1/68 (1.5); [0.0;7.9]	1/88 (1.1) ; [0.0;6.2]

Regarding *other adverse events*, overall there was no evidence of any differences between patients who received fondaparinux and those who received placebo. There were 2 fatal pulmonary embolisms (PE) in the placebo treatment group.

Immune thrombocytopenia and an increase in transaminases are ADRs often associated with heparins. *Clinical laboratory evaluations* revealed that no patient experienced a platelet count <100 x 10^9/l in either treatment group, and changes in liver enzymes were equally common in both treatment groups.

The possibility of a *thrombotic rebound phenomenon* induced by fondaparinux has also been addressed by the MAH, who concluded that the VTE rate following treatment discontinuation (in the placebo group) did not exceed the historical norm for a non-prophylaxed patient (i.e.: ~50%). Furthermore, there was no significant excess in AE rates in the placebo group after treatment discontinuation compared with patients who continued the treatment. Consequently, the VTE events observed after discontinuation of prophylactic therapy following the peri-operative period suggest a persisting VTE risk that should be prevented, rather than a rebound. The CPMP concur that the VTE events recorded probably represent a persisting risk rather than a rebound phenomenon. The high incidence of venographically detected DVT in the placebo group is not unexpectedly high when compared to the incidences recorded in similar studies with other prophylactic agents. Nevertheless, considering the new pharmacodynamic principle that fondaparinux represents, with an intense and selective inhibition of Factor Xa mediated via AT, there could be some concern for decreased AT levels during prolonged treatment, which in turn could lead to an increased thrombotic tendency. Further to a request from the CPMP, the MAH confirmed that AT levels had not been recorded at the end of the 4 weeks of fondaparinux treatment nor was there any external support for a lack of a clinically relevant reduction of AT activity during prolonged fondaparinux treatment.

Discussion

The over-all design of the study is acceptable for the intended primary objective, although the follow-up period after treatment ended is short and, thus, the incidences of symptomatic VTE or bleeding occurring after day 25 are unknown. The number of patients excluded before randomisation from the extended prophylaxis period and the number of patients not undergoing venography at the end of treatment correspond to what could be expected. The population included is judged to reflect the target population. It should be noted that, as observed in the pivotal studies in the original MAA, patients with severe RI (CL_{crea} <30 ml/min) were not to be included in this study. In violation of this exclusion criterion a fairly large proportion (8.6%) of the patients was included, possibly reflecting the confidence treating physicians today feel for the safety of pharmacological prophylaxis of VTE.

Efficacy

Not surprisingly, the statistically significant reduction in the primary endpoint is largely driven by the reduction in venographically detected, non-symptomatic DVTs. The reduction of symptomatic VTE also reaches statistical significance, although this is based on very few events. A study aiming to demonstrate an overall clinical benefit from prolonged prophylaxis would have to be of considerably greater size and would have to be designed differently, with a longer follow-up time and possibly with a third arm of patients not being treated and not undergoing venography after treatment.

The most important objection to routinely applied prolonged prophylaxis regimens in HRS has probably been the uncertainty on the clinical importance of the non-symptomatic venographically detected DVTs. The relationship between non-symptomatic DVT and symptomatic VTE probably differs in different clinical situations and could be suspected to change with time elapsed after surgery. The clinical importance of venographically detected DVTs 4 weeks after HFS is to a large extent unknown. Indeed, the lower number of patients receiving curative treatment relative to patients classified as having VTE (50 vs. 77 in the placebo group) raises the question as to whether these thrombi were small and difficult to diagnose, or whether they were detected locally but judged to be clinically irrelevant. These findings, together with the short observational follow-up period after treatment cessation, further contribute to the uncertainty concerning the clinical relevance of non-symptomatic venographically detected DVT 28 days after HFS. Despite this uncertainty, it is accepted that in a specific clinical situation there is a relationship between venographically detected DVTs and symptomatic DVTs and this assumption could be utilised in a direct comparison between different AT

agents, as was done in the original MAA. It is also well understood that once a DVT has been diagnosed at a prescheduled venography it cannot be left untreated in the majority of cases. However, this generally applied rule for clinical decision-making cannot be regarded as scientific proof for the clinical importance of non-symptomatic DVTs 4 weeks after HFS.

As regards extrapolating the Penthifra trial results to HRS patients, the MAH argues that given the already documented persistence of VTE risk in patients undergoing HRS and the demonstrated efficacy of a less effective agent (enoxaparin), the efficacy of fondaparinux in preventing persisting VTE risk in both types of hip surgery (HRS and HFS) is unquestionable. While the CPMP concur that prolonged prophylaxis in HRS can be expected to be effective to an extent that is similar (although not necessarily identical) to the demonstrated efficacy in HFS, the mean incidence of symptomatic VTE after day 11 was, in relative terms, 27% lower in HRS as compared to HFS. The extrapolation is thus not endorsed, as reflected in the adopted SPC.

Based on the above reasoning, the CPMP does not believe that a general recommendation for routinely applied prolonged prophylaxis in all patients undergoing HFS is justified. Nevertheless, the results of this study support a change in the labelling allowing prolonged prophylaxis in patients who are deemed by the treating physician to suffer from an increased thrombotic risk. This is reflected in the SPC.

Safety:
The number of patients who discontinued treatment prematurely was similar in both treatment groups, with more symptomatic VTE in the placebo group and a tendency for more bleedings in the actively treated group. As suggested from the results of the studies of perioperative prohylaxis in the original MAA, a temporal association between time of surgery and the incidence of MB was also observed in the Penthifra plus trial, although no trend for increased bleeding with increased treatment time is seen, which is interpreted by the MAH as an indication of a lack of a clinically relevant accumulation of fondaparinuxin plasma during the 3 weeks extended treatment. However, considering i) the well-known difficulties in evaluating bleeding tendency in clinical studies, ii) the limited size of the study, iii) the lack of external support for the safety of fondaparinux prophylaxis longer than 9 days, iv) the exclusion of patients with increased bleeding risk and severe RI and v) the avoidance of concomitant medication interfering with the haemostatic mechanisms in the clinical trial setting which seems to have been well controlled, it is difficult to conclude from these findings on the risk of bleedings in clinical routine and on the claimed lack of clinical relevance of possible plasma accumulation of fondaparinux (plasma levels were not measured in this study). Plasma concentrations can be viewed as a relevant marker for the safety (and efficacy) of fondaparinux.

REMOVAL OF THE CONTRAINDICATION IN SEVERE RENAL IMPAIRMENT

Scientific background
Arixtra was initially contraindicated in patients with severe renal impairment (CL_{crea}<30 ml/min). The elimination of Arixtra is highly dependent on renal function and there is a clear relationship between fondaparinux CL and CL_{crea}. In a RI study from the original application, CL was approximately 5-fold lower in severely impaired subjects compared with normal subjects

The MAH requested the deletion of the contraindication for patients with severe renal impairment (RI) and instead proposed treatment with a lower dose (1.5 mg q.d.). No new pharmacokinetic (PK) data have been submitted and the proposed changes are mainly based on new analyses of the original MAA data and Penthifra Plus results using PK modelling and simulation.

Modelling and Simulations
Population modelling was initially conducted using data from the moderate and severe RI groups in the RI-study (P-pharm), rendering population estimates and individual Bayesian parameter estimates. The 2 groups were analysed separately using a two-compartment model, thus not taking advantage of the information that arises from the other group, e.g. with respect to the CL- CL_{crea} relationship. Mild

and normal RI were not included in the analysis and data from the Phase II/III studies were not used, although they included many patients with moderate RI and a few patients with CL_{crea} 20 - 30 ml/min.

Further to a request from CPMP, the population analysis was redone. A population pharmacokinetic (POPPK) model using all available sparse data by SC route from the phase II/III studies was built with NONMEM software (FOCE interaction) and implemented on Pharsight Trial Simulator (TS2) software. The objective of this new analysis was to build a POPPK model including at least CL_{crea} as covariate of fondaparinux CL in patients undergoing MOSLL. A total of 756 patients (3413 time points) with an available CL_{crea} ranging from 23.5 to 231.5 ml/min (550 from study DRI2643, 65 from study ECF2442 and 141 from study EFC2698) were used to develop this model. A 2-compartment model with a first order absorption and elimination from the central compartment best fitted available data. Two covariates were included in the final model: CL_{crea} on CL, and the body weight (WGT) on central compartment volume (V2).

Table 5 – Description of final population pharmacokinetic model

Parameter	Population Estimate	Standard Error	Coefficient of Variation (%)	Interindividual Variability (%)
CL (L/h)	0.0409	0.0160	39	24
CL_{cr}(CL)	0.320	0.0169	5	-
CL(CLcr) = 0.0409 + 0.320 * (CLcr / Median CLcr)				
V2 (L)	7.21	0.123	2	14
WGT (V2)	0.0996	0.00626	6	-
V2 (WGT) = 7.21 + 0.0996 * (Weight - Median Weight)				
k_a (1/h)	1.58	0.184	12	71
Q (L/h)	0.145	0.0143	10	-
V3 (L)	17.8	3.78	21	138

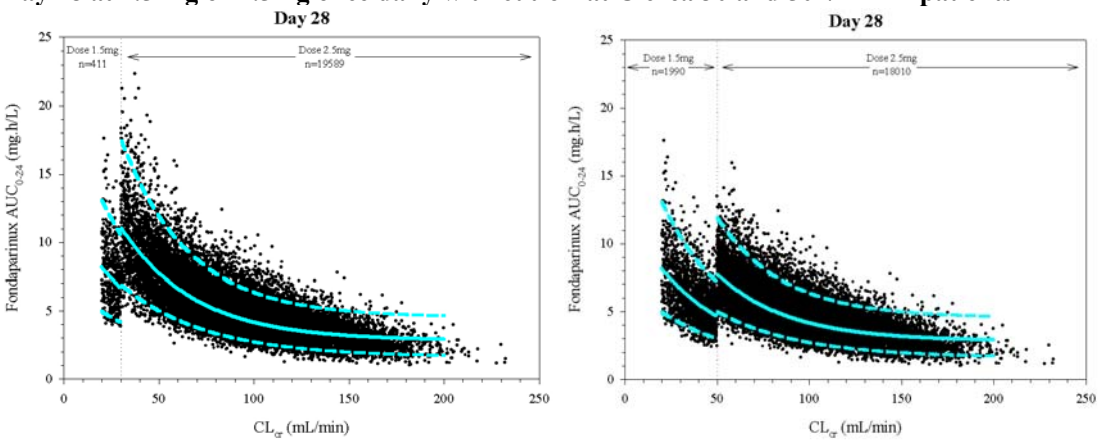
Residual variability 5.78 10^{-3} mg/l. CL: Clearance from first compartment; Q: Inter-compartmental Clearance; V2: Distribution Volume of first (central) compartment; V3: Distribution Volume of second (peripheral) compartment; k_a: Rate of absorption. The covariance of ηCL and ηV2 within the omega block was 0.0276, correlation=0.84.

Results

A total of 20,000 patients were simulated to receive fondaparinux 2.5 mg for 28 days with samples "collected" at appropriate time points on Day 7 and Day 28. No specific simulation was run at the 1.5 mg dose level: same C_{max} and AUC values obtained at 2.5 mg dose level were normalised to 1.5 mg. Empirical 5th, 50th and 95th percentiles were computed for a unit of CL_{crea} every 10 ml/min from 20 to 150 ml/min.

In order to provide reasonable estimates of the distribution of simulated Cmax and AUC_{0-24} for a given CL_{crea} value, empirical 5th, 50th and 95th percentiles were computed for a unit of CL_{crea} every 10 m/min. For graphic representations, exponential decay regression curves ($y=y_0 + a*e^{-bx}$) were estimated for each percentile (Fig 3).

Figure 3 -Individual predicted AUC_{0-24} (mg/l) and corresponding 5th, 50th and 95th percentiles on Day 28 at 1.5 mg or 2.5mg once daily with cut-off at Clcrea 30 and 50 l/min in patients



The model shows that increasing the CL_{crea} cut-off to a value above 30ml/min (i.e. 50ml/min) decreases the variability in the population and generates more comparable exposure in RI and "normal" patients for a switch between 1.5 and 2.5 mg dose.

Table 6- Descriptive statistics on predicted C_{max} (mg/l) and AUC_{0-24} (mg.h/l) on Day 28 at 1.5 mg and 2.5 mg q.d. for a CL_{crea} value at 20, 30, 40, 50 and 80 ml/min.

	Creatinine clearance value				
Dose	***20 ml/min***	***30 mL/min***	***40 ml/min***	***50 ml/min***	***80 ml/min***
C_{max} (mg/l)					
2.5 mg					
n	30	56	86	112	235
Mean (CV%)	0.760 (30)	0.612 (26)	0.530 (25)	0.456 (23)	0.359 (22)
5th percentile	0.464	0.403	0.325	0.299	0.250
Median	0.714	0.600	0.508	0.459	0.347
95th percentile	1.149	0.905	0.747	0.630	0.506
1.5 mg					
n	30	56	86	112	235
Mean (CV%)	0.456 (30)	0.367 (26)	0.318 (25)	0.274 (23)	0.215 (22)
5th percentile	0.278	0.242	0.195	0.179	0.150
Median	0.428	0.360	0.305	0.275	0.208
95th percentile	0.689	0.543	0.448	0.378	0.304
AUC_{0-24} (mg.h/l)					
2.5 mg					
n	30	56	86	112	235
Mean (CV%)	14.51 (33)	11.18 (31)	9.35 (27)	7.73 (24)	5.43 (25)
5th percentile	8.62	6.57	5.76	4.85	3.54
Median	13.95	10.88	8.91	7.81	5.22
95th percentile	21.92	17.96	14.28	10.62	7.89
1.5 mg					
n	30	56	86	112	235
Mean (CV%)	8.71 (33)	6.71 (31)	5.61 (27)	4.64 (24)	3.26 (25)
5th percentile	5.17	3.94	3.46	2.91	2.13
Median	8.37	6.53	5.35	4.68	3.13
95th percentile	13.15	10.77	8.57	6.37	4.73

The MAH has also looked at controlled MB data from the original MAA and from Penthifra Plus in order to help establish a cut-off value (Table 7).

Table 7- MB [number (%) of patients] by CL_{crea} and study categories in fondaparinux MOSLL studies – patients actively treated with fondaparinux

	Pre-Operative Studies (ACT2545, 63118, EFC2698)		Post-Operative Studies (DRI2643, EFC2442, 095-002)		Extended Prophylaxis (EFC4582)	
CL_{crea}	**Fonda 2.5 mg qd**	**Enox 40 mg qd**	**Fonda 2.5 mg qd**	**Enox 30 q12hr**	**Fonda 2.5 mg qd**	**Placebo**
<30 ml/min	4/72 (5.6)	1/75 (1.3)	0/11 (0.0)	1/12 (8.3)	1/28 (3.6)	0/25 (0.0)
30 – 40 ml/min	5/151 (3.3)	6/164 (3.7)	0/31 (0.0)	1/42 (2.4)	0/35 (0.0)	0/44 (0.0)
40 – 50 ml/min	15/235 (6.4)	9/277 (3.2)	0/90 (0.0)	2/103 (1.9)	3/69 (4.3)	0/40 (0.0)
50 – 80 ml/min	26/788 (3.3)	24/789 (3.0)	14/502 (2.8)	5/658 (0.8)	3/125 (2.4)	1/131 (0.8)
≥80 ml/min	14/647 (2.2)	14/664 (2.1)	17/932 (1.8)	11/992 (1.1)	1/68 (1.5)	1/88 (1.1)

Fonda=fondaparinux. Enox=enoxaparin

The limited number of events greatly hinders the interpretation of the above results. However, it should be remembered that an increased bleeding tendency has been observed in patients with reduced renal function. This is confounded by the observation that patients with renal impairment may be at higher risk of VTE.

Discussion
Due to limited data (1 subject with CL_{crea} of 8 ml/min), the lower CL_{crea} cut-off for treatment with fondaparinux has been set to 20ml/min and thus Arixtra should remain contraindicated in patients with CL_{crea} below this value. Given the comparable AUC and Cmax estimates in the severe and moderate group, the 1.5mg dose is approvable in severe renal impairment (>20ml/min).

The CPMP believes that, in the absence of clinical data to the contrary, it is preferable to opt for a dosing regimen that will give similar exposure in RI as in non-impaired patients, especially during prolonged prophylaxis, as reflected in the adopted SPC. This is relevant since patients with RI in the lower moderate range may not have achieved steady state with the 2.5 mg dose at the end of the previously approved 9-day treatment period. The fact that patients with renal impairment may be at higher risk for VTE and in special need of prophylaxis does not justify a higher exposure in this population. It is more reasonable that the VTE risk is a reflection of overall morbidity rather than related to renal impairment *per se*. Moreover, the safety data available for prolonged prohylaxis in RI stem from study EFC4582 and are not extensive.

NEW INDICATION IN THE TREATMENT OF VTE (new pre-filled syringes of 5mg/0.4ml, 7.5mg/0.6ml and 10mg/0.8ml)

Rationale for New Indication
VTE disease is the usual terminology for referring to DVT and PE, two clinical expressions of the same underlying pathophysiology. The mean annual reported incidence of DVT ranges between 48-180 per 100,000 population. Whereas a lower annual incidence of 23/100,000 is reported for symptomatic PE, asymptomatic defect of pulmonary perfusion is reported in up to 80% of patients suffering from DVT, especially proximal DVT. Conversely, the presence of DVT could be documented in up to 93% of PE patients. In addition, the reported rates of VTE recurrences in patients with only symptoms of DVT associated or not to asymptomatic PE or in patients with symptoms of PE are similar. These data emphasise the intimate relationship between DVT and PE.

DVT and PE are treated with the same therapeutic approach aiming to prevent further thrombotic extension with increased risk for post-thrombotic syndrome and pulmonary embolisation that may be life-threatening or lead to restriction of pulmonary function and/or chronic pulmonary hypertension. Current management of patients with acute VTE requires initial treatment with an anticoagulant

exhibiting rapid onset of action, such as Unfractionated Heparin (UFH) or Low Molecular Weight Heparin (LMWH), followed by chronic anticoagulation with oral anti-vitamin K agents (AVK) for secondary prevention. The approved UFH regimen for this initial treatment of patients with DVT and/or PE requires activated partial thromboplastin time (aPTT) monitoring due to inter-individual differences in dose-response relationship. LMWHs, such as bodyweight-adjusted dose enoxaparin sodium represent therapeutic alternatives for DVT patients with superior or equal efficacy, with some suggestions for decreased bleeding complications and heparin-induced thrombocytopenia (HIT) type II, which is a serious complication of heparin therapy. This therapeutic alternative, consisting of once or twice daily sc administration, allows home treatment for suitable patients.

Unlike fondapanirux, which is chemically synthesised, both UFHs and LMWHs are animal-sourced products with potential for contamination and exposure of patients to immunoallergic reactions and to other non-haemorrhagic adverse drug reactions. There is, therefore, a need to improve the initial anticoagulant therapy of patients with VTE.

This application concerns 3 new product strengths (pre-filled syringes of 5mg/0.4ml, 7.5mg/0.6ml and 10mg/0.8ml) developed for a new indication in the treatment of DVT and PE. Various health authorities were consulted prior to the finalisation of the clinical development plan. The studies follow the main recommendations made in CHMP Note for guidance (NfG) on clinical investigation of medicinal products for the treatment of VTE disease (CHMP/EWP/563/98) and CHMP scientific advice provided in September 1999.

1. Part II: Chemical, pharmaceutical and biological aspects

Composition
Arixtra 5mg/0.4ml, 7.5mg/0.6ml and 10mg/0.8ml contain fondaparinux sodium as the active ingredient in a concentration of 12.5 mg/ml. The medicinal product is presented as a solution for injection in a prefilled syringe with an automatic needle protection system.

Other ingredients include an isotonic solution of sodium chloride and water for injections. Sodium hydroxide and hydrochloric acid are used as pH adjusters and sterile nitrogen is used as an aid to filtration, but is not present in the finished product.
The product is packaged in a single dose syringe consisting of a glass barrel with a stainless steel needle and a rubber needle shield and closed with a plunger stopper. To differentiate between the different doses available, the plunger rod and the automatic needle protection system have different colours for each strength.

Active substance
The drug substance is identical to the one used in the already approved strengths.

Other ingredients
The same excipients are used as in the already approved strengths. All materials are of non-animal origin and comply with Ph. Eur. requirements.

Product development and finished product
Arixtra 5mg/0.4ml, 7.5mg/0.6ml and 10mg/0.8ml have been developed using the same qualitative composition, manufacturing process and primary packaging material as the already approved strengths. Since the proposed indication requires a higher dose compared to the approved ones, a higher concentration was needed in order to keep the injection volume below 1 ml. For this reason the concentration of the solution has been increased to 12.5 mg/ml as compared to the already authorised 5 mg/ml and the sodium chloride concentration has been changed from 0.84 to 0.76% in order to obtain similar osmolality (284-285 mOsm/kg) for both fondaparinux sodium solutions.

The manufacturing process is the same as the one employed in the already approved strengths. It is a standard process that involves the following steps: compounding, sterile filtration, aseptic filling, terminal sterilisation, inspection and secondary packaging. Filtration and terminal sterilisation have

been identified as the critical steps of the manufacturing process and have been appropriately validated together with the proposed holding times. From the results presented it can be concluded that the manufacturing process is reproducible and can consistently produce a product that meets the proposed specifications.

Product specification
The specifications include tests for the appearance, identification (LC), particulate matter, pH, extractable volume, degradation products (LC), sterility, bacterial endotoxins and assay by validated analytical methods. They have been kept identical with the ones for the approved strenghts except from some minor changes concerning the colour, extractable volume and assay.

Stability of the product
Stability data from 3 batches of the 5mg/0.4ml strength, 1 batch of the 7.5mg/0.6ml strength and 3 batches of the 10mg/0.8ml strength stored at 25°C/60%RH and 30°C/60%RH for 12 months and at 40°C/75%RH for 6 months have been presented. The samples were tested for appearance, particulate matter, pH, extractable volume, degradation products, free sulfates, sterility, bacterial endotoxins and assay, by validated stability indicating methods. In all cases the batch analysis results met the proposed specification.
Data from photostability and temperature cycling studies conducted according to ICH guidelines have also been provided. All results remained within the acceptance criteria.
The stability data provided indicate that the medicinal product is stable for the proposed shelf life when stored under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects.
The quality of Arixtra 5mg/0.4ml, 7.5mg/0.6ml and 10mg/0.8ml is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for the marketing authorization. There are no major deviations from EU and ICH requirements.

The proposed new strengths are similar to the already approved ones. They have the same qualitative composition and only differ slightly in quantitative composition. The same manufacturing process and primary packaging material are used as in the approved strengths and stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2. Non-clinical aspects

2.1 Toxicology

The mean maximum human exposure is about three-fold higher with the new proposed dosage regimen than with the hitherto approved posology. No new preclinical information has been made available since the product was originally approved. Further to a request from CHMP, the Applicant has submitted a non clinical overview including animal/human AUC-exposure ratios with the new proposed posology, together with a justification as to why the available preclinical information is sufficient to support the safety of the product at the higher proposed doses. Thus, the exposure ratios between the highest dosed animals of the pivotal repeat dose toxicity studies and patients with normal renal function (~20 μgxh/ml) have decreased from 5 to 1.75 in rat, 13 to 4.25 in rabbit, and from 16 to 5.3 in monkey. In renally impaired patients the exposure ratios will be even lower (1, 2.4 and 3 with the applicant's dose-adjustment proposal given ~35 μgxh/ml).

As explained in the Toxico-Pharmacological Critical Assessment of the original application, a combination of safety, pharmacokinetic and ethical considerations justified why studies with doses higher than those used cannot be performed; consequently, no additional toxicological studies with higher doses have been performed. The Applicant refers to this justification and argues that the animal/human exposure ratios obtained for the recommended therapeutic treatment dose of 7.5 mg are adequate and sufficient to support the safety of Arixtra for the intended indication, and concludes that no changes in the preclinical safety sections of the SmPC are necessary.

Discussion on the non-clinical aspects

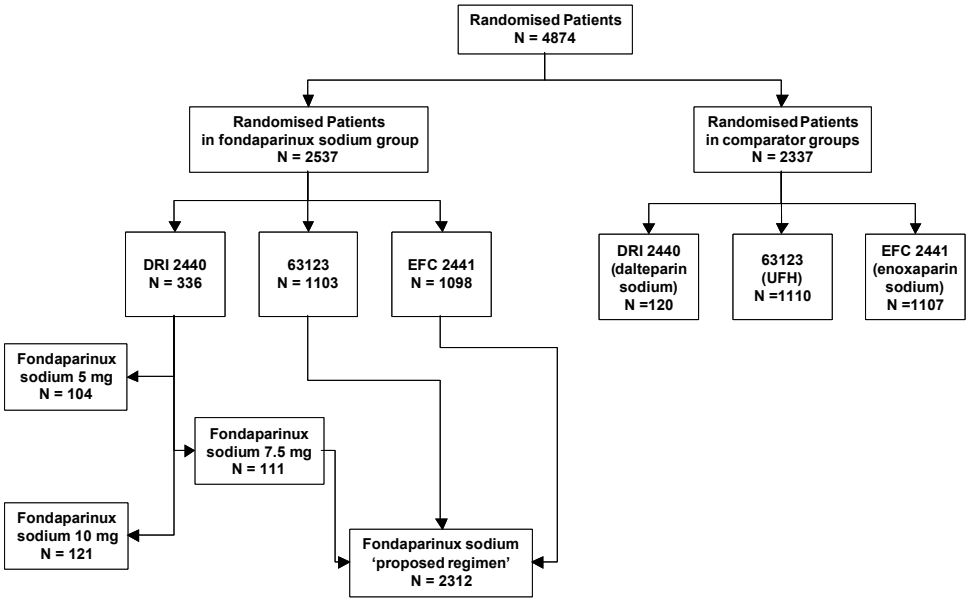
The investigated margins of toxicity are generally low. The question arises if more can be done to cover the new higher exposure scenario. In the earlier submitted repeat dose/reproduction toxicity studies (max dose 10 mg/kg/day in all species), the maximum tolerated dose (MTD) appears not to have been reached in the rat and rabbit (mostly minor injection site haemorrhage reported) in contrast to the more exposed monkeys (up to 3-month iv treatment), where a relatively more severe toxicity profile of primary bleeding and secondary associated events was reported. Hence, the full feasible toxicity profile of fondaparinux appears to have been explored in a species considered relevant regarding the pharmacological effects of heparins on the coagulation system. There were no apparent indications of other toxic events in the monkey, considered unrelated to effects on the coagulation system, up to 3-5 fold the clinical exposure level. The monkey data indicate that, upon short-term treatment, unacceptable bleeding would arise before any other potential harmful reaction occurs. Given the MTD studies available in monkeys, the CHMP concurs that it is not necessary to collect further data in the rodent species. Nonetheless, in contrast to the applicant's view, the CHMP considers that the toxicological profile of fondaparinux is not fully characterised for this higher dose indication. Hence, the fact that the repeated dose and reproduction toxicity studies are insufficient due to the limited exposure has been appropriately reflected in section 5.3 of the SPC.

3. Clinical aspects

3.1 Introduction

The efficacy and safety of Arixtra 5mg/0.4 ml, 7.5 mg/0.6 ml, and 10 mg/0.8 ml solution for injection in the treatment of Venous Thromboembolic Events was investigated in 3 multicentre studies conducted in Europe, North America and Australia, and additional pharmacokinetic (PK) and pharmacodynamic (PD) data were collected. The phase II REMBRANDT study (DRI2440) was a dose-response study conducted in patients with a bodyweight of 50-100 kg and tested 5 mg, 7.5 mg and 10 mg once daily sc fondaparinux versus q12h sc dalteparin in the initial treatment of symptomatic proximal DVT. Two pivotal phase III non-inferiority studies using the proposed weight adjusted dosing scheme (5mg <50kg, 7.5mg in 50-100kg, 10mg >100kg) were performed: one double-blind enoxaparin-controlled study in the curative treatment of DVT (MATISSE-DVT- study EFC2441) and one open-label UFH-controlled study in the curative treatment of PE (MATISSE-PE-study 63121). All studies were performed in compliance with the GCP regulations effective in Europe, North America and Australia. In addition, clinical protocols, amendments to the protocols, patient informed consents were reviewed and approved by independent Ethics Committee or Institutional Review Board.

Overall, the development program randomised 4,874 patients, as follows.



3.2 Pharmacokinetics

Bioequivalence

The clinical formulation employed in the phase II and phase III Matisse-DVT study was identical to that used for the clinical trials presented in the original prophylaxis dossier. In the formulation used for the other phase III study (Matisse-PE), the fondaparinux sodium concentration was increased to 12.5 mg/ml in anticipation of the market formulation. The bioequivalence of the new formulation and the reference formulation has been shown with respect to both rate and extent of absorption.

Pharmacokinetics in target population

The pharmacokinetics were evaluated on Days 1 and 5. The results show a tendency towards a non-proportional dose-concentration relationship (AUC is increased by 50% when doubling the dose) indicating that a non-linear process is occurring. It has been previously shown *in vitro* that protein binding is saturated above 2 mg/l. Since the effect and bleeding events of fondaparinux are related to drug bound to antithrombin, saturated binding could hypothetically result in approaching the maximal effect. Further to a request from CHMP, the Applicant has provided data showing that, within the concentration range achieved with 5-10 mg fondaparinux once daily (up to 3 mg/l), AT III binding is not saturated. Increasing the dose further may result in a saturation of AT III binding.

A comparison of steady state plasma concentrations observed in patients with DVT at a regimen of 10 mg fondaparinux (study DRI2440) with data obtained in healthy volunteer studies (previous dossier) indicates a close similarity in the PK of fondaparinux in the 2 populations, suggesting that the PK observations in previous studies in healthy volunteers hold true for the patient population under discussion.

In addition, a detailed NONMEM population PK analysis was conducted pooling all PK data obtained in studies DRI2440, EFC2441 and 63121 investigating numerous possible covariate relationships (gender, age, body weight, renal function, etc) and their effect on the kinetics of fondaparinux. Renal function was identified as the most important covariate affecting clearance, and the simulations demonstrated that with dosage adjusted to renal function, variability in exposure can be reduced. Hence, for fondaparinux, dosage primarily according to renal function would be the optimal posology. However, given the data available, the CHMP did not find that a change from the weight-based dosage used in clinical trials to renal function-based dosage would be possible in the present application.

Having identified renal function as the most important variable affecting exposure to fondaparinux, the CHMP raised several questions to better understand the kinetic and dynamic findings in patients with moderate or severe renal impairment. As seen from the applicant's response, the numbers of

subjects with CLcr 30-40 and 40-50 ml/min are fairly large (129 and 189, respectively). Although there is a clear trend to increased incidence of VTE and bleedings in severe renal impairment (CLcr 20-30 ml/min) – see below, the data for patients with moderate renal impairment do not raise new concerns and do not reveal any clear differences between patients with CLcr 30-40 and 40-50 ml/min. It should be noted, however, that the majority of patients with moderate renal impairment had a body weight of 50-100 kg and that there is truly limited information in patients with low body weight and moderate renal impairment, and no information in patients with high body weight and moderate renal impairment.

Patients with Severe renal impairment (CL cr <30 ml/min)
Patients with CLcr 20-30 ml/min treated with fondaparinux is a small subgroup (n=57) which showed an increased rate of major bleeding, an increased rate of "any bleeding", an increased frequency of transfusion, and an increased frequency of haemoglobin (Hb) decrease ≥2 g/dl, compared with both enoxaparin and UFH. This applies specifically in patients with body weight between 50-100 kg (n=36). Almost no clinical information is available in severe renally impaired patients with low or high body weight. Based on the paucity of clinical experience, the CHMP considers that fondaparinux should be contra-indicated in patients with severe renal failure (CLcr <30 ml/min), regardless of bodyweight.

Patients with Moderate renal impairment (CL cr 30-50 ml/min)
The phase III data obtained in a large number of 50-100 kg patients with moderate renal failure treated with fondaparinux showed that the safety of fondaparinux was at least similar to that of enoxaparin or UFH, both in fondaparinux patients with either CLcr 40-50 ml/min (n=189) or CLcr 30-40 ml/min (n=129). Thus, in 50-100 kg patients with moderate renal failure treated with 7.5 mg fondaparinux there was no increase in either "major bleeding" or "any bleeding", and no increase in the percentage of patients requiring transfusion nor in the percentage of patients with Hb decrease ≥2 g/dl compared with patients on enoxaparin or UFH. The CHMP therefore accept that the study dose regimen of 7.5 mg daily should be the SPC dose regimen in these patients.

There is no clinical experience in patients weighing >100 kg with moderate renal impairment. This is reflected in the SPC. As the pharmacokinetics of fondaparinux are more dependent on renal function than on body weight, heavy weight patients with moderate renal impairment are expected to have an increased exposure with the 10 mg dose used in clinical trials. A lower dose might be sufficient; indeed, a subsequent pharmacokinetic analysis has shown that this sub-group is expected to have a mean AUC up to 35 mg·h/l. Reducing the dose to 7.5 mg would reduce the exposure to a mean AUC of up to 27 mg·h/l, which would be more in line with the exposure in normal weight patients with moderate renal impairment. If fondaparinux administration is necessary in this patient group, and based on PK simulation data, a reduction of the daily dose to 7.5 mg daily may be considered (after an initial 10 mg dose on Day 1 if renal status is not available at the time of starting treatment).

Appropriate warnings in patients of low body weight and patients of high body weight with moderate renal impairment have been added to the SPC.

Pharmacodynamics

The clinical pharmacology of fondaparinux was reviewed in the original application for prophylactic use in MOSLL. As a result of its specific anti-factor Xa activity, fondaparinux at prophylactic concentrations produces minimal changes in aPTT, activated clotting time, INR, or thrombin time.

Two additional pharmacodynamic studies have been submitted in support of the present application. The first is the investigation of the dose-response relationship within the phase II Rembrandt study with respect to PD markers such as the thrombin-antithrombin complex, D-dimer, aPTT - for details of the study design see later. Decreases in D-dimers and TAT levels, the latter somewhat dose-related, were observed on Day 5±1 in the 4 treatment groups (5, 7.5 and 10 mg fondaparinux sodium, and dalteparin sodium), without significant differences between groups. A slight increase in aPTT was observed on Day 7±1 in the 3 fondaparinux treatment groups and in the dalteparin sodium group in the

presence of concomitant VKA therapy. The changes in aPTT seem dose-dependent but moderate, of similar amplitude to those observed with dalteparin and difficult to interpret in the presence of concomitant VKA treatment. Thus, monitoring of the pharmacodynamic activity of fondaparinux sodium by aPTT does not seem appropriate.

Fondaparinux sodium has been shown in healthy subjects not to interact with the pharmacokinetics and pharmacodynamics of warfarin. During the VTE treatment studies, the pharmacodynamic activity of VKA (started within 72 hours of randomisation) was assessed by INR. No differences between the treatment groups were recorded in either the mean INR values achieved at the end of the study drug administration period or in the time to reach an INR ≥2.0. Somewhat more fondaparinux treated patients had an INR >3 at the time of study drug discontinuation as compared with the active controls. Unfortunately, the mean doses of VKA at discontinuation of study drug in the different treatment groups, requested by CHMP, were not recorded during the studies. The Applicant has subsequently clarified that fondaparinux increases the prothrombin time to a slight extent, an effect judged to be of minor clinical relevance.

Age and renal function play a major role on fondaparinux elimination and there is an increased risk of dangerously high levels in these fragile populations. Further to a request from CHMP, the Applicant has addressed the question of whether indirectly monitoring fondaparinux concentrations by measuring plasma factor Xa levels could be considered in fragile patients. The Applicant refers to the difficulties in defining a therapeutic range and concludes that it is not useful. However, it may in selected cases be regarded as desirable by the treating physician to have the possibility to check the plasma levels achieved in fragile patients, especially when treatment is prolonged. The situation can be compared to that of LMWH, where monitoring of plasma levels is seldom part of clinical routine but can be easily determined by chromogenic substrate tests in selected cases. Similar tests could be performed for estimation of fondaparinux concentrations. To this effect, and despite the absence of a treatment target range, information on the fondaparinux plasma concentrations obtained during treatment with fondaparinux in the clinical studies (as estimated by FXa inhibition assay) has been provided in the SPC.

Further to a request from CHMP it has been demonstrated that the concentration of antithrombin is not significantly reduced during short-term treatment with fondaparinux. In addition, an *in vitro* study of the inhibition rate constants for different coagulation factors seems to demonstrate that fondaparinux inhibits activated factor IX substantially less than UFH and LMWH at the typical molar concentrations achieved during treatment. The inhibition of FVIIa by fondaparinux and LMWH, however, seems to be comparable at these concentrations.

The other pharmacodynamic study (63128) was undertaken to address the uncertainty of how to clinically handle a major bleeding event during fondaparinux treatment, considering the rather long half life of the agent and the lack of antidotes with documented efficacy. It was a phase I interaction study to investigate the PK and PD of recombinant factor VIIa (rVIIa; 90 μg/kg IV) on the inhibition of thrombin generation by Arixtra (10 mg sc) in 16 healthy male volunteers. The results showed that rVIIa partially reverses the pharmacological effect of fondaparinux and in fact activates the coagulation cascade. However, the observed effect was only partial and some inhibition of factor Xa persisted. Therefore, an increased bleeding tendency may continue that requires additional awareness. There is not yet any clinical evidence available on the translation of the reversal properties of this agent into a rapid cessation of bleeding complications and whether the counteracting pharmacological effect of recombinant factor VIIa would not lead to a procoagulant status. In view of the above, it is premature to include a recommendation in the SmPC to use rVIIa in case of severe uncontrollable bleeding.

Discussion

The main discussion at CHMP has centred around the most appropriate dosing schedule. The 2 main alternatives considered were either according to body weight, as used in the pivotal phase III trials and proposed by the MAH, or according to renal function using creatinine clearance cut-off values to recommend particular doses – see clinical efficay discussion for more details.

Unfortunately, there are few PK data in patients with Major Bleedings and, as discussed for the original prophylaxis dossier, it is not possible to determine an exposure (ie. Anti-Xa) cut-off value that would predict a higher risk of bleeding or VTE recurrence.

Finally, the results of a pharmacodynamic study failed to show an effective antiacoagulant profile of rVIIa. Hence, to date, there is no known antidote to fondaparinux, and this has been included in section 4.9 of the SPC.

3.3 Clinical efficacy

1.4.3.1 Dose response studies

Study DRI2440 is the basis for the dose selection for the pivotal studies. This study was a multicentre, randomised, double-blind study testing in parallel 5, 7,5 and 10 mg of fondaparinux once daily by sc injections versus dalteparin in the initial treatment of DVT without symptomatic PE. Fondaparinux was administered for a minimum of 5 days and until the INR was ≥2.0 at two consecutive measurements and up to a maximum of 10 days. An oral AVK, adjusted for INR between 2 and 3, was initiated on day 1 or day 2 and continued for 3 months.

Males or females (of non-childbearing potential or with negative pregnancy tests and contraceptive protection) of 18 years or older with a compression ultrasonography (US)-confirmed symptomatic proximal DVT were included. Main exclusion criteria were symptomatic PE, body weight <50 kg or >100 kg and known renal insufficiency. The intention to treat (ITT) population included 438 patients, of which 396 were included in the per protocol (PP) population.

The *primary efficacy endpoint* was the change (improvement, no change or worsening of thrombus mass) between baseline and Day 7±1 in the composite of US of the venous bed of the lower limbs and perfusion lung scan (PLS). A positive outcome was defined as an improvement in US and/or PLS results without deterioration of either test, and a negative outcome resulted in all other instances, including death occurring less than 24 hours following the last day of study drug administration. *Secondary efficacy criteria* were the incidence of patients with symptomatic recurrence or extension of VTE during the entire study (including the study drug period from day 1 up to 48 hours after the last administration and a follow-up up to day 90), and the US and PLS results analysed separately. The *primary safety endpoint* was the incidence of major and minor bleeding events. Related bleeding criteria were assessed by haemoglobin (Hb) levels and transfusions. Primary and secondary efficacy endpoints, the primary safety endpoint and death were evaluated blindly by an independent adjudication committee (IAC).

Results
The following tables present the PP population results; similar results were observed for the ITT population.

Table 1 Primary endpoint: Number (%) of patients with a positive outcome

	Fondaparinux Sodium				Dalteparin Sodium (N=107)
Positive Outcome	5 mg (N=84)	7.5 mg (N=99)	10 mg (N=106)	Total (N=289)	
n (%)	39 (46.4%)	49 (49.5%)	46 (43.4%)	134 (46.4%)	50 (46.7%)
95% CI	[35.47; 57.65]	[39.29; 59.73]	[33.80; 53.37]	[40.51; 52.30]	[37.02; 56.62]

No dose effect was observed for the primary endpoint. Pairwise comparisons between the different dose groups or between these groups and the dalteparin sodium group did not show any significant differences. Similarly, the comparison of the pooled fondaparinux results with the dalteparin group did not show a significant difference [relative risk of 0.992 (95% CI: 0.76; 1.34)].

Table 2 - Number (%) of patients with worsening, no change or improvement in US

Outcome (Day 7±1)	Fondaparinux Sodium				Dalteparin Sodium
	5 mg (N=84)	7.5 mg (N=99)	10 mg (N=106)	Total (N=289)	(N=107)
Improvement	29 (34.9%)	25 (25.3%)	32 (30.5%)	86 (30.0%)	33 (30.8%)
No change	49 (59.0%)	70 (70.7%)	67 (63.8%)	186 (64.8%)	70 (65.4%)
Worsening	5 (6.0%)	4 (4.0%)	6 (5.7%)	15 (5.2%)	4 (3.7%)
Inadequate/not done	1	0	1	2	0

Table 3 - Number (%) of patients with worsening, no change or improvement in PLS results

Conclusion on Baseline PLS	Outcome (Day 7±1)	Fondaparinux Sodium				Dalteparin Sodium
		5 mg (N=84)	7.5 mg (N=99)	10 mg (N=106)	Total (N=289)	(N=107)
No perfusion defect	Unchanged	13 (15.5%)	10 (10.1%)	29 (27.4%)	52 (18.0%)	14 (13.1%)
	Worsening	1 (1.2%)	1 (1.0%)	1 (0.9%)	3 (1.0%)	0 (0.0%)
Perfusion defect	Improvement	23 (27.4%)	45 (45.5%)	31 (29.2%)	99 (34.3%)	31 (29.0%)
	Unchanged	37 (44.0%)	36 (36.4%)	37 (34.9%)	110 (38.1%)	49 (45.8%)
	Worsening	10 (11.9%)	7 (7.1%)	8 (7.5%)	25 (8.7%)	13 (12.1%)
Whatever the baseline	Improvement	23 (27.4%)	45 (45.5%)	31 (29.2%)	99 (34.3%)	31 (29.0%)
	Unchanged	50 (59.5%)	46 (46.5%)	66 (62.3%)	162 (56.1%)	63 (58.9%)
	Worsening	11 (13.1%)	8 (8.1%)	9 (8.5%)	28 (9.7%)	13 (12.1%)

While there was no obvious dose effect for the US evaluation, fewer patients in the 7.5 mg or 10 mg dose groups tended to experience a worsening of pulmonary perfusion defects compared with either the 5 mg fondaparinux group or the dalteparin group.

Table 4 -Symptomatic adjudicated recurrent VTE occurring during the entire study - All treated patients

Symptomatic VTEs	Fondaparinux Sodium				Dalteparin Sodium
	5 mg (N=103)	7.5 mg (N=111)	10 mg (N=120)	Total (N=334)	(N=119)
DVT alone	2 (1.9%)	2 (1.8%)	1 (0.8%)	5 (1.5%)	3 (2.5%)
Non-fatal PE	0 (0.0%)	0 (0.0%)	3 (2.5%)	3 (0.9%)	3 (2.5%)
Total VTE 95% CI	2 (1.9%) [0.24; 6.84]	2 (1.8%) [0.22; 6.36]	4 (3.3%) [0.92; 8.31]	8 (2.4%) [1.04; 4.66]	6 (5.0%) [1.87; 10.65]

No significant differences between the different groups were observed. However, it is worth noting that the 2 clinical recurrences in the 5 mg group occurred during the study drug treatment period.

Regarding the *safety endpoints*, no dose effects were observed for either "all bleedings" or major bleedings (MB) alone.

Table 5. The number (%) [95% CI] of patients with a bleeding event during the treatment period.

Patients With	Fondaparinux				Dalteparin
	5 mg (N=103)	7.5 mg (N=111)	10 mg (N=120)	Total Fondaparinux (N=334)	(N=119)
Major Bleeding (MB)	3 (2.91) [0.60; 8.28]	2 (1.80) [0.22 ; 6.36]	1 (0.83) [0.02; 4.56]	6 (1.80) [0.66; 3.87]	0 (0.00) [0.00; 3.05]
Minor bleeding only	5 (4.85) [1.59; 10.97]	7 (6.31) [2.57; 12.56]	5 (4.17) [1.37; 9.46]	17 (5.09) [2.99; 8.02]	13 (10.92) [5.95; 17.96]
All bleedings	8 (7.77) [3.41; 14.73]	9 (8.11) [3.77; 14.83]	6 (5.00) [1.86; 10.57]	23 (6.89) [4.42; 10.15]	13 (10.92) [5.95; 17.96]

No fatal bleeding and no bleeding into a critical organ were adjudicated. Four of the 6 MB events occurred at the site of a cancer lesion (two each in the 5 mg and 7.5 mg groups), one (thigh haematoma in the 5 mg group) occurred in the presence of a high INR (4.7 and 4.4) on the days preceding the day of the symptom, and one was an abdominal wall haematoma at the injection site reported in the 10 mg group.

In summary, despite the failure of study DRI2440 to demonstrate a clear dose relationship, the selection of the dose for the phase III studies was made based on the following considerations: i) treatment with fondaparinux sodium 7.5 or 10 mg doses was associated with less frequent worsening of the perfusion lung scan than treatment with fondaparinux sodium 5 mg or dalteparin sodium, ii) the only clearly product-related MB with no mitigating circumstances occurred in the 10 mg group, iii) two clinical recurrences occurred in the 5 mg group during study drug treatment and iv) the thrombin-antithrombin complex (TAT) levels were higher in the 5 mg dose group.

1.4.3.2 Main studies

Methods
The two multinational, multicentre, randomised, parallel-group phase III studies were of similar design. Matisse DVT (study EFC2441) was double-blind and included patients with confirmed (US or venography) DVT in the trifurcation of the calf veins, or more proximally. Matisse PE (study 63123) was open-label and enrolled patients with confirmed (ventilation/perfusion lung scan, pulmonary angiography, spiral CT) PE. Body weight-adjusted doses of fondaparinux given qd subcutaneously (5 mg <50 kg, 7.5 mg for 50-100 kg, and 10 mg for >100 kg) were compared with 1mg/kg enoxaparin sodium q12h in the DVT study and with an iv infusion of UFH, adjusted to aPTT (target of 1.5-2.5 x control), in the PE study. In both studies, study drugs were to be administered for at least 5 consecutive days and could be stopped when the INR was above 2.0 on two consecutive days. Concomitant AVK therapy was to be initiated as soon as possible and usually within 72 hours after the first study drug administration (on Day 1), with dose adjustments to achieve a target INR of 2.5 (range 2.0 to 3.0), and was to be continued up to Day 90. Treatment with study drugs had to be started within 6 hours after randomisation.

In Matisse PE, randomised patients could have been pre-treated with UFH during the screening phase, but patients that had been on anticoagulant treatment for more than 24 hours before randomisation were excluded. Other *exclusion criteria* were a serum creatinine level >2.0 mg/dl (180 μmol/l, uncontrolled hypertension, and patients requiring thrombolyis or embolectomy or vena cava filter.

The *primary efficacy endpoint* for both studies was recurrent VTE recorded up to the end of the follow-up period (Day 97), as adjudicated by a blinded Central Independent Adjudication Committee (CIAC) and composed of i) symptomatic non-fatal VTE (DVT and/or PE) and ii) fatal VTE (death related to VTE or for which VTE could not be ruled out). The *secondary efficacy endpoints* included the individual components of the primary efficacy endpoint, investigator-suspected VTE recurrences up to Day 97, and the primary endpoint at the end of the study drug treatment period.

The primary *efficacy analysis* included all randomised patients. A secondary efficacy analysis was performed on the PP population. The primary analysis of both studies computed the difference in the crude VTE rates between the two treatment groups (fondaparinux minus enoxaparin or UFH) with its 2-sided 95% CI. The pre-specified non-inferiority margin for both studies was 3.5%.

Results

The *baseline demographics and risk factors* were essentially similar in both pivotal studies (EFC2441, 63123) and the dose finding study (DRI2440).

Diagnostic measures and treatment compliance
The duration of study drug treatment was very similar in the treatment groups in all 3 trials (mean of 7 days). The DVT diagnosis (EFC2441 study) was confirmed by US in 95%, by venography in 4% or by both in 1% of cases. The PE diagnosis (study 63123) was confirmed by either a high probability lung scan or a positive spiral CT scan (in approximately equal numbers) in the majority of cases, or by a pulmonary angiogram in 50 cases. Inclusion in study 63123 was based on a non-high probability lung scan combined with a confirmed DVT in approximately 8% of cases.

AVK was introduced on day 1 or earlier in 56% of EFC2441 patients and 60 % of 63123 patients, and the large majority of patients (98-99%) started the AVK treatment within the first 3 study days.

The main *efficacy results* are displayed in the tables below.

Table 6. Study EFC2441 Summary of efficacy results up to Day 97. - Number (%) of patients,

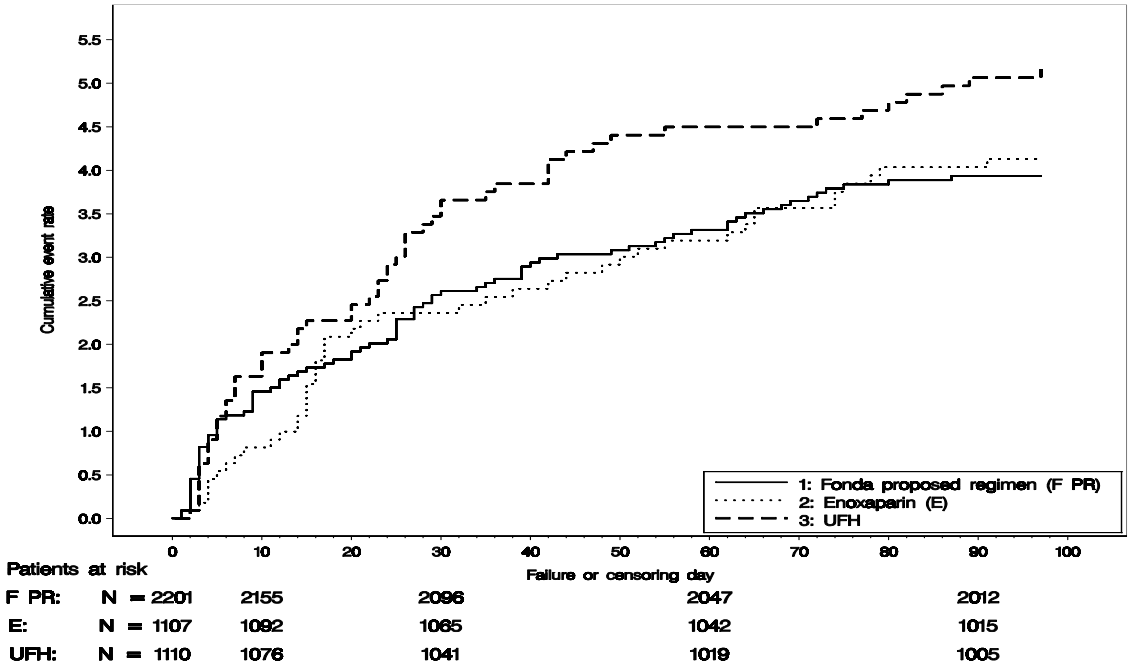
Endpoint	**Fondaparinux Sodium** (N=1098)	**Enoxaparin Sodium** (N=1107)	**95% CI for Difference**
Total VTE	43 (3.9%)	45 (4.1%)	-1.8%; 1.5%
DVT only	18 (1.6%)	28 (2.5%)	
Non-fatal PE	20 (1.8%)	12 (1.1%)	
Fatal VTE	5 (0.5%)	5 (0.5%)	
PP analysis			
	(N=988)	(N=976)	
Total VTE	34 (3.4%)	42 (4.3%)	-2.6%; 0.8%

Table 7 Study 63123 Summary of efficacy results up to Day 97, - Number (%) of patients,

Endpoint	**Fondaparinux sodium**	**UFH**	**95% CI for difference**
Primary analysis (all randomised)			
	N=1103	**N=1110**	
Total VTE	42 (3.8 %)	56 (5.0 %)	-3.0% – 0.5%
DVT only	12 (1.1 %)	17 (1.5 %)	
Non Fatal PE	14 (1.3 %)	24 (2.2 %)	
Fatal event	16 (1.5 %)	15 (1.4 %)	
PP analysis			
	N=920	**N=794**	
Total VTE	27 (2.9 %)	35 (4.4 %)	-3.3% – 0.3%

Overall, the non-inferiority criteria were fulfilled in both studies; the upper limit of the 95% CI is well below the predefined non-inferiority margin of 3.5: 0.8 (PP) and 1.5 ("all randomised") in the DVT study and 0.3 (PP) and 0.5 ("all randomised") in the PE study. The impression from the results is that fondaparinux is approximately as efficacious as enoxaparin and at least as efficacious, possibly better, than UFH.

The following graph depicts the symptomatic recurrent VTE cumulative event rates up to Day 97 in studies EFC2441 and 63123 for all randomised patients.



As can be seen in the graph, in study EFC244 there were numerically more symptomatic recurrences during the study drug treatment period with fondaparinux (18 recurrences, 1.6%) than with enoxaparin (10, 0.9%), but this difference was not statistically significant. The Applicant has provided case summaries for all patients experiencing fatal PE during the initial treatment period (7 *vs.* 8 in the pooled fondaparinux comparator groups, respectively) and no specific concerns arise from these analyses. A lack of anti-inflammatory effects of fondaparinux, as compared with LMWH and UFH, could possibly have contributed to this numerical difference. Moreover, a reverse trend in favour of fondaparinux was observed in study 63123 as during the initial treatment period, 12 (1.1%) patients treated with fondaparinux sodium and 19 (1.7%) patients treated with UFH had a VTE endpoint.

The MAH has provided comparisons of the results in different subgroups and there is no evidence of any effect of demographic or baseline characteristics on the efficacy results.

Discussion on clinical efficacy

The choice of comparator, design and conduct of the dose selection study are acceptable and in line with the NfG document, although a more common approach to evaluate optimal doses for new anti-thrombotic agents for DVT treatment has been to use scoring systems (e.g. Marder score) based on repeated ascending venography for comparisons. The results were less informative than expected and the support for the selected doses is somewhat limited, although the MAH's arguments for the choice of 7.5 mg dose are reasonable. It should be noted that it has been difficult to demonstrate clear dose-response relationships for other anti-thrombotic agents in earlier similar studies, also when repeated venography has been utilised

The two phase III studies are large, well designed, adequately performed and are considered to be informative. Efficacy of fondaparinux with regard to the composite primary endpoint (non-fatal symptomatic VTE or fatal VTE) that is non-inferior to enoxaparin in DVT treatment and to UFH in PE treatment has been demonstrated. The VTE rate observed in the enoxaparin reference group was consistent with historical data and the protocol hypothesis. However, overall mortality and mortality rates linked to PE were lower in the Matisse PE study when compared to data from published registries (such as Icoper and Mappet) and data from the Columbus study. Further to a request from CHMP it has become apparent that the these lower rates can probably be explained by differences in the included patient populations. Thus, there is limited experience with Arixtra in haemodynamically unstable patients and no experience in patients requiring thrombolysis, embolectomy or insertion of a

vena cava filter, as these latter 3 categories of patients were excluded from the Matisse-PE trial. Therefore, the indication has been amended accordingly and a relevant warning statement has been introduced in section 4.4 of the SPC.

The major discussion at CHMP centred on the most appropriate dosing schedule. The two main alternatives considered were dosing according to body weight, as used in the pivotal phase III trials and proposed by the MAH, or according to renal function using creatinine clearance cut-off values to recommend particular doses. The NONMEM population PK analysis indicated that dosing primarily according to renal function provided the most consistent exposure levels in the various patient populations and might be considered as the most optimal posology. Thus, several potential dosing schedules were discussed, notably one of 7.5 mg daily in patients with CLcr > 50 ml/min and 7.5 mg on Day 1 and thereafter 5 mg daily for CLcr of 20-50 ml/min. Despite the clear dose-exposure relationship for bleeding (the main safety concern with Arixtra) seen in dose-ranging studies for the prophylaxis indication, major bleeding events, as anticipated, were few in the studied "treatment" population, making major bleeding a poorly sensitive marker for detecting differences between subgroups or for predictions regarding risk in clinical practice. No correlation could be found in the data submitted for this application between exposure and either efficacy or safety endpoints, and bleeding rates in patients at risk were similar between fondaparinux and the comparators. Moreover, the possibility of underexposure is a major concern when treating patients with life-threatening VTE. Therefore, in view of the available data, the CHMP decided against a change from the weight-based dosage tested in the clinical trials to a renal function-based dosage derived from kinetic modelling.

3.4 Clinical safety

A total of 4829 patients were randomised and treated in the 3 studies. The total patient population exposed is large, with 2,294 patients receiving the fondaparinux proposed dose regimen of 7.5 mg. The duration of exposure to active study drug was similar for the fondaparinux and comparator groups (mean duration 7 days) and there is limited exposure with fondaparinux (5 % of patients) beyond 10 days. This is reflected in section 4.2 of the SPC.

The incidence of SAEs grouped by WHO organ class was low, dominated by bleedings and with no differences between the treatment groups.
The overall rate of permanent study drug treatment discontinuation due to AEs was low and similar in the fondaparinux and enoxaparin treatment groups (1.6 % and 2.3 %, respectively). In MATISSE-PE, it was slightly lower in the fondaparinux than in the UFH treatment group (2.0 % and 3.2%, respectively, excluding deaths).

Bleeding and bleeding-related criteria
The percentages of patients with major bleedings (MB) were similar between fondaparinux and the comparator groups during the study drug treatment period and during the whole study period. Most clinically overt MB were considered major because of a fall in Hb and/or the need for blood transfusion, and there was a slight tendency for more clinically serious bleedings in the fondaparinux group during the study drug treatment period.

Table 8 - Number (%) of patients with MB events during study drug treatment period by adjudication criterion - As treated patients

Adjudication Criteria	**Fondaparinux Sodium**			Dalteparin Sodium	Enoxaparin Sodium	UFH
	5 mg (<50kg)	Proposed Regimen	10 mg (>100 kg)			
	(N=103)	(N=2294)	(N=120)	(N=119)	(N=1101)	(N=1092)
Any major bleeding	3 (2.9%)	28 (1.2%)	1 (0.8%)	0 (0.0%)	13 (1.2%)	12 (1.1%)
Bleeding event contributing to death during treatment period	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Non-fatal clinically overt bleeding within a critical organ	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

- intracranial	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- retroperitoneal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Non-fatal clinically overt bleeding associated with a fall in Hb ≥2 g/dl and/or leading to a transfusion of ≥2 units of PRBC or whole blood	3 (2.9%)	22 (1.0%)	1 (0.8%)	0 (0.0%)	13 (1.2%)	10 (0.9%)

* it should be noted that for these 3 cases of intracranial haemorrhage one occurred following thrombolytic treatment of the PE and concomitant administration of UFH and aspirin, another in a patient who received only one injection of fondaparinux sodium and then received UFH and argatroban before occurrence of bleeding and the last one was multifocal intracranial bleeding in a patient with prostate cancer and high INR values (>7).

Most of the patients who experienced fatal bleeds or bleeds into a critical organ had clear risk factors for increased bleeding (malignancy, cachexia, administration of other antihaemostatic drugs). In patients with major bleeding, "Supratherapeutic" INR (i.e. >3) was more frequently observed at the time of bleeding in the fondaparinux patients (12 out of 28 MBs) than with the comparators (6 out of 27 in the UFH/enoxaparin groups combined).

The percentages of transfused patients during the study drug treatment period were similar across treatment groups (1,5, 2.0, 1.8% in the fondaparinux, enoxaparin, UFH groups, respectively). Significantly more fondaparinux patients tended to experience a Hb decrease of ≥2 g/dl than enoxaparin patients, and a similar trend was observed for the incidence of a Hb <8 g/l. However, UFH-treated patients had the highest incidences in these parameters (Table 9).

Table 9 - Number (%) of patients with a Hb <8 g/dl after start of study treatment and/or a decrease ≥2 g/dl between baseline and the end of study drug treatment - As treated patients

	Fondaparinux Sodium					
Haemoglobin	**5 mg (50-100 kg) (N=103)**	**Proposed Regimen (N=2294)**	**10 mg (50-100 kg) (N=120)**	**Dalteparin Sodium (N=119)**	**Enoxaparin Sodium (N=1101)**	**UFH (N=1092)**
Value <8 g/dl[a,b]	0/100 (0.0%)	23/2160 (1.1%)	0/118 (0.0%)	2/116 (1.7%)	7/1062 (0.7%)	13/1014 (1.3%)
Decrease ≥2 g/dl[c]	2 /86 (2.3%)	109/2107 (5.2%)	1 /94 (1.1%)	1 /87 (1.1%)	34/1053 (3.2%)	67/993 (6.7%)
Both	0 /86 (0.0%)	13/2107 (0.6%)	0 /94 (0.0%)	0 /87 (0.0%)	4/1053 (0.4%)	5/993 (0.5%)

As observed in earlier clinical studies with fondaparinux, there was a tendency to an increased incidence of bleedings with decreasing weight, malignancy, decreasing GFR and increasing age (3.0% 4.5 % and 6.5 % in patients aged <65 years, 65-75 and >75 years, respectively). A relevant warning has been included in the SPC. Similar tendencies were seen in the comparator groups.

Table 10 Number (%) of patients with bleeding events (any bleeding) during the study drug treatment period according to selected baseline covariates - As treated patients

	Fondaparinux Sodium					
Covariate	5 mg (50-100 kg) (N=103) n/N (%)	Proposed regimen (N=2294) n/N (%)	10 mg (50-100 kg) (N=120) n/N (%)	Dalteparin Sodium (N=119) n/N (%)	Enoxaparin Sodium (N=1101) n/N (%)	UFH (N=1092) n/N (%)
Age						
<65 years	3/48 (6.3)	**35/1151 (3.0)**	3/61 (4.9)	1/48 (2.1)	**14/555 (2.5)**	**29/526 (5.5)**
[65-75[years	2/25 (8.0)	**25/560 (4.5)**	0/38 (0.0)	7/36 (19.4)	**10/280 (3.6)**	**17/257 (6.6)**
≥75 years	3/30 (10.0)	**38/583 (6.5)**	3/21 (14.3)	5/35 (14.3)	**22/266 (8.3)**	**23/309 (7.4)**
Weight						
<50 kg	**0/0 (NA)**	**3/53 (5.7)**	**0/0 (NA)**	**1/2 (50.0)**	**0/24 (0.0)**	**2/25 (8.0)**
[50-100] kg	8/100 (8.0)	**87/1986 (4.4)**	6/118 (5.1)	12/115 (10.4)	44/967 (4.6)	56/932 (6.0)
>100 kg	0/3 (0.0)	8/253 (3.2)	0/2 (0.0)	0/2 (0.0)	2/110 (1.8)	11/134 (8.2)
Missing	0/0 (NA)	0/2 (0.0)	0/0 (NA)	0/0 (NA)	0/0 (NA)	0/1 (0.0)
Neoplastic disease						
Active/past	3/19 (15.8)	28/390 **(7.2)**	1/23 (4.3)	3/20 (15.0)	20/186 **(10.8)**	13/176 (7.4)
No known cancer	5/84 (6.0)	70/1904 **(3.7)**	5/97 (5.2)	10/99 (10.1)	26/915 **(2.8)**	56/916 (6.1)
Baseline creatinine clearance						
Missing	1/14 (7.1)	3/56 (5.4)	0/20 (0.0)	0/25 (0.0)	0/11 (0.0)	1/27 (3.7)
<30ml/min	1/4 (25.0)	8/55 (14.5)	0/0 (NA)	0/4 (0.0)	2/18 (11.1)	3/28 (10.7)
[30-50[ml/min	3/20 (15.0)	**21/318 (6.6)**	2/10 (20.0)	4/17 (23.5)	**14/145 (9.7)**	**18/162 (11.1)**
[50-80[ml/min	0/26 (0.0)	**32/733 (4.4)**	1/41 (2.4)	5/32 (15.6)	**17/368 (4.6)**	**11/352 (3.1)**
≥80ml/min	3/39 (7.7)	**34/1132 (3.0)**	3/49 (6.1)	4/41 (9.8)	**13/559 (2.3)**	**36/523 (6.9)**

The group of patients <50 Kg and treated with fondaparinux 5 mg is very small (n=53) and an appropriate warning has been included in the SPC. Patients with a body weight over 100 Kg and treated with fondaparinux 10 mg are better represented (n=253).

Around 23 % of phase III patients had had relatively recent surgery, although it was more than 3 days before study inclusion. Available data on type of surgery and delay between surgery and inclusion, as well as main efficacy and safety outcomes indicate that there are no significant differences between the treatment arms.

Regarding *deaths*, most were related to cancer. The following table shows the Number (%) of patients who died between first injection and Day 97 by adjudication criterion.

Table 11

	Fondaparinux Proposed Regimen (N=2294)	**Enoxaparin Sodium (N=1101)**	**UFH (N=1092)**
Related to efficacy endpoint	19/2294(0.8%)	5/1101(0.5%)	15/1092(1.4%)
Related to bleeding event	8/2294(0.3%)	0/1101(0.0%)	1/1092(0.1%)
Related to other disease	76/2294(3.3%)	28/1101(2.5%)	32/1092(2.9%)
Related to cancer[a]	52/2183(2.4%)	19/1101(1.7%)	22/1092(2.0%)
Related to other disease than cancer[a]	19/2183(0.9%)	9/1101(0.8%)	10/1092(0.9%)
Total[b]	103/2294(4.5%)	33/1101(3.0%)	48/1092(4.4%)

a. Information not available for DRI2440.
b. Total deaths between first injection and Day 97

Deaths in the individual phase III studies are summarised in the following table.

Table 12

	Fondaparinux	Comparator
EFC2441 (DVT)		**Enoxaparin**
Total deaths during initial treatment[a]	5 (0.5%)	0 (0%)
Total deaths between first injection and day 97[b]	41 (3.8%)	33 (3.0%)
63123 (PE)		**UFH**
Total deaths during initial treatment[c]	9 (0.8%)	12 (1.1%)
Total deaths between first injection and day 97[d]	57 (5.4%)	50 (4.6%)

a. Difference 95% CI=[0.1, 0.9%]

b. Difference 95% CI=[-0.8, 2.3%]

c. Difference 95% CI=[-1.1, 0.5%]

d. Difference 95% CI=[-1.0, 2.6%]

There were no significant differences in overall 3-month mortality rates in the individual studies. There was, however, a tendency towards slightly higher mortality in the fondaparinux group, with increased mortality due to bleedings and a trend to increased mortality due to cancer, which has been extensively discussed during the evaluation. These observations are not judged to affect the overall benefit/risk assessment and it would appear difficult to draw any conclusions from these statistically non-significant trends. No such trends were seen in the comparison with UFH (Matisse PE study).

During the study drug treatment period 14 deaths (0.6 %) were observed in the fondaparinux proposed regimen group versus 0/119 (0 %) with dalteparin, 0/1101 (0 %) with enoxaparin and 12/1092 (1.1 %) with UFH. In Matisse DVT, deaths during the study drug administration period were significantly increased in the fondaparinux group: 5/1091 vs 0/1101 [p = 0.03 Fisher's test]. Out of the 5 deaths during fondaparinux treatment, 2 patients had a fatal bleed, 2 deaths were related to cancer, and PE could not be excluded in 1. In Matisse PE alone, there were 6 deaths during the study drug administration period in the fondaparinux group versus 8 in the UFH group. The case reports of the fatal cases in the Matisse DVT studies have been reviewed and no specific safety concerns arise from these analyses.

The results for platelet levels, platelet antibodies and hepatically related laboratory tests were consistent with previous clinical trials and post-marketing experience, and no specific concerns are identified in relation to the clinical laboratory results.

1.4.4.1 Discussion on clinical safety

As observed in earlier clinical studies of fondaparinux there is a tendency for an increased incidence of bleedings with increasing age, decreasing weight, malignancy and decreasing GFR. The clinical evidence and the experience from the pharmacodynamic studies point to a relation between bleeding tendency and fondaparinux exposure. Considering the pharmacokinetic characteristics of fondaparinux and the available safety data, it is considered that the adherence to the dosing recommendations and the warnings and contraindications introduced in the SPC will ensure an adequate exposure in the different patient subgroups.

The observations regarding the observed bleeding incidences have been extensively discussed during the evaluation. It is concluded that the bleeding tendency with fondaparinux is of the same order of magnitude as that observed with the comparators. Unfortunately, plasma samples for measurements of fondaparinux concentration in patients suffering from MB were not collected and there are insufficient

PK data in patients with MB to determine an exposure (ie. Anti-Xa) cut-off value that would predict a higher risk of bleeding.

The incidences of other clinical adverse events did not differ between treatment groups and the pattern for AEs and SAEs was also consistent. Similarly, no specific concerns were identified regarding platelet levels, platelet antibodies and hepatically related laboratory tests. Platelet monitoring is not considered justified in routine clinical practice.

Finally, the safety of fondaparinux at curative doses has not been assessed in patients with very recent surgery (<3 days), and has been adequately reflected with the inclusion of a warning in section 4.4 of the SPC.

Overall Conclusion and Benefit Risk Assessment

Quality
The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Preclinical
No additional toxicological studies with higher doses have been performed. The animal/human exposure ratios obtained for the recommended therapeutic treatment dose of 7.5 mg are sufficient to support the safety of Arixtra for the intended indication. Nonetheless, the toxicological profile of fondaparinux is not fully characterised for this higher dose indication. Hence, the limited exposure in the repeated dose and reproduction toxicity studies has been reflected in section 5.3 of the SPC.

Clinical
The studies provided in support of the indications treatment of DVT and PE are large, well designed and performed and are considered to be informative. Efficacy of fondaparinux with regard to the composite primary endpoint of non-fatal symptomatic VTE or fatal VTE that is non-inferior to enoxaparin in DVT treatment and to UFH in PE treatment has been demonstrated.

Adequate safety has been demonstrated in patients with normal renal function and mild to moderate renal impairment with the weight based dosage regimen used in clinical trials. In patients with severe renal impairment (CLcr <30 ml/min), an increased rate of "major bleeding", an increased rate of "any bleeding", an increased frequency of transfusion, and an increased frequency of Hb decrease ≥2 g/dl compared to both enoxaparin and UFH was observed. Fondaparinux should therefore be contra-indicated in patients with severe renal failure. There is no actual clinical experience in patients weighing >100 kg with moderate renal impairment. Based on pharmacokinetic modelling results, a reduction of the daily dose to 7.5 mg daily may be considered after an initial 10 mg dose on Day 1 (if renal status is not available at the time of starting treatment) in this patient group.

The once daily sc injection of fondaparinux will be easier to apply than the aPTT-adjusted IV infusion of UFH and does not require coagulation monitoring in clinical routine. The synthetic nature of fondaparinux prevents any potential infectious contamination compared with the animal sourced therapies.