ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 1.5 mg/0.3 ml solution for injection, pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.3 ml) contains 1.5 mg of fondaparinux sodium.

Excipient(s): Contains less than 1 mmol of sodium (23 mg) per dose, and therefore is essentially sodium free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
The solution is a clear and colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery (see section 5.1).

Prevention of Venous Thromboembolic Events (VTE) in medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.

4.2 Posology and method of administration

Patients undergoing major orthopaedic or abdominal surgery
The recommended dose of fondaparinux is 2.5 mg once daily administered post-operatively by subcutaneous injection.

The initial dose should be given 6 hours following surgical closure provided that haemostasis has been established.

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. Experience shows that in patients undergoing hip fracture surgery, the risk of VTE continues beyond 9 days after surgery. In these patients the use of prolonged prophylaxis with fondaparinux should be considered for up to an additional 24 days (see section 5.1).

Medical patients who are at high risk for thromboembolic complications based on an individual risk assessment
The recommended dose of fondaparinux is 2.5 mg once daily administered by subcutaneous injection.
A treatment duration of 6-14 days has been clinically studied in medical patients (see section 5.1).

Special populations
In patients undergoing surgery, timing of the first fondaparinux injection requires strict adherence in patients ≥75 years, and/or with body weight <50 kg and/or with renal impairment with creatinine clearance ranging between 20 to 50 ml/min.

The first fondaparinux administration should be given not earlier than 6 hours following surgical closure. The injection should not be given unless haemostasis has been established (see section 4.4).

Renal impairment - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min).

Hepatic impairment - No dosing adjustment is necessary. In patients with severe hepatic impairment, fondaparinux should be used with care (see section 4.4).

Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy.

Method of administration
Fondaparinux is administered by deep subcutaneous injection while the patient is lying down. Sites of administration should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger; the skin fold should be held throughout the injection.

For additional instructions for use and handling and disposal see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients
- active clinically significant bleeding
- acute bacterial endocarditis
- severe renal impairment defined by creatinine clearance < 20 ml/min.

4.4 Special warnings and precautions for use

Fondaparinux is intended for subcutaneous use only. Do not administer intramuscularly.

Haemorrhage
Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm^3), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.

Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). When required, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.

Spinal / Epidural anaesthesia
In patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in long-term or permanent paralysis cannot be excluded with the concurrent use of fondaparinux and

spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting haemostasis.

Elderly patients
The elderly population is at increased risk of bleeding. As renal function is generally decreasing with age, elderly patients may show reduced elimination and increased exposure of fondaparinux (see section 5.2). Fondaparinux should be used with caution in elderly patients (see section 4.2).

Low body weight
Patients with body weight <50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients (see section 4.2).

Renal impairment
Fondaparinux is known to be mainly excreted by the kidney. Patients with creatinine clearance <50 ml/min are at increased risk of bleeding and VTE and should be treated with caution (see sections 4.2, 4.3 and 5.2). There are limited clinical data available from patients with creatinine clearance less than 30 ml/min.

Severe hepatic impairment
Dosing adjustment of fondaparinux is not necessary. However, the use of fondaparinux should be considered with caution because of an increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic impairment (see section 4.2).

Patients with Heparin Induced Thrombocytopenia
Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II.

4.5 Interaction with other medicinal products and other forms of interaction

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (see section 4.4).

Oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics of fondaparinux. The fondaparinux dose (10 mg) in the interaction studies was higher than the dose recommended for the present indications. Fondaparinux neither influenced the INR activity of warfarin, nor the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics of digoxin at steady state.

Follow-up therapy with another anticoagulant medicinal product
If follow-up treatment is to be initiated with heparin or LMWH, the first injection should, as a general rule, be given one day after the last fondaparinux 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of fondaparinux in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development because of limited exposure. Fondaparinux should not be prescribed to pregnant women unless clearly necessary.

Fondaparinux is excreted in rat milk but it is not known whether fondaparinux is excreted in human milk. Breast-feeding is not recommended during treatment with fondaparinux. Oral absorption by the child is however unlikely.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

The safety of fondaparinux 2.5 mg has been evaluated in 3,595 patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days, in 327 patients undergoing hip fracture surgery treated for 3 weeks following an initial prophylaxis of 1 week, 1407 patients undergoing abdominal surgery treated up to 9 days, and in 425 medical patients who are at risk for thromboembolic complications treated up to 14 days.

The adverse reactions reported by the investigator as at least possibly related to fondaparinux are presented within each frequency grouping (very common ≥ 1/10; common: ≥1/100 to < 1/10; uncommon: ≥ 1/1,000 to ≤ 1/100; rare: ≥ 1/10,000 to ≤1/1,000; very rare ≤1/10,000) and system organ class by decreasing order of seriousness; these adverse reactions should be interpreted within the surgical and medical context.

System organ class **MedDRA**	**Undesirable effects in patients undergoing major orthopaedic surgery of lower limbs and/or abdominal surgery**	**Undesirable effects in medical patients**
Infections and infestations	*Rare:* post-operative wound infection	
Blood and lymphatic system disorders	*Common:* post-operative haemorrhage, anaemia *Uncommon:* bleeding (epistaxis, gastrointestinal, haemoptysis, haematuria, haematoma) thrombocytopenia, purpura, thrombocythaemia, platelet abnormal, coagulation disorder	*Common:* bleeding (haematoma, haematuria, haemoptysis, gingival bleeding) *Uncommon:* anaemia
Immune system disorders	*Rare:* allergic reaction	
Metabolism and nutrition disorders	*Rare:* hypokalaemia	
Nervous system disorders	*Rare:* anxiety, somnolence, vertigo, dizziness, headache, confusion	
Vascular disorders	*Rare:* hypotension	
Respiratory, thoracic and mediastinal disorders	*Rare:* dyspnoea, coughing	*Uncommon:* dyspnoea

Gastrointestinal disorders	*Uncommon:* nausea, vomiting *Rare:* abdominal pain, dyspepsia, gastritis, constipation, diarrhoea	
Hepatobiliary disorders	*Uncommon:* hepatic enzymes increased, hepatic function abnormal *Rare:* bilirubinaemia	
Skin and subcutaneous tissue disorders	*Uncommon:* rash, pruritus	*Uncommon*: rash, pruritus
General disorders and administration site conditions	*Uncommon:* oedema, oedema peripheral, fever, wound secretion *Rare:* chest pain, fatigue, hot flushes, leg pain, oedema genital, flushing, syncope	*Uncommon*: chest pain

In other studies or in post-marketing experience, rare cases of intracranial / intracerebral and retroperitoneal bleedings have been reported.

4.9 Overdose

Fondaparinux doses above the recommended regimen may lead to an increased risk of bleeding. There is no known antidote to fondaparinux.

Overdose associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents.
ATC code: B01AX05

Pharmacodynamic effects

Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of Factor Xa. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated Factor II) and has no effects on platelets.

At the 2.5 mg dose, fondaparinux 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 nor bleeding time or fibrinolytic activity.

Fondaparinux does not cross-react with sera from patients with heparin-induced thrombocytopaenia.

Clinical studies

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days
The fondaparinux clinical program was designed to demonstrate the efficacy of fondaparinux for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery. Over 8,000 patients (hip fracture – 1,711, hip replacement – 5,829, major knee surgery – 1,367) were studied in controlled Phase II and III clinical studies. Fondaparinux 2.5 mg once daily started 6-8 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours before surgery, or 30 mg twice daily started 12-24 hours after surgery.

In a pooled analysis of these studies, the recommended dose regimen of fondaparinux versus enoxaparin was associated with a significant decrease (54% - 95% CI, 44 %; 63%) in the rate of VTE evaluated up to day 11 after surgery, irrespective of the type of surgery performed. The majority of endpoint events were diagnosed by a prescheduled venography and consisted mainly of distal DVT, but the incidence of proximal DVT was also significantly reduced. The incidence of symptomatic VTE, including PE was not significantly different between treatment groups.

In studies versus enoxaparin 40 mg once daily started 12 hours before surgery, major bleeding was observed in 2.8% of fondaparinux patients treated with the recommended dose, compared to 2.6% with enoxaparin.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing hip fracture surgery treated for up to 24 days following an initial prophylaxis of 1 week
In a randomised double-blind clinical trial, 737 patients were treated with fondaparinux 2.5 mg once daily for 7 +/- 1 days following hip fracture surgery. At the end of this period, 656 patients were randomised to receive fondaparinux 2.5 mg once daily or placebo for an additional 21 +/- 2 days. Fondaparinux provided a significant reduction in the overall rate of VTE compared with placebo [3 patients (1.4%) vs 77 patients (35%), respectively]. The majority (70/80) of the recorded VTE events were venographically detected non-symptomatic cases of DVT. Fondaparinux also provided a significant reduction in the rate of symptomatic VTE (DVT, and / or PE) [1 (0.3%) vs 9 (2.7%) patients, respectively] including two fatal PE reported in the placebo group. Major bleedings, all at surgical site and none fatal, were observed in 8 patients (2.4%) treated with fondaparinux 2.5 mg compared to 2 (0.6%) with placebo.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery
In a double-blind clinical study, 2927 patients were randomized to receive fondaparinux 2.5mg once daily or dalteparin 5000 IU once daily, with one 2500 IU preoperative injection and a first 2500 IU post-operative injection, for 7±2 days. The main sites of surgery were colonic/rectal, gastric, hepatic, cholecystectomy or other biliary. Sixty-nine percent of the patients underwent surgery for cancer. Patients under-going urological (other than kidney) or gynaecological surgery, laparoscopic surgery or vascular surgery were not included in the study.

In this study, the incidence of total VTE was 4.6% (47/1027) with fondaparinux, versus 6.1%: (62/1021) with dalteparin: odds ratio reduction [95%CI] = -25.8% [-49.7%, 9.5%]. The difference in total VTE rates between the treatment groups, which was not statistically significant, was mainly due to a reduction of asymptomatic distal DVT. The incidence of symptomatic DVT was similar between treatment groups: 6 patients (0.4%) in the fondaparinux group vs 5 patients (0.3%) in the dalteparin group. In the large subgroup of patients undergoing cancer surgery (69% of the patient population), the VTE rate was 4.7% in the fondaparinux group, versus 7.7% in the dalteparin group.

Major bleeding was observed in 3.4% of the patients in the fondaparinux group and in 2.4% of the dalteparin group.

Prevention of Venous Thromboembolic Events (VTE) in medical patients who are at high risk for thromboembolic complications due to restricted mobility during acute illness
In a randomised double-blind clinical trial, 839 patients were treated with fondaparinux 2.5 mg once daily or placebo for 6 to 14 days. This study included acutely ill medical patients, aged ≥ 60 years, expected to require bed rest for at least four days, and hospitalized for congestive heart failure NYHA class III/IV and/or acute respiratory illness and/or acute infectious or inflammatory disease. Fondaparinux significantly reduced the overall rate of VTE compared to placebo [18 patients (5.6%) vs 34 patients (10.5%), respectively]. The majority of events were asymptomatic distal DVT. Fondaparinux also significantly reduced the rate of adjudicated fatal PE [0 patients (0.0%) vs 5 patients (1.2%), respectively]. Major bleedings were observed in 1 patient (0.2%) of each group.

5.2 Pharmacokinetic properties

Absorption
After subcutaneous dosing, fondaparinux is completely and rapidly absorbed (absolute bioavailability 100%). Following a single subcutaneous injection of fondaparinux 2.5 mg to young healthy subjects, peak plasma concentration (mean C_{max} = 0.34 mg/l) is obtained 2 hours post-dosing. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.

In elderly healthy subjects, pharmacokinetics of fondaparinux are linear in the range of 2 to 8 mg by subcutaneous route. Following once daily dosing, steady state of plasma levels is obtained after 3 to 4 days with a 1.3-fold increase in C_{max} and AUC.

Mean (CV%) steady state pharmacokinetic parameters estimates of fondaparinux in patients undergoing hip replacement surgery receiving fondaparinux 2.5 mg once daily are: C_{max} (mg/l) - 0.39 (31%), T_{max} (h) - 2.8 (18%) and C_{min} (mg/l) -0.14 (56%). In hip fracture patients, associated with their increased age, fondaparinux steady state plasma concentrations are: C_{max} (mg/l) - 0.50 (32%), C_{min} (mg/l) - 0.19 (58%).

Distribution
The distribution volume of fondaparinux is limited (7-11 litres). *In vitro*, fondaparinux is highly and specifically bound to antithrombin protein with a dose-dependant plasma concentration binding (98.6% to 97.0% in the concentration range from 0.5 to 2 mg/l). Fondaparinux does not bind significantly to other plasma proteins, including platelet factor 4 (PF4).

Since fondaparinux does not bind significantly to plasma proteins other than ATIII, no interaction with other medicinal products by protein binding displacement are expected.

Metabolism
Although not fully evaluated, there is no evidence of fondaparinux metabolism and in particular no evidence for the formation of active metabolites.

Fondaparinux does not inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*. Thus, fondaparinux is not expected to interact with other medicinal products *in vivo* by inhibition of CYP-mediated metabolism.

Excretion/Elimination
The elimination half-life ($t_{½}$) is about 17 hours in healthy young subjects and about 21 hours in healthy elderly subjects. Fondaparinux is excreted to 64 – 77 % by the kidney as unchanged compound.

<u>*Special populations*</u>

Paediatric patients - Fondaparinux has not been investigated in this population.

Elderly patients - Renal function may decrease with age and thus, the elimination capacity for fondaparinux may be reduced in elderly. In patients >75 years undergoing orthopaedic surgery, the estimated plasma clearance was 1.2 to 1.4 times lower than in patients <65 years.

Renal impairment - Compared with patients with normal renal function (creatinine clearance > 80 ml/min), plasma clearance is 1.2 to 1.4 times lower in patients with mild renal impairment (creatinine clearance 50 to 80 ml/min) and on average 2 times lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min). In severe renal impairment (creatinine clearance < 30 ml/min), plasma clearance is approximately 5 times lower than in normal renal function. Associated terminal half-life values were 29 h in moderate and 72 h in patients with severe renal impairment.

Gender - No gender differences were observed after adjustment for body weight.

Race - Pharmacokinetic differences due to race have not been studied prospectively. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to Caucasian healthy subjects. Similarly, no plasma clearance differences were observed between black and Caucasian patients undergoing orthopaedic surgery.

Body weight - Plasma clearance of fondaparinux increases with body weight (9% increase per 10 kg).

Hepatic impairment - Fondaparinux pharmacokinetics has not been evaluated in hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type I glass barrel (1 ml) affixed with a 27 gauge x 12.7 mm needle and stoppered with a bromobutyl or chlorobutyl elastomer plunger stopper.

Quixidar is available in pack sizes of 2, 7, 10 and 20 pre-filled syringes with a yellow automatic safety system. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The subcutaneous injection is administered in the same way as with a classical syringe.

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration.

Instruction for self-administration is mentioned in the Package Leaflet.

The needle protection system of the Quixidar pre-filled syringe has been designed with an automatic safety system to protect from needle stick injuries following injection.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/207/005-008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2002
Date of latest renewal: 21 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 2.5 mg/0.5 ml solution for injection, pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.5 ml) contains 2.5 mg of fondaparinux sodium.

Excipient(s): Contains less than 1 mmol of sodium (23 mg) per dose, and therefore is essentially sodium free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
The solution is a clear and colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery (see section 5.1).

Prevention of Venous Thromboembolic Events (VTE) in medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.

Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 mins) invasive management (PCI) is not indicated (see sections 4.4 and 5.1).

Treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.

4.2 Posology and method of administration

Patients undergoing major orthopaedic or abdominal surgery
The recommended dose of fondaparinux is 2.5 mg once daily administered post-operatively by subcutaneous injection.

The initial dose should be given 6 hours following surgical closure provided that haemostasis has been established.

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. Experience shows that in patients undergoing hip fracture surgery, the risk of VTE continues beyond 9 days after surgery. In these patients the use of prolonged prophylaxis with fondaparinux should be considered for up to an additional 24 days (see section 5.1).

Medical patients who are at high risk for thromboembolic complications based on an individual risk assessment
The recommended dose of fondaparinux is 2.5 mg once daily administered by subcutaneous injection. A treatment duration of 6-14 days has been clinically studied in medical patients (see section 5.1).

Treatment of unstable angina/non- ST segment elevation myocardial infarction (UA/NSTEMI)
The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

If a patient is to undergo percutaneous coronary intervention (PCI), unfractionated heparin (UFH) as per local practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux (see section 4.4). The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the pivotal UA/NSTEMI clinical trial, treatment with fondaparinux was restarted no earlier than 2 hours after sheath removal.

Treatment of ST segment elevation myocardial infarction (STEMI)
The recommended dose of fondaparinux is 2.5 mg once daily. The first dose of fondaparinux is administered intravenously and subsequent doses are administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

If a patient is to undergo non-primary PCI, unfractionated heparin (UFH) as per local practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux (see section 4.4). The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the pivotal STEMI clinical trial, treatment with fondaparinux was restarted no earlier than 3 hours after sheath removal.

In STEMI or UA/NSTEMI patients who are to undergo coronary artery bypass graft (CABG) surgery, fondaparinux where possible, should not be given during the 24 hours before surgery and may be restarted 48 hours post-operatively**.**

<u>*Special populations*</u>

Prevention of VTE following Surgery
In patients undergoing surgery, timing of the first fondaparinux injection requires strict adherence in patients ≥75 years, and/or with body weight <50 kg and/or with renal impairment with creatinine clearance ranging between 20 to 50 ml/min.

The first fondaparinux administration should be given not earlier than 6 hours following surgical closure. The injection should not be given unless haemostasis has been established (see section 4.4).

Renal impairment
- *Prophylaxis of VTE* - Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min).

- *Treatment of UA/NSTEMI and* STEMI - fondaparinux should not be used in patients with creatinine clearance < 20 ml/min (see section 4.3). No dosage reduction is required for patients with creatinine clearance > 20 ml/min.

Hepatic impairment - No dosing adjustment is necessary. In patients with severe hepatic impairment, fondaparinux should be used with care (see section 4.4).

Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy.

Method of administration

- *Subcutaneous administration*
  Fondaparinux is administered by deep subcutaneous injection while the patient is lying down. Sites of administration should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger; the skin fold should be held throughout the injection.

- *Intravenous administration (first dose in patients with STEMI only)*
  Intravenous administration should be through an existing intravenous line either directly or using a small volume (25 or 50ml) 0.9% saline minibag**.** To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The intravenous tubing should be well flushed with saline after injection to ensure that all of the medicinal product is administered. If administered via a minibag, the infusion should be given over 1 to 2 minutes.

For additional instructions for use and handling and disposal see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients
- active clinically significant bleeding
- acute bacterial endocarditis
- severe renal impairment defined by creatinine clearance < 20 ml/min.

4.4 Special warnings and precautions for use

Fondaparinux must not be administered intramuscularly.

Haemorrhage
Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm^3), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.

For prevention of VTE, agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). When required, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.

For treatment of UA/NSTEMI and STEMI, fondaparinux should be used with caution in patients who are being treated concomitantly with other agents that increase the risk of haemorrhage (such as GPIIb/IIIa inhibitors or thrombolytics).

PCI and risk of guiding catheter thrombus
In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended. Similarly, in UA/NSTEMI patients with life threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during PCI is not recommended. These are

patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life-threatening arrhythmias or haemodynamic instability.

In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended, therefore UFH should be used according to local practice (see section 4.2).

There are limited data on the use of UFH during non-primary PCI in patients treated with fondaparinux (see section 5.1). In those patients who underwent non-primary PCI 6-24 hours after the last dose of fondaparinux, the median dose of UFH was 8000 IU and the incidence of major bleeding was 2% (2/98). In those patients who underwent non-primary PCI <6 hours after the last dose of fondaparinux, the median dose of UFH was 5000 IU and the incidence of major bleeding was 4.1% (2/49).

Clinical trials have shown a low but increased risk of guiding catheter thrombus in patients treated with fondaparinux for anticoagulation during PCI compared to control. Incidences in non-primary PCI in UA/NSTEMI were 1.0% vs 0.3% (fondaparinux vs. enoxaparin) and in primary PCI in STEMI were 1.2% vs 0% (fondaparinux vs. control).

Spinal / Epidural anaesthesia
In patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in long-term or permanent paralysis cannot be excluded with the concurrent use of fondaparinux and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting haemostasis.

Elderly patients
The elderly population is at increased risk of bleeding. As renal function is generally decreasing with age, elderly patients may show reduced elimination and increased exposure of fondaparinux (see section 5.2). Fondaparinux should be used with caution in elderly patients (see section 4.2).

Low body weight
Patients with body weight <50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients (see section 4.2).

Renal impairment
Fondaparinux is known to be mainly excreted by the kidney.

- *Prophylaxis of VTE* - Patients with creatinine clearance <50 ml/min are at increased risk of bleeding and VTE and should be treated with caution (see sections 4.2, 4.3 and 5.2). There are limited clinical data available from patients with creatinine clearance less than 30 ml/min.

- *Treatment of UA/NSTEMI and* STEMI - For the treatment of UA/NSTEMI and STEMI, there are limited clinical data available on the use of fondaparinux 2.5mg once daily in patients with creatinine clearance between 20 and 30 ml/min. Therefore the physician should determine if the benefit of treatment outweighs the risk (see sections 4.2 and 4.3).

Severe hepatic impairment
Dosing adjustment of fondaparinux is not necessary. However, the use of fondaparinux should be considered with caution because of an increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic impairment (see section 4.2).

Patients with Heparin Induced Thrombocytopenia
Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II.

4.5 Interaction with other medicinal products and other forms of interaction

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (see section 4.4).

Oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics of fondaparinux. The fondaparinux dose (10 mg) in the interaction studies was higher than the dose recommended for the present indications. Fondaparinux neither influenced the INR activity of warfarin, nor the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics of digoxin at steady state.

Follow-up therapy with another anticoagulant medicinal product
If follow-up treatment is to be initiated with heparin or LMWH, the first injection should, as a general rule, be given one day after the last fondaparinux 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.

4.6 Pregnancy and lactation

There are no adequate data from the use of fondaparinux in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development because of limited exposure. Fondaparinux should not be prescribed to pregnant women unless clearly necessary.

Fondaparinux is excreted in rat milk but it is not known whether fondaparinux is excreted in human milk. Breast-feeding is not recommended during treatment with fondaparinux. Oral absorption by the child is however unlikely.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

The safety of fondaparinux 2.5 mg has been evaluated in:
- 3,595 patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days
- 327 patients undergoing hip fracture surgery treated for 3 weeks following an initial prophylaxis of 1 week
- 1407 patients undergoing abdominal surgery treated up to 9 days
- 425 medical patients who are at risk for thromboembolic complications treated up to 14 days
- 10,057 patients undergoing treatment of UA or NSTEMI ACS
- 6,036 patients undergoing treatment of STEMI ACS.

For the prevention of VTE, the adverse reactions reported by the investigator as at least possibly related to fondaparinux are presented within each frequency grouping (very common ≥ 1/10; common: ≥1/100 to < 1/10; uncommon: ≥ 1/1,000 to ≤ 1/100; rare: ≥ 1/10,000 to ≤1/1,000; very rare ≤1/10,000) and system organ class by decreasing order of seriousness; these adverse reactions should be interpreted within the surgical and medical context.

System organ class **MedDRA**	**Undesirable effects in patients undergoing major orthopaedic surgery of lower limbs and/or abdominal surgery**	**Undesirable effects in medical patients**
Infections and infestations	*Rare:* post-operative wound infection	
Blood and lymphatic system disorders	*Common:* post-operative haemorrhage, anaemia *Uncommon:* bleeding (epistaxis, gastrointestinal, haemoptysis, haematuria, haematoma) thrombocytopenia, purpura, thrombocythaemia, platelet abnormal, coagulation disorder	*Common:* bleeding (haematoma, haematuria, haemoptysis, gingival bleeding) *Uncommon:* anaemia
Immune system disorders	*Rare:* allergic reaction	
Metabolism and nutrition disorders	*Rare:* hypokalaemia	
Nervous system disorders	*Rare:* anxiety, somnolence, vertigo, dizziness, headache, confusion	
Vascular disorders	*Rare:* hypotension	
Respiratory, thoracic and mediastinal disorders	*Rare:* dyspnoea, coughing	*Uncommon:* dyspnoea
Gastrointestinal disorders	*Uncommon:* nausea, vomiting *Rare:* abdominal pain, dyspepsia, gastritis, constipation, diarrhoea	
Hepatobiliary disorders	*Uncommon:* hepatic enzymes increased, hepatic function abnormal *Rare:* bilirubinaemia	

Skin and subcutaneous tissue disorders	*Uncommon:* rash, pruritus	*Uncommon*: rash, pruritus
General disorders and administration site conditions	*Uncommon:* oedema, oedema peripheral, fever, wound secretion *Rare:* chest pain, fatigue, hot flushes, leg pain, oedema genital, flushing, syncope	*Uncommon*: chest pain

In other studies or in post-marketing experience, rare cases of intracranial / intracerebral and retroperitoneal bleedings have been reported.

The adverse event profile reported in the ACS program is consistent with the adverse drug reactions identified for VTE prophylaxis.

Bleeding was a commonly reported event in patients with UA/NSTEMI and STEMI. The incidence of adjudicated major bleeding was 2.1% (fondaparinux) vs. 4.1% (enoxaparin) up to and including Day 9 in the Phase III UA/NSTEMI study, and the incidence of adjudicated severe hemorrhage by modified TIMI criteria was 1.1% (fondaparinux) vs. 1.4% (control [UFH/placebo]) up to and including Day 9 in the Phase III STEMI study.

In the Phase III UA/NSTEMI study, the most commonly reported non-bleeding adverse events (reported in at least 1% of subjects on fondaparinux) were headache, chest pain and atrial fibrillation.

In the Phase III study in STEMI patients, the most commonly reported non-bleeding adverse events (reported in at least 1% of subjects on fondaparinux) were atrial fibrillation, pyrexia, chest pain, headache, ventricular tachycardia, vomiting, and hypotension.

4.9 Overdose

Fondaparinux doses above the recommended regimen may lead to an increased risk of bleeding. There is no known antidote to fondaparinux.

Overdose associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents.
ATC code: B01AX05

Pharmacodynamic effects

Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of Factor Xa. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated Factor II) and has no effects on platelets.

At the 2.5 mg dose, fondaparinux 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 nor bleeding time or fibrinolytic activity.

Fondaparinux does not cross-react with sera from patients with heparin-induced thrombocytopaenia.

Clinical studies

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days
The fondaparinux clinical program was designed to demonstrate the efficacy of fondaparinux for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery. Over 8,000 patients (hip fracture – 1,711, hip replacement – 5,829, major knee surgery – 1,367) were studied in controlled Phase II and III clinical studies. Fondaparinux 2.5 mg once daily started 6-8 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours before surgery, or 30 mg twice daily started 12-24 hours after surgery.

In a pooled analysis of these studies, the recommended dose regimen of fondaparinux versus enoxaparin was associated with a significant decrease (54% - 95% CI, 44 %; 63%) in the rate of VTE evaluated up to day 11 after surgery, irrespective of the type of surgery performed. The majority of endpoint events were diagnosed by a prescheduled venography and consisted mainly of distal DVT, but the incidence of proximal DVT was also significantly reduced. The incidence of symptomatic VTE, including PE was not significantly different between treatment groups.

In studies versus enoxaparin 40 mg once daily started 12 hours before surgery, major bleeding was observed in 2.8% of fondaparinux patients treated with the recommended dose, compared to 2.6% with enoxaparin.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing hip fracture surgery treated for up to 24 days following an initial prophylaxis of 1 week
In a randomised double-blind clinical trial, 737 patients were treated with fondaparinux 2.5 mg once daily for 7 +/- 1 days following hip fracture surgery. At the end of this period, 656 patients were randomised to receive fondaparinux 2.5 mg once daily or placebo for an additional 21 +/- 2 days. Fondaparinux provided a significant reduction in the overall rate of VTE compared with placebo [3 patients (1.4%) vs 77 patients (35%), respectively]. The majority (70/80) of the recorded VTE events were venographically detected non-symptomatic cases of DVT. Fondaparinux also provided a significant reduction in the rate of symptomatic VTE (DVT, and / or PE) [1 (0.3%) vs 9 (2.7%) patients, respectively] including two fatal PE reported in the placebo group. Major bleedings, all at surgical site and none fatal, were observed in 8 patients (2.4%) treated with fondaparinux 2.5 mg compared to 2 (0.6%) with placebo.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery
In a double-blind clinical study, 2927 patients were randomized to receive fondaparinux 2.5mg once daily or dalteparin 5000 IU once daily, with one 2500 IU preoperative injection and a first 2500 IU post-operative injection, for 7±2 days. The main sites of surgery were colonic/rectal, gastric, hepatic, cholecystectomy or other biliary. Sixty-nine percent of the patients underwent surgery for cancer. Patients under-going urological (other than kidney) or gynaecological surgery, laparoscopic surgery or vascular surgery were not included in the study.

In this study, the incidence of total VTE was 4.6% (47/1027) with fondaparinux, versus 6.1%: (62/1021) with dalteparin: odds ratio reduction [95%CI] = -25.8% [-49.7%, 9.5%]. The difference in total VTE rates between the treatment groups, which was not statistically significant, was mainly due to a reduction of asymptomatic distal DVT. The incidence of symptomatic DVT was similar between

treatment groups: 6 patients (0.4%) in the fondaparinux group vs 5 patients (0.3%) in the dalteparin group. In the large subgroup of patients undergoing cancer surgery (69% of the patient population), the VTE rate was 4.7% in the fondaparinux group, versus 7.7% in the dalteparin group.

Major bleeding was observed in 3.4% of the patients in the fondaparinux group and in 2.4% of the dalteparin group.

Prevention of Venous Thromboembolic Events (VTE) in medical patients who are at high risk for thromboembolic complications due to restricted mobility during acute illness
In a randomised double-blind clinical trial, 839 patients were treated with fondaparinux 2.5 mg once daily or placebo for 6 to 14 days. This study included acutely ill medical patients, aged ≥ 60 years, expected to require bed rest for at least four days, and hospitalized for congestive heart failure NYHA class III/IV and/or acute respiratory illness and/or acute infectious or inflammatory disease. Fondaparinux significantly reduced the overall rate of VTE compared to placebo [18 patients (5.6%) vs 34 patients (10.5%), respectively]. The majority of events were asymptomatic distal DVT. Fondaparinux also significantly reduced the rate of adjudicated fatal PE [0 patients (0.0%) vs 5 patients (1.2%), respectively]. Major bleedings were observed in 1 patient (0.2%) of each group.

Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)
OASIS 5 was a double-blind, randomised, non-inferiority study with fondaparinux 2.5 mg subcutaneously once daily versus enoxaparin 1 mg/kg subcutaneously twice daily in approximately 20,000 patients with UA/NSTEMI. All patients received standard medical treatment for UA/NSTEMI, with 34% of patients undergoing PCI and 9% undergoing CABG. The mean treatment duration was 5.5 days in the fondaparinux group and 5.2 days in the enoxaparin group. If PCI was performed, patients received either intravenous fondaparinux (fondaparinux patients) or weight adjusted intravenous UFH (enoxaparin patients) as adjunctive therapy, dependent on the timing of the last subcutaneous dose and planned use of GP IIb/IIIa inhibitor. The mean age of the patients was 67 years, and approximately 60% were at least 65 years old. Approximately 40% and 17% of patients had mild (creatinine clearance ≥50 to <80 ml/min) or moderate (creatinine clearance ≥30 to <50 ml/min) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death, myocardial infarction (MI) and refractory ischaemia (RI) within 9 days of randomisation. Of the patients in the fondaparinux group, 5.8% experienced an event by Day 9 compared to 5.7% for enoxaparin-treated patients (hazard ratio 1.01, 95% CI, 0.90, 1.13, one-sided non-inferiority p value = 0.003).

By Day 30, the incidence of all cause mortality was significantly reduced from 3.5% on enoxaparin to 2.9% on fondaparinux (hazard ratio 0.83, 95% CI, 0.71;0.97, p = 0.02). The effects on the incidence of MI and RI were not statistically different between the fondaparinux and enoxaparin treatment groups.

At Day 9 the incidence of major bleeding on fondaparinux and enoxaparin was 2.1% and 4.1%, respectively (hazard ratio 0.52, 95% CI, 0.44;0.61, p < 0.001).

The efficacy findings and results on major bleeding were consistent across prespecified subgroups such as elderly, renally impaired patients, type of concomitant platelet aggregation inhibitors (aspirin, thienopyridines or GP IIb/IIIa inhibitors).

In the subgroup of patients treated with fondaparinux or enoxaparin who underwent PCI, 8.8% and 8.2% of patients respectively, experience death/MI/RI within 9 days of randomisation (hazard ratio 1.08, 95% CI, 0.92;1.27). In this subgroup, the incidence of major bleeding on fondaparinux and enoxaparin at Day 9 was 2.2% and 5.0% respectively (hazard ratio 0.43, 95% CI, 0.33;0.57).

Treatment of ST segment elevation myocardial infarction (STEMI)
OASIS 6 was a double blind, randomised study assessing the safety and efficacy of fondaparinux 2.5 mg once daily, versus usual care (placebo (47%) or UFH (53%)) in approximately 12000 patients with STEMI. All patients received standard treatments for STEMI, including primary PCI (31%), thrombolytics (45%) or no reperfusion (24%). Of the patients treated with a thrombolytic, 84% were

treated with a non-fibrin specific agent (primarily streptokinase). The mean treatment duration was 6.2 days on fondaparinux. The mean age of the patients was 61 years, and approximately 40% were at least 65 years old. Approximately 40% and 14% of patients had mild (creatinine clearance ≥50 to <80 ml/min) or moderate (creatinine clearance ≥30 to <50 ml/min) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death and recurrent MI (re-MI) within 30 days of randomisation. The incidence of death/re-MI at Day 30 was significantly reduced from 11.1% for the control group to 9.7% for the fondaparinux group (hazard ratio 0.86, 95% CI, 0.77, 0.96, p = 0.008). In the predefined stratum comparing fondaparinux to placebo (i.e patients treated with non-fibrin specific lytics (77.3%), no reperfusion (22%), fibrin-specific lytics (0.3%), primary PCI (0.4%)), the incidence of death/re-MI at Day 30 was significantly reduced from 14.0% on placebo to 11.3% (hazard ratio 0.80, 95% CI, 0.69, 0.93, p = 0.003). In the predefined stratum comparing fondaparinux to UFH (patients treated with primary PCI (58.5%), fibrin-specific lytics (13%), non-fibrin-specific lytics (2.6%) and no reperfusion (25.9%)), the effects of fondaparinux and UFH on the incidence of death/re-MI at Day 30 were not statistically different: respectively, 8.3% vs 8.7% (hazard ratio 0.94, 95% CI, 0.79, 1.11 p = 0.460). However, in this stratum, in the subgroup of indicated population undergoing thrombolysis or no reperfusion (i.e patients not undergoing primary PCI), the incidence of death/re-MI at Day 30 was significantly reduced from 14.3% on UFH to 11.5% with fondaparinux (hazard ratio 0.79, 95% CI, 0.64, 0.98, p = 0.03).

The incidence of all cause mortality at Day 30 was also significantly reduced from 8.9% for the control group to 7.8% in the fondaparinux group (hazard ratio 0.87, 95% CI, 0.77;0.98, p = 0.02). The difference in mortality was statistically significant in stratum 1 (placebo comparator) but not in stratum 2 (UFH comparator). The mortality benefit shown in the fondaparinux group was maintained until the end of follow-up at Day 180.

In patients who were revascularised with a thrombolytic, fondaparinux significantly reduced the incidence of death/re-MI at Day 30 from 13.6% for the control group to 10.9% (hazard ratio 0.79, 95%CI, 0.68;0.93, p = 0.003). Among patients initially not reperfused, the incidence of death/re-MI at Day 30 was significantly reduced from 15% for the control group to 12.1% for the fondaparinux group (hazard ratio 0.79, 95% CI, 0.65;0.97, p = 0.023). In patients treated with primary PCI, the incidence of death/re-MI at Day 30 was not statistically different between the two groups [6.0% in fondaparinux group vs 4.8% in the control group; hazard ratio 1.26, 95% CI, 0.96, 1.66)].

By Day 9, 1.1% of patients treated with fondaparinux and 1.4% of control patients experienced a severe haemorrhage. In patients given a thrombolytic, severe haemorrhage occurred in 1.3% of the fondaparinux patients and in 2.0% of controls. In patients initially not reperfused, the incidence of severe haemorrhage was 1.2% for fondaparinux vs 1.5% for controls. For patients receiving primary PCI, the incidence of severe haemorrhage was 1.0% for fondaparinux and 0.4% for controls.

The efficacy findings and results on severe haemorrhage were consistent across prespecified subgroups such as elderly, renally impaired patients, type of concomitant platelet aggregation inhibitors (aspirin, thienopyridines).

5.2 Pharmacokinetic properties

Absorption
After subcutaneous dosing, fondaparinux is completely and rapidly absorbed (absolute bioavailability 100%). Following a single subcutaneous injection of fondaparinux 2.5 mg to young healthy subjects, peak plasma concentration (mean C_{max} = 0.34 mg/l) is obtained 2 hours post-dosing. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.

In elderly healthy subjects, pharmacokinetics of fondaparinux are linear in the range of 2 to 8 mg by subcutaneous route. Following once daily subcutaneous dosing, steady state of plasma levels is obtained after 3 to 4 days with a 1.3-fold increase in C_{max} and AUC.

Mean (CV%) steady state pharmacokinetic parameters estimates of fondaparinux in patients undergoing hip replacement surgery receiving fondaparinux 2.5 mg once daily are: C_{max} (mg/l) - 0.39 (31%), T_{max} (h) - 2.8 (18%) and C_{min} (mg/l) -0.14 (56%). In hip fracture patients, associated with their increased age, fondaparinux steady state plasma concentrations are: C_{max} (mg/l) - 0.50 (32%), C_{min} (mg/l) - 0.19 (58%).

Distribution
The distribution volume of fondaparinux is limited (7-11 litres). *In vitro*, fondaparinux is highly and specifically bound to antithrombin protein with a dose-dependant plasma concentration binding (98.6% to 97.0% in the concentration range from 0.5 to 2 mg/l). Fondaparinux does not bind significantly to other plasma proteins, including platelet factor 4 (PF4).

Since fondaparinux does not bind significantly to plasma proteins other than ATIII, no interaction with other medicinal products by protein binding displacement are expected.

Metabolism
Although not fully evaluated, there is no evidence of fondaparinux metabolism and in particular no evidence for the formation of active metabolites.

Fondaparinux does not inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*. Thus, fondaparinux is not expected to interact with other medicinal products *in vivo* by inhibition of CYP-mediated metabolism.

Excretion/Elimination
The elimination half-life ($t_{½}$) is about 17 hours in healthy young subjects and about 21 hours in healthy elderly subjects. Fondaparinux is excreted to 64 – 77 % by the kidney as unchanged compound.

Special populations

Paediatric patients - Fondaparinux has not been investigated in this population.

Elderly patients - Renal function may decrease with age and thus, the elimination capacity for fondaparinux may be reduced in elderly. In patients >75 years undergoing orthopaedic surgery, the estimated plasma clearance was 1.2 to 1.4 times lower than in patients <65 years.

Renal impairment - Compared with patients with normal renal function (creatinine clearance > 80 ml/min), plasma clearance is 1.2 to 1.4 times lower in patients with mild renal impairment (creatinine clearance 50 to 80 ml/min) and on average 2 times lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min). In severe renal impairment (creatinine clearance < 30 ml/min), plasma clearance is approximately 5 times lower than in normal renal function. Associated terminal half-life values were 29 h in moderate and 72 h in patients with severe renal impairment.

Gender - No gender differences were observed after adjustment for body weight.

Race - Pharmacokinetic differences due to race have not been studied prospectively. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to Caucasian healthy subjects. Similarly, no plasma clearance differences were observed between black and Caucasian patients undergoing orthopaedic surgery.

Body weight - Plasma clearance of fondaparinux increases with body weight (9% increase per 10 kg).

Hepatic impairment - Fondaparinux pharmacokinetics has not been evaluated in hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

If fondaparinux sodium is added to a 0.9% saline minibag it should ideally be infused immediately, but can be stored at room temperature for up to 24 hours.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type I glass barrel (1 ml) affixed with a 27 gauge x 12.7 mm needle and stoppered with a bromobutyl or chlorobutyl elastomer plunger stopper.

Quixidar is available in pack sizes of 2, 7, 10 and 20 pre-filled syringes with a blue automatic safety system. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The subcutaneous injection is administered in the same way as with a classical syringe. Intravenous administration should be through an existing intravenous line either directly or using a small volume (25 or 50ml) 0.9% saline minibag.

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration.

Instruction on self-administration by subcutaneous injection is included in the Package Leaflet.

The needle protection system of the Quixidar pre-filled syringe has been designed with an automatic safety system to protect from needle stick injuries following injection.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/207/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2002
Date of latest renewal: 21 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 5 mg/0.4 ml solution for injection, pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 5 mg of fondaparinux sodium in 0.4 ml solution for injection.

Excipient(s): Contains less than 1 mmol of sodium (23 mg) per dose, and therefore is essentially sodium free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
The solution is a clear and colourless to slightly yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute Deep Vein Thrombosis (DVT) and treatment of acute Pulmonary Embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy**.**

4.2 Posology and method of administration

The recommended dose of fondaparinux is 7.5 mg (patients with body weight ≥ 50, ≤ 100kg) once daily administered by subcutaneous injection. For patients with body weight < 50 kg, the recommended dose is 5 mg. For patients with body weight > 100 kg, the recommended dose is 10 mg.

Treatment should be continued for at least 5 days and until adequate oral anticoagulation is established (International Normalised Ratio 2 to 3). Concomitant oral anticoagulation treatment should be initiated as soon as possible and usually within 72 hours. The average duration of administration in clinical trials was 7 days and the clinical experience from treatment beyond 10 days is limited.

Special populations

Elderly patients - No dosing adjustment is necessary. In patients ≥75 years, fondaparinux should be used with care, as renal function decreases with age (see section 4.4).

Renal impairment - Fondaparinux should be used with caution in patients with moderate renal impairment (see section 4.4).

There is no experience in the subgroup of patients with *both* high body weight (>100 kg) and moderate renal impairment (creatinine clearance 30-50 ml/min). In this subgroup, after an initial 10 mg daily dose, a reduction of the daily dose to 7.5 mg may be considered, based on pharmacokinetic modelling (see section 4.4).

Fondaparinux should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3).

Hepatic impairment - No dosing adjustment is necessary. In patients with severe hepatic impairment, fondaparinux should be used with care (see section 4.4).

Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy.

Method of administration
Fondaparinux is administered by deep subcutaneous injection while the patient is lying down. Sites of administration should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger; the skin fold should be held throughout the injection.

For additional instructions for use and handling and disposal see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients
- active clinically significant bleeding
- acute bacterial endocarditis
- severe renal impairment defined by creatinine clearance < 30 ml/min.

4.4 Special warnings and precautions for use

Fondaparinux is intended for subcutaneous use only. Do not administer intramuscularly.

There is limited experience from treatment with fondaparinux in haemodynamically unstable patients and no experience in patients requiring thrombolysis, embolectomy or insertion of a vena cava filter.

Haemorrhage
Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm^3), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.

As for other anticoagulants, fondaparinux should be used with caution in patients who have undergone recent surgery (<3 days) and only once surgical haemostasis has been established.

Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). During treatment of VTE, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.

Spinal / Epidural anaesthesia
In patients receiving fondaparinux for treatment of VTE rather than prophylaxis, spinal/epidural anaesthesia in case of surgical procedures should not be used.

Elderly patients
The elderly population is at increased risk of bleeding. As renal function generally decreases with age, elderly patients may show reduced elimination and increased exposure of fondaparinux (see section 5.2). Incidences of bleeding events in patients receiving the recommended regimen in the treatment of DVT or PE and aged <65 years, 65-75 and >75 years were 3.0 %, 4.5 % and 6.5 %, respectively. The corresponding incidences in patients receiving the recommended regimen of enoxaparin in the

treatment of DVT were 2.5%, 3.6% and 8.3% respectively, while the incidences in patients receiving the recommended regimen of UFH in the treatment of PE were 5.5%, 6.6% and 7.4%, respectively. Fondaparinux should be used with caution in elderly patients (see section 4.2).

Low body weight
Clinical experience is limited in patients with body weight <50 kg. Fondaparinux should be used with caution at a daily dose of 5 mg in this population (see sections 4.2 and 5.2).

Renal impairment
The risk of bleeding increases with increasing renal impairment. Fondaparinux is known to be excreted mainly by the kidney. Incidences of bleeding events in patients receiving the recommended regimen in the treatment of DVT or PE with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment were 3.0 % (34/1132), 4.4 % (32/733), 6.6% (21/318), and 14.5 % (8/55) respectively. The corresponding incidences in patients receiving the recommended regimen of enoxaparin in the treatment of DVT were 2.3% (13/559), 4.6% (17/368), 9.7% (14/145) and 11.1% (2/18) respectively, and in patients receiving the recommended regimen of unfractionated heparin in the treatment of PE were 6.9% (36/523), 3.1% (11/352), 11.1% (18/162) and 10.7% (3/28), respectively.

Fondaparinux is contra-indicated in severe renal impairment (creatinine clearance <30 ml/min) and should be used with caution in patients with moderate renal impairment (creatinine clearance 30-50 ml/min). The duration of treatment should not exceed that evaluated during clinical trial (mean 7 days) (see sections 4.2, 4.3 and 5.2).

There is no experience in the subgroup of patients with both high body weight (>100 kg) and moderate renal impairment (creatinine clearance 30-50 ml/min). Fondaparinux should be used with care in these patients. After an initial 10 mg daily dose, a reduction of the daily dose to 7.5 mg may be considered, based on pharmacokinetic modelling (see section 4.2).

Severe hepatic impairment
The use of fondaparinux should be considered with caution because of an increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic impairment (see section 4.2).

Patients with Heparin Induced Thrombocytopenia
Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II.

4.5 Interaction with other medicinal products and other forms of interaction

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (see section 4.4).

In clinical studies performed with fondaparinux, oral anticoagulants (warfarin) did not interact with the pharmacokinetics of fondaparinux; at the 10 mg dose used in the interaction studies, fondaparinux did not influence the anticoagulation monitoring (INR) activity of warfarin.

Platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics of fondaparinux. At the 10 mg dose used in the interaction studies, fondaparinux did not influence the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics of digoxin at steady state.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development because of limited exposure. Fondaparinux should not be prescribed to pregnant women unless clearly necessary.

Fondaparinux is excreted in rat milk but it is not known whether fondaparinux is excreted in human milk. Breast-feeding is not recommended during treatment with fondaparinux. Oral absorption by the child is however unlikely.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

The safety of fondaparinux has been evaluated in 2,517 patients treated for Venous Thrombo-Embolism and treated with fondaparinux for an average of 7 days. The most common adverse reactions were bleeding complications (see section 4.4).

The adverse reactions reported by the investigator as at least possibly related to fondaparinux are presented within each frequency grouping (very common ≥ 1/10; common: ≥1/100 to < 1/10; uncommon: ≥ 1/1,000 to ≤ 1/100; rare: ≥ 1/10,000 to ≤1/1,000; very rare ≤1/10,000) and system organ class by decreasing order of seriousness.

System organ class MedDRA	Undesirable effects in patients treated for VTE[1]
Blood and lymphatic system disorders	*Common:* bleeding (gastrointestinal, haematuria, haematoma, epistaxis, haemoptysis, utero-vaginal haemorrhage, haemarthrosis, ocular, purpura, bruise) *Uncommon:* anaemia, thrombocytopaenia *Rare:* other bleeding (hepatic, retroperitoneal, intracranial/intracerebral), thrombocythaemia
Immune system disorders	*Rare:* allergic reaction
Metabolism and nutrition disorders	*Rare:* non-protein-nitrogen (Npn) [2] increased
Nervous system disorders	*Uncommon*: headache *Rare:* dizziness
Gastrointestinal disorders	*Uncommon:* nausea, vomiting
Hepatobiliary disorders	*Uncommon*: abnormal liver function
Skin and subcutaneous tissue disorders	*Rare:* rash erythematous
General disorders and administration site conditions	*Uncommon:* pain, oedema, *Rare:* reaction at injection site

(1) Isolated AEs have not been considered except if they were medically relevant.
(2) Npn stands for non-protein-nitrogen such as urea, uric acid, amino acid, etc.

4.9 Overdose

Fondaparinux doses above the recommended regimen may lead to an increased risk of bleeding. There is no known antidote to fondaparinux.

Overdose associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents.
ATC code: B01AX05

Pharmacodynamic effects

Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (antithrombin) mediated selective inhibition of Factor Xa. By binding selectively to antithrombin, fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa by antithrombin. 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 has no effects on platelets.

At the doses used for treatment, fondaparinux does not, to a clinically relevant extent, 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 nor bleeding time or fibrinolytic activity. At higher doses, moderate changes in aPTT can occur. At the 10 mg dose used in interaction studies, fondaparinux did not significantly influence the anticoagulation activity (INR) of warfarin.

Fondaparinux does not cross-react with sera from patients with heparin-induced thrombocytopaenia.

Clinical studies

The fondaparinux clinical program in treatment of Venous Thromboembolism was designed to demonstrate the efficacy of fondaparinux for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Over 4874 patients were studied in controlled Phase II and III clinical studies.

Treatment of Deep Venous Thrombosis
In a randomised, double-blind, clinical trial in patients with a confirmed diagnosis of acute symptomatic DVT, fondaparinux 5 mg (body weight < 50 kg), 7.5 mg (body weight ≥ 50 kg, ≤ 100 kg) or 10 mg (body weight >100 kg) SC once daily was compared to enoxaparin sodium 1 mg/kg SC twice daily. A total of 2192 patients were treated; for both groups, patients were treated for at least 5 days and up to 26 days (mean 7 days). Both treatment groups received Vitamin K antagonist therapy usually initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2-3. The primary efficacy endpoint was the composite of confirmed symptomatic recurrent non-fatal VTE and fatal VTE reported up to Day 97. Treatment with fondaparinux was demonstrated to be non-inferior to enoxaparin (VTE rates 3.9% and 4.1%, respectively).

Major bleeding during the initial treatment period was observed in 1.1% of fondaparinux patients, compared to 1.2% with enoxaparin.

Treatment of Pulmonary Embolism
A randomised, open-label, clinical trial was conducted in patients with acute symptomatic PE. The diagnosis was confirmed by objective testing (lung scan, pulmonary angiography or spiral CT scan). Patients who required thrombolysis or embolectomy or vena cava filter were excluded. Randomised patients could have been pre-treated with UFH during the screening phase but patients treated for more than 24 hours with therapeutic dose of anticoagulant or with uncontrolled hypertension were excluded. Fondaparinux 5 mg (body weight < 50 kg), 7.5 mg (body weight ≥ 50kg, ≤ 100 kg) or 10 mg (body weight >100 kg) SC once daily was compared to unfractionated heparin IV bolus (5000 IU) followed by a continuous IV infusion adjusted to maintain 1.5–2.5 times aPTT control value.. A total of 2184 patients were treated; for both groups, patients were treated for at least 5 days and up to 22 days (mean 7 days). Both treatment groups received Vitamin K antagonist therapy usually initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2-3. The primary efficacy endpoint was the composite of confirmed symptomatic recurrent non-fatal VTE and fatal VTE reported up to Day 97. Treatment with fondaparinux was demonstrated to be non-inferior to unfractionated heparin (VTE rates 3.8% and 5.0%, respectively).

Major bleeding during the initial treatment period was observed in 1.3% of fondaparinux patients, compared to 1.1% with unfractionated heparin.

5.2 Pharmacokinetic properties

The pharmacokinetics of fondaparinux sodium are derived from fondaparinux plasma concentrations quantified via anti factor Xa activity. Only fondaparinux can be used to calibrate the anti-Xa assay (the international standards of heparin or LMWH are not appropriate for this use). As a result, the concentration of fondaparinux is expressed as milligrams (mg).

Absorption
After subcutaneous dosing, fondaparinux is completely and rapidly absorbed (absolute bioavailability 100%). Following a single subcutaneous injection of fondaparinux 2.5 mg to young healthy subjects, peak plasma concentration (mean C_{max} = 0.34 mg/l) is obtained 2 hours post-dosing. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.

In elderly healthy subjects, pharmacokinetics of fondaparinux is linear in the range of 2 to 8 mg by subcutaneous route. Following once daily dosing, steady state of plasma levels is obtained after 3 to 4 days with a 1.3-fold increase in C_{max} and AUC.

Mean (CV%) steady state pharmacokinetic parameters estimates of fondaparinux in patients undergoing hip replacement surgery receiving fondaparinux 2.5 mg once daily are: C_{max} (mg/l) - 0.39 (31%), T_{max} (h) - 2.8 (18%) and C_{min} (mg/l) -0.14 (56%). In hip fracture patients, associated with their increased age, fondaparinux steady state plasma concentrations are: C_{max} (mg/l) - 0.50 (32%), C_{min} (mg/l) - 0.19 (58%).

In DVT and PE treatment, patients receiving fondaparinux 5 mg (body weight <50 kg), 7.5 mg (body weight 50-100 kg inclusive) and 10 mg (body weight >100 kg) once daily, the body weight-adjusted doses provide similar exposure across all body weight categories. The mean (CV%) steady state pharmacokinetic parameters estimates of fondaparinux in patients with VTE receiving the fondaparinux proposed dose regimen once daily are: C_{max} (mg/l) - 1.41 (23 %), T_{max} (h) – 2.4 (8%) and C_{min} (mg/l) -0.52 (45 %). The associated 5th and 95th percentiles are, respectively, 0.97 and 1.92 for C_{max} (mg/l), and 0.24 and 0.95 for C_{min} (mg/l).

Distribution
The distribution volume of fondaparinux is limited (7-11 litres). *In vitro*, fondaparinux is highly and specifically bound to antithrombin protein with a dose-dependant plasma concentration binding (98.6% to 97.0% in the concentration range from 0.5 to 2 mg/l). Fondaparinux does not bind significantly to other plasma proteins, including platelet factor 4 (PF4).

Since fondaparinux does not bind significantly to plasma proteins other than antithrombin, no interaction with other medicinal products by protein binding displacement are expected.

Metabolism
Although not fully evaluated, there is no evidence of fondaparinux metabolism and in particular no evidence for the formation of active metabolites.

Fondaparinux does not inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*. Thus, fondaparinux is not expected to interact with other medicinal products *in vivo* by inhibition of CYP-mediated metabolism.

Excretion/Elimination
The elimination half-life ($t_{½}$) is about 17 hours in healthy young subjects and about 21 hours in healthy elderly subjects. Fondaparinux is excreted to 64 – 77 % by the kidney as unchanged compound.

Special populations

Paediatric patients - Fondaparinux has not been investigated in this population.

Elderly patients - Renal function may decrease with age and thus, the elimination capacity for fondaparinux may be reduced in elderly. In patients >75 years undergoing orthopaedic surgery and receiving fondaparinux 2.5 mg once daily, the estimated plasma clearance was 1.2 to 1.4 times lower than in patients <65 years. A similar pattern is observed in DVT and PE treatment patients.

Renal impairment - Compared with patients with normal renal function (creatinine clearance > 80 ml/min) undergoing orthopaedic surgery and receiving fondaparinux 2.5 mg once daily, plasma clearance is 1.2 to 1.4 times lower in patients with mild renal impairment (creatinine clearance 50 to 80 ml/min) and on average 2 times lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min). In severe renal impairment (creatinine clearance <30 ml/min), plasma clearance is approximately 5 times lower than in normal renal function. Associated terminal half-life values were 29 h in moderate and 72 h in patients with severe renal impairment. A similar pattern is observed in DVT and PE treatment patients.

Body weight - Plasma clearance of fondaparinux increases with body weight (9% increase per 10 kg).

Gender - No gender differences were observed after adjustment for body weight.

Race - Pharmacokinetic differences due to race have not been studied prospectively. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to Caucasian healthy subjects. Similarly, no plasma clearance differences were observed between black and Caucasian patients undergoing orthopaedic surgery.

Hepatic impairment - Fondaparinux pharmacokinetics has not been evaluated in hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity. The repeated dose and reproduction toxicity studies did not reveal any special risk but did not provide adequate documentation of safety margins due to limited exposure in the animal species**.**

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type I glass barrel (1 ml) affixed with a 27 gauge x 12.7 mm needle and stoppered with a chlorobutyl elastomer plunger stopper.

Quixidar 5 mg/0.4 ml is available in pack sizes of 2, 7, 10 and 20 pre-filled syringes with an orange automatic safety system. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The subcutaneous injection is administered in the same way as with a classical syringe.

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration.

Instruction for self-administration is mentioned in the Package Leaflet.

The Quixidar pre-filled syringe has been designed with an automatic needle protection system to prevent needle stick injuries following injection.

Any unused product or waste material should be disposed of in accordance with local requirements. This medicinal product is for single use only.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/207/009-011, 018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2002
Date of latest renewal: 21 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 7.5 mg/0.6 ml solution for injection, pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 7.5 mg of fondaparinux sodium in 0.6 ml solution for injection.
Excipient(s): Contains less than 1 mmol of sodium (23 mg) per dose, and therefore is essentially sodium free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
The solution is a clear and colourless to slightly yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute Deep Vein Thrombosis (DVT) and treatment of acute Pulmonary Embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy**.**

4.2 Posology and method of administration

The recommended dose of fondaparinux is 7.5 mg (patients with body weight ≥ 50, ≤ 100kg) once daily administered by subcutaneous injection. For patients with body weight < 50 kg, the recommended dose is 5 mg. For patients with body weight > 100 kg, the recommended dose is 10 mg.

Treatment should be continued for at least 5 days and until adequate oral anticoagulation is established (International Normalised Ratio 2 to 3). Concomitant oral anticoagulation treatment should be initiated as soon as possible and usually within 72 hours. The average duration of administration in clinical trials was 7 days and the clinical experience from treatment beyond 10 days is limited.

Special populations

Elderly patients - No dosing adjustment is necessary. In patients ≥75 years, fondaparinux should be used with care, as renal function decreases with age (see section 4.4).

Renal impairment - Fondaparinux should be used with caution in patients with moderate renal impairment (see section 4.4).

There is no experience in the subgroup of patients with *both* high body weight (>100 kg) and moderate renal impairment (creatinine clearance 30-50 ml/min). In this subgroup, after an initial 10 mg daily dose, a reduction of the daily dose to 7.5 mg may be considered, based on pharmacokinetic modelling (see section 4.4).

Fondaparinux should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3).

Hepatic impairment - No dosing adjustment is necessary. In patients with severe hepatic impairment, fondaparinux should be used with care (see section 4.4).

Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy.

Method of administration
Fondaparinux is administered by deep subcutaneous injection while the patient is lying down. Sites of administration should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger; the skin fold should be held throughout the injection.

For additional instructions for use and handling and disposal see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients
- active clinically significant bleeding
- acute bacterial endocarditis
- severe renal impairment defined by creatinine clearance < 30 ml/min.

4.4 Special warnings and precautions for use

Fondaparinux is intended for subcutaneous use only. Do not administer intramuscularly.

There is limited experience from treatment with fondaparinux in haemodynamically unstable patients and no experience in patients requiring thrombolysis, embolectomy or insertion of a vena cava filter.

Haemorrhage
Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm^3), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.

As for other anticoagulants, fondaparinux should be used with caution in patients who have undergone recent surgery (<3 days) and only once surgical haemostasis has been established.

Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). During treatment of VTE, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.

Spinal / Epidural anaesthesia
In patients receiving fondaparinux for treatment of VTE rather than prophylaxis, spinal/epidural anaesthesia in case of surgical procedures should not be used.

Elderly patients
The elderly population is at increased risk of bleeding. As renal function generally decreases with age, elderly patients may show reduced elimination and increased exposure of fondaparinux (see section 5.2). Incidences of bleeding events in patients receiving the recommended regimen in the treatment of DVT or PE and aged <65 years, 65-75 and >75 years were 3.0 %, 4.5 % and 6.5 %, respectively. The corresponding incidences in patients receiving the recommended regimen of enoxaparin in the treatment of DVT were 2.5%, 3.6% and 8.3% respectively, while the incidences in patients receiving

the recommended regimen of UFH in the treatment of PE were 5.5%, 6.6% and 7.4%, respectively. Fondaparinux should be used with caution in elderly patients (see section 4.2).

Low body weight
Clinical experience is limited in patients with body weight <50 kg. Fondaparinux should be used with caution at a daily dose of 5 mg in this population (see sections 4.2 and 5.2).

Renal impairment
The risk of bleeding increases with increasing renal impairment. Fondaparinux is known to be excreted mainly by the kidney. Incidences of bleeding events in patients receiving the recommended regimen in the treatment of DVT or PE with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment were 3.0 % (34/1132), 4.4 % (32/733), 6.6% (21/318), and 14.5 % (8/55) respectively. The corresponding incidences in patients receiving the recommended regimen of enoxaparin in the treatment of DVT were 2.3% (13/559), 4.6% (17/368), 9.7% (14/145) and 11.1% (2/18) respectively, and in patients receiving the recommended regimen of unfractionated heparin in the treatment of PE were 6.9% (36/523), 3.1% (11/352), 11.1% (18/162) and 10.7% (3/28), respectively.

Fondaparinux is contra-indicated in severe renal impairment (creatinine clearance <30 ml/min) and should be used with caution in patients with moderate renal impairment (creatinine clearance 30-50 ml/min). The duration of treatment should not exceed that evaluated during clinical trial (mean 7 days) (see sections 4.2, 4.3 and 5.2).

There is no experience in the subgroup of patients with both high body weight (>100 kg) and moderate renal impairment (creatinine clearance 30-50 ml/min). Fondaparinux should be used with care in these patients. After an initial 10 mg daily dose, a reduction of the daily dose to 7.5 mg may be considered, based on pharmacokinetic modelling (see section 4.2).

Severe hepatic impairment
The use of fondaparinux should be considered with caution because of an increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic impairment (see section 4.2).

Patients with Heparin Induced Thrombocytopenia
Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II.

4.5 Interaction with other medicinal products and other forms of interaction

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (see section 4.4).

In clinical studies performed with fondaparinux, oral anticoagulants (warfarin) did not interact with the pharmacokinetics of fondaparinux; at the 10 mg dose used in the interaction studies, fondaparinux did not influence the anticoagulation monitoring (INR) activity of warfarin.

Platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics of fondaparinux. At the 10 mg dose used in the interaction studies, fondaparinux did not influence the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics of digoxin at steady state.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development because of limited exposure. Fondaparinux should not be prescribed to pregnant women unless clearly necessary.

Fondaparinux is excreted in rat milk but it is not known whether fondaparinux is excreted in human milk. Breast-feeding is not recommended during treatment with fondaparinux. Oral absorption by the child is however unlikely.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

The safety of fondaparinux has been evaluated in 2,517 patients treated for Venous Thrombo-Embolism and treated with fondaparinux for an average of 7 days. The most common adverse reactions were bleeding complications (see section 4.4).

The adverse reactions reported by the investigator as at least possibly related to fondaparinux are presented within each frequency grouping (very common ≥ 1/10; common: ≥1/100 to < 1/10; uncommon: ≥ 1/1,000 to ≤ 1/100; rare: ≥ 1/10,000 to ≤1/1,000; very rare ≤1/10,000) and system organ class by decreasing order of seriousness.

System organ class MedDRA	**Undesirable effects in patients treated for VTE[1]**
Blood and lymphatic system disorders	*Common:* bleeding (gastrointestinal, haematuria, haematoma, epistaxis, haemoptysis, utero-vaginal haemorrhage, haemarthrosis, ocular, purpura, bruise) *Uncommon:* anaemia, thrombocytopaenia *Rare:* other bleeding (hepatic, retroperitoneal, intracranial/intracerebral), thrombocythaemia
Immune system disorders	*Rare*: allergic reaction
Metabolism and nutrition disorders	*Rare:* non-protein-nitrogen (Npn) [2] increased
Nervous system disorders	*Uncommon*: headache *Rare:* dizziness
Gastrointestinal disorders	*Uncommon:* nausea, vomiting
Hepatobiliary disorders	*Uncommon*: abnormal liver function
Skin and subcutaneous tissue disorders	*Rare:* rash erythematous
General disorders and administration site conditions	*Uncommon:* pain, oedema, *Rare:* reaction at injection site

(1) Isolated AEs have not been considered except if they were medically relevant.
(2) Npn stands for non-protein-nitrogen such as urea, uric acid, amino acid, etc.

4.9 Overdose

Fondaparinux doses above the recommended regimen may lead to an increased risk of bleeding. There is no known antidote to fondaparinux.

Overdose associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents.
ATC code: B01AX05

Pharmacodynamic effects

Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (antithrombin) mediated selective inhibition of Factor Xa. By binding selectively to antithrombin, fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa by antithrombin. 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 has no effects on platelets.

At the doses used for treatment, fondaparinux does not, to a clinically relevant extent, 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 nor bleeding time or fibrinolytic activity. At higher doses, moderate changes in aPTT can occur. At the 10 mg dose used in interaction studies, fondaparinux did not significantly influence the anticoagulation activity (INR) of warfarin.

Fondaparinux does not cross-react with sera from patients with heparin-induced thrombocytopaenia.

Clinical studies

The fondaparinux clinical program in treatment of Venous Thromboembolism was designed to demonstrate the efficacy of fondaparinux for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Over 4874 patients were studied in controlled Phase II and III clinical studies.

Treatment of Deep Venous Thrombosis
In a randomised, double-blind, clinical trial in patients with a confirmed diagnosis of acute symptomatic DVT, fondaparinux 5 mg (body weight < 50 kg), 7.5 mg (body weight ≥ 50 kg, ≤ 100 kg) or 10 mg (body weight >100 kg) SC once daily was compared to enoxaparin sodium 1 mg/kg SC twice daily. A total of 2192 patients were treated; for both groups, patients were treated for at least 5 days and up to 26 days (mean 7 days). Both treatment groups received Vitamin K antagonist therapy usually initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2-3. The primary efficacy endpoint was the composite of confirmed symptomatic recurrent non-fatal VTE and fatal VTE reported up to Day 97. Treatment with fondaparinux was demonstrated to be non-inferior to enoxaparin (VTE rates 3.9% and 4.1%, respectively).

Major bleeding during the initial treatment period was observed in 1.1% of fondaparinux patients, compared to 1.2% with enoxaparin.

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A randomised, open-label, clinical trial was conducted in patients with acute symptomatic PE. The diagnosis was confirmed by objective testing (lung scan, pulmonary angiography or spiral CT scan). Patients who required thrombolysis or embolectomy or vena cava filter were excluded. Randomised patients could have been pre-treated with UFH during the screening phase but patients treated for more than 24 hours with therapeutic dose of anticoagulant or with uncontrolled hypertension were excluded. Fondaparinux 5 mg (body weight < 50 kg), 7.5 mg (body weight ≥ 50kg, ≤ 100 kg) or 10 mg (body weight >100 kg) SC once daily was compared to unfractionated heparin IV bolus (5000 IU) followed by a continuous IV infusion adjusted to maintain 1.5–2.5 times aPTT control value.. A total of 2184 patients were treated; for both groups, patients were treated for at least 5 days and up to 22 days (mean 7 days). Both treatment groups received Vitamin K antagonist therapy usually initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2-3. The primary efficacy endpoint was the composite of confirmed symptomatic recurrent non-fatal VTE and fatal VTE reported up to Day 97. Treatment with fondaparinux was demonstrated to be non-inferior to unfractionated heparin (VTE rates 3.8% and 5.0%, respectively).

Major bleeding during the initial treatment period was observed in 1.3% of fondaparinux patients, compared to 1.1% with unfractionated heparin.

5.2 Pharmacokinetic properties

The pharmacokinetics of fondaparinux sodium are derived from fondaparinux plasma concentrations quantified via anti factor Xa activity. Only fondaparinux can be used to calibrate the anti-Xa assay (the international standards of heparin or LMWH are not appropriate for this use). As a result, the concentration of fondaparinux is expressed as milligrams (mg).

Absorption
After subcutaneous dosing, fondaparinux is completely and rapidly absorbed (absolute bioavailability 100%). Following a single subcutaneous injection of fondaparinux 2.5 mg to young healthy subjects, peak plasma concentration (mean C_{max} = 0.34 mg/l) is obtained 2 hours post-dosing. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.

In elderly healthy subjects, pharmacokinetics of fondaparinux is linear in the range of 2 to 8 mg by subcutaneous route. Following once daily dosing, steady state of plasma levels is obtained after 3 to 4 days with a 1.3-fold increase in C_{max} and AUC.

Mean (CV%) steady state pharmacokinetic parameters estimates of fondaparinux in patients undergoing hip replacement surgery receiving fondaparinux 2.5 mg once daily are: C_{max} (mg/l) - 0.39 (31%), T_{max} (h) - 2.8 (18%) and C_{min} (mg/l) -0.14 (56%). In hip fracture patients, associated with their increased age, fondaparinux steady state plasma concentrations are: C_{max} (mg/l) - 0.50 (32%), C_{min} (mg/l) - 0.19 (58%).

In DVT and PE treatment, patients receiving fondaparinux 5 mg (body weight <50 kg), 7.5 mg (body weight 50-100 kg inclusive) and 10 mg (body weight >100 kg) once daily, the body weight-adjusted doses provide similar exposure across all body weight categories. The mean (CV%) steady state pharmacokinetic parameters estimates of fondaparinux in patients with VTE receiving the fondaparinux proposed dose regimen once daily are: C_{max} (mg/l) - 1.41 (23 %), T_{max} (h) – 2.4 (8%) and C_{min} (mg/l) -0.52 (45 %). The associated 5th and 95th percentiles are, respectively, 0.97 and 1.92 for C_{max} (mg/l), and 0.24 and 0.95 for C_{min} (mg/l).

Distribution
The distribution volume of fondaparinux is limited (7-11 litres). *In vitro*, fondaparinux is highly and specifically bound to antithrombin protein with a dose-dependant plasma concentration binding (98.6% to 97.0% in the concentration range from 0.5 to 2 mg/l). Fondaparinux does not bind significantly to other plasma proteins, including platelet factor 4 (PF4).

Since fondaparinux does not bind significantly to plasma proteins other than antithrombin, no interaction with other medicinal products by protein binding displacement are expected.

Metabolism
Although not fully evaluated, there is no evidence of fondaparinux metabolism and in particular no evidence for the formation of active metabolites.

Fondaparinux does not inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*. Thus, fondaparinux is not expected to interact with other medicinal products *in vivo* by inhibition of CYP-mediated metabolism.

Excretion/Elimination
The elimination half-life ($t_{½}$) is about 17 hours in healthy young subjects and about 21 hours in healthy elderly subjects. Fondaparinux is excreted to 64 – 77 % by the kidney as unchanged compound.

Special populations

Paediatric patients - Fondaparinux has not been investigated in this population.

Elderly patients - Renal function may decrease with age and thus, the elimination capacity for fondaparinux may be reduced in elderly. In patients >75 years undergoing orthopaedic surgery and receiving fondaparinux 2.5 mg once daily, the estimated plasma clearance was 1.2 to 1.4 times lower than in patients <65 years. A similar pattern is observed in DVT and PE treatment patients.

Renal impairment - Compared with patients with normal renal function (creatinine clearance > 80 ml/min) undergoing orthopaedic surgery and receiving fondaparinux 2.5 mg once daily, plasma clearance is 1.2 to 1.4 times lower in patients with mild renal impairment (creatinine clearance 50 to 80 ml/min) and on average 2 times lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min). In severe renal impairment (creatinine clearance <30 ml/min), plasma clearance is approximately 5 times lower than in normal renal function. Associated terminal half-life values were 29 h in moderate and 72 h in patients with severe renal impairment. A similar pattern is observed in DVT and PE treatment patients.

Body weight - Plasma clearance of fondaparinux increases with body weight (9% increase per 10 kg).

Gender - No gender differences were observed after adjustment for body weight.

Race - Pharmacokinetic differences due to race have not been studied prospectively. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to Caucasian healthy subjects. Similarly, no plasma clearance differences were observed between black and Caucasian patients undergoing orthopaedic surgery.

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Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity. The repeated dose and reproduction toxicity studies did not reveal any special risk but did not provide adequate documentation of safety margins due to limited exposure in the animal species**.**

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type I glass barrel (1 ml) affixed with a 27 gauge x 12.7 mm needle and stoppered with a chlorobutyl elastomer plunger stopper.

Quixidar 7.5 mg/0.6 ml is available in pack sizes of 2, 7, 10 and 20 pre-filled syringes with a magenta automatic safety system. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The subcutaneous injection is administered in the same way as with a classical syringe.

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration.

Instruction for self-administration is mentioned in the Package Leaflet.

The Quixidar pre-filled syringe has been designed with an automatic needle protection system to prevent needle stick injuries following injection.

Any unused product or waste material should be disposed of in accordance with local requirements. This medicinal product is for single use only.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/207/012-014, 019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2002
Date of latest renewal: 21 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 10 mg/0.8 ml solution for injection, pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 10 mg of fondaparinux sodium in 0.8 ml solution for injection.

Excipient(s): Contains less than 1 mmol of sodium (23 mg) per dose, and therefore is essentially sodium free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
The solution is a clear and colourless to slightly yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute Deep Vein Thrombosis (DVT) and treatment of acute Pulmonary Embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy**.**

4.2 Posology and method of administration

The recommended dose of fondaparinux is 7.5 mg (patients with body weight ≥ 50, ≤ 100kg) once daily administered by subcutaneous injection. For patients with body weight < 50 kg, the recommended dose is 5 mg. For patients with body weight > 100 kg, the recommended dose is 10 mg.

Treatment should be continued for at least 5 days and until adequate oral anticoagulation is established (International Normalised Ratio 2 to 3). Concomitant oral anticoagulation treatment should be initiated as soon as possible and usually within 72 hours. The average duration of administration in clinical trials was 7 days and the clinical experience from treatment beyond 10 days is limited.

Special populations

Elderly patients - No dosing adjustment is necessary. In patients ≥75 years, fondaparinux should be used with care, as renal function decreases with age (see section 4.4).

Renal impairment - Fondaparinux should be used with caution in patients with moderate renal impairment (see section 4.4).

There is no experience in the subgroup of patients with *both* high body weight (>100 kg) and moderate renal impairment (creatinine clearance 30-50 ml/min). In this subgroup, after an initial 10 mg daily dose, a reduction of the daily dose to 7.5 mg may be considered, based on pharmacokinetic modelling (see section 4.4).

Fondaparinux should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (See section 4.3).

Hepatic impairment - No dosing adjustment is necessary. In patients with severe hepatic impairment, fondaparinux should be used with care (see section 4.4).

Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy

Method of administration
Fondaparinux is administered by deep subcutaneous injection while the patient is lying down. Sites of administration should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger; the skin fold should be held throughout the injection.

For additional instructions for use and handling and disposal see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients
- active clinically significant bleeding
- acute bacterial endocarditis
- severe renal impairment defined by creatinine clearance < 30 ml/min.

4.4 Special warnings and precautions for use

Fondaparinux is intended for subcutaneous use only. Do not administer intramuscularly.

There is limited experience from treatment with fondaparinux in haemodynamically unstable patients and no experience in patients requiring thrombolysis, embolectomy or insertion of a vena cava filter.

Haemorrhage
Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm^3), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.

As for other anticoagulants, fondaparinux should be used with caution in patients who have undergone recent surgery (<3 days) and only once surgical haemostasis has been established**.**

Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). During treatment of VTE, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of Section 4.5. Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.

Spinal / Epidural anaesthesia
In patients receiving fondaparinux for treatment of VTE rather than prophylaxis, spinal/epidural anaesthesia in case of surgical procedures should not be used.

Elderly patients
The elderly population is at increased risk of bleeding. As renal function generally decreases with age, elderly patients may show reduced elimination and increased exposure of fondaparinux (see section 5.2). Incidences of bleeding events in patients receiving the recommended regimen in the treatment of DVT or PE and aged <65 years, 65-75 and >75 years were 3.0 %, 4.5 % and 6.5 %, respectively. The corresponding incidences in patients receiving the recommended regimen of enoxaparin in the

treatment of DVT were 2.5%, 3.6% and 8.3% respectively, while the incidences in patients receiving the recommended regimen of UFH in the treatment of PE were 5.5%, 6.6% and 7.4%, respectively. Fondaparinux should be used with caution in elderly patients (see section 4.2).

Low body weight
Clinical experience is limited in patients with body weight <50 kg. Fondaparinux should be used with caution at a daily dose of 5 mg in this population (see sections 4.2 and 5.2).

Renal impairment
The risk of bleeding increases with increasing renal impairment. Fondaparinux is known to be excreted mainly by the kidney. Incidences of bleeding events in patients receiving the recommended regimen in the treatment of DVT or PE with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment were 3.0 % (34/1132), 4.4 % (32/733), 6.6% (21/318), and 14.5 % (8/55) respectively. The corresponding incidences in patients receiving the recommended regimen of enoxaparin in the treatment of DVT were 2.3% (13/559), 4.6% (17/368), 9.7% (14/145) and 11.1% (2/18) respectively, and in patients receiving the recommended regimen of unfractionated heparin in the treatment of PE were 6.9% (36/523), 3.1% (11/352), 11.1% (18/162) and 10.7% (3/28), respectively.

Fondaparinux is contra-indicated in severe renal impairment (creatinine clearance <30 ml/min) and should be used with caution in patients with moderate renal impairment (creatinine clearance 30-50 ml/min). The duration of treatment should not exceed that evaluated during clinical trial (mean 7 days) (see sections 4.2, 4.3 and 5.2).

There is no experience in the subgroup of patients with both high body weight (>100 kg) and moderate renal impairment (creatinine clearance 30-50 ml/min). Fondaparinux should be used with care in these patients. After an initial 10 mg daily dose, a reduction of the daily dose to 7.5 mg may be considered, based on pharmacokinetic modelling (see section 4.2).

Severe hepatic impairment
The use of fondaparinux should be considered with caution because of an increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic impairment (see section 4.2).

Patients with Heparin Induced Thrombocytopenia
Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II.

4.5 Interaction with other medicinal products and other forms of interaction

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (see section 4.4).

In clinical studies performed with fondaparinux, oral anticoagulants (warfarin) did not interact with the pharmacokinetics of fondaparinux; at the 10 mg dose used in the interaction studies, fondaparinux did not influence the anticoagulation monitoring (INR) activity of warfarin.

Platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics of fondaparinux. At the 10 mg dose used in the interaction studies, fondaparinux did not influence the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics of digoxin at steady state.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development because of limited exposure. Fondaparinux should not be prescribed to pregnant women unless clearly necessary.

Fondaparinux is excreted in rat milk but it is not known whether fondaparinux is excreted in human milk. Breast-feeding is not recommended during treatment with fondaparinux. Oral absorption by the child is however unlikely.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and to use machines have been performed.

4.8 Undesirable effects

The safety of fondaparinux has been evaluated in 2,517 patients treated for Venous Thrombo-Embolism and treated with fondaparinux for an average of 7 days. The most common adverse reactions were bleeding complications (see section 4.4).

The adverse reactions reported by the investigator as at least possibly related to fondaparinux are presented within each frequency grouping (very common ≥ 1/10; common: ≥1/100 to < 1/10; uncommon: ≥ 1/1,000 to ≤ 1/100; rare: ≥ 1/10,000 to ≤1/1,000; very rare ≤1/10,000) and system organ class by decreasing order of seriousness.

System organ class MedDRA	Undesirable effects in patients treated for VTE[1]
Blood and lymphatic system disorders	*Common:* bleeding (gastrointestinal, haematuria, haematoma, epistaxis, haemoptysis, utero-vaginal haemorrhage, haemarthrosis, ocular, purpura, bruise) *Uncommon:* anaemia, thrombocytopaenia *Rare:* other bleeding (hepatic, retroperitoneal, intracranial/intracerebral), thrombocythaemia
Immune system disorders	*Rare:* allergic reaction
Metabolism and nutrition disorders	*Rare:* non-protein-nitrogen (Npn) [2] increased
Nervous system disorders	*Uncommon*: headache *Rare:* dizziness
Gastrointestinal disorders	*Uncommon:* nausea, vomiting
Hepatobiliary disorders	*Uncommon*: abnormal liver function
Skin and subcutaneous tissue disorders	*Rare:* rash erythematous
General disorders and administration site conditions	*Uncommon:* pain, oedema, *Rare:* reaction at injection site

(1) Isolated AEs have not been considered except if they were medically relevant.
(2) Npn stands for non-protein-nitrogen such as urea, uric acid, amino acid, etc.

4.9 Overdose

Fondaparinux doses above the recommended regimen may lead to an increased risk of bleeding. There is no known antidote to fondaparinux.

Overdose associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents.
ATC code: B01AX05

Pharmacodynamic effects

Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (antithrombin) mediated selective inhibition of Factor Xa. By binding selectively to antithrombin, fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa by antithrombin. 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 has no effects on platelets.

At the doses used for treatment, fondaparinux does not, to a clinically relevant extent, 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 nor bleeding time or fibrinolytic activity. At higher doses, moderate changes in aPTT can occur. At the 10 mg dose used in interaction studies, fondaparinux did not significantly influence the anticoagulation activity (INR) of warfarin.

Fondaparinux does not cross-react with sera from patients with heparin-induced thrombocytopaenia.

Clinical studies

The fondaparinux clinical program in treatment of Venous Thromboembolism was designed to demonstrate the efficacy of fondaparinux for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Over 4874 patients were studied in controlled Phase II and III clinical studies.

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Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

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Date of first authorisation: 21 March 2002
Date of latest renewal: 21 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Glaxo Wellcome Production
1, rue de l'Abbaye
F-76960 Notre Dame de Bondeville
France

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISTION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in the June 2006 version presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.2 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 1.5 mg/0.3 ml solution for injection
Fondaparinux sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe (0.3 ml) contains 1.5 mg fondaparinux sodium.

3. LIST OF EXCIPIENTS

Also contains: sodium chloride, water for injections, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 2 pre-filled syringes with an automatic safety system
Solution for injection, 7 pre-filled syringes with an automatic safety system
Solution for injection, 10 pre-filled syringes with an automatic safety system
Solution for injection, 20 pre-filled syringes with an automatic safety system

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/207/005- 2 pre-filled syringes
EU/1/02/207/006 - 7 pre-filled syringes
EU/1/02/207/007 - 10 pre-filled syringes
EU/1/02/207/008 - 20 pre-filled syringes

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Quixidar 1.5 mg/0.3 ml injection
fondaparinux Na

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 2.5 mg/0.5 ml solution for injection
Fondaparinux sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe (0.5 ml) contains 2.5 mg fondaparinux sodium.

3. LIST OF EXCIPIENTS

Also contains: sodium chloride, water for injections, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 2 pre-filled syringes with an automatic safety system
Solution for injection, 7 pre-filled syringes with an automatic safety system
Solution for injection, 10 pre-filled syringes with an automatic safety system
Solution for injection, 20 pre-filled syringes with an automatic safety system

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/207/001 - 2 pre-filled syringes
EU/1/02/207/002 - 7 pre-filled syringes
EU/1/02/207/003 - 10 pre-filled syringes
EU/1/02/207/004 - 20 pre-filled syringes

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Quixidar 2.5 mg/0.5 ml injection
fondaparinux Na

SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 5 mg/0.4 ml solution for injection
Fondaparinux sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe (0.4 ml) contains 5 mg fondaparinux sodium.

3. LIST OF EXCIPIENTS

Also contains: sodium chloride, water for injections, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 2 pre-filled syringes with an automatic safety system
Solution for injection, 7 pre-filled syringes with an automatic safety system
Solution for injection, 10 pre-filled syringes with an automatic safety system
Solution for injection, 20 pre-filled syringes with an automatic safety system

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Body weight below 50 kg

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/207/009- 2 pre-filled syringes
EU/1/02/207//010 - 7 pre-filled syringes
EU/1/02/207/011 - 10 pre-filled syringes
EU/1/02/207/018 - 20 pre-filled syringe

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Quixidar 5 mg/0.4 ml injection
fondaparinux Na

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 7.5 mg/0.6 ml solution for injection
Fondaparinux sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe (0.6 ml) contains 7.5 mg fondaparinux sodium.

3. LIST OF EXCIPIENTS

Also contains: sodium chloride, water for injections, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 2 pre-filled syringes with an automatic safety system
Solution for injection, 7 pre-filled syringes with an automatic safety system
Solution for injection, 10 pre-filled syringes with an automatic safety system
Solution for injection, 20 pre-filled syringes with an automatic safety system

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Body weight 50-100 kg

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/207/012- 2 pre-filled syringes
EU/1/02/207/013 - 7 pre-filled syringes
EU/1/02/207/014 - 10 pre-filled syringes
EU/1/02/207/019 - 20 pre-filled syringe

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Quixidar 7.5 mg/0.6 ml injection
fondaparinux Na

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Quixidar 10 mg/0.8 ml solution for injection
Fondaparinux sodium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe (0.8 ml) contains 10 mg fondaparinux sodium.

3. LIST OF EXCIPIENTS

Also contains: sodium chloride, water for injections, hydrochloric acid, sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection, 2 pre-filled syringes with an automatic safety system
Solution for injection, 7 pre-filled syringes with an automatic safety system
Solution for injection, 10 pre-filled syringes with an automatic safety system
Solution for injection, 20 pre-filled syringes with an automatic safety system

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Body weight above 100 kg

8. EXPIRY DATE

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd
Greenford
Middlesex
UB6 0NN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/207/015 - 2 pre-filled syringes
EU/1/02/207/016 - 7 pre-filled syringes
EU/1/02/207/017 - 10 pre-filled syringes
EU/1/02/207/020 - 20 pre-filled syringe

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Quixidar 10 mg/0.8 ml injection
fondaparinux Na

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Quixidar 1.5 mg/0.3 ml solution for injection
fondaparinux sodium

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you personally. Do not pass it on to others. It may harm them, even if their symptoms seem to be the same as yours.
- If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT QUIXIDAR IS AND WHAT IT IS USED FOR

Quixidar is a medicine that helps prevent blood clots from forming in the blood vessels (*an antithrombotic agent*).

Quixidar contains a synthetic substance called fondaparinux sodium. This stops a clotting factor Xa ("ten-A") from working in the blood, and so prevents unwanted blood clots (*thromboses*) from forming in the blood vessels.

Quixidar is used to:
- prevent the formation of blood clots in the blood vessels of the legs or lungs after orthopaedic surgery (such as hip or knee surgery) or abdominal surgery
- prevent the formation of blood clots during and shortly after a period of restricted mobility due to acute illness**.**

2. BEFORE YOU USE QUIXIDAR

Do not use Quixidar:
- **if you are allergic** (*hypersensitive*) to fondaparinux sodium or to any of the other ingredients of Quixidar
- **if you are bleeding excessively**
- **if you have a bacterial heart infection**
- **if you have very severe kidney disease.**

→ **Tell your doctor** if you think any of these applies to you. If they do, you must **not** use Quixidar.

Take special care with Quixidar:
Your doctor needs to know before you take Quixidar:
- **if you have a risk of uncontrolled bleeding** (*haemorrhage*) including:
  - **stomach ulcer**
  - **bleeding disorders**
  - recent **bleeding into the brain** (*intracranial bleeding*)
  - **recent surgery** on the brain, spine or eye

- **if you have severe liver disease**
- **if you have kidney disease**
- **if you are 75 years old or older**
- **if you weigh less than 50 kg**.

→ **Tell your doctor** if any of these applies to you.

Children
Quixidar has not been tested in children and adolescents under the age of 17 years.

Using other medicines
Tell your doctor or pharmacist if you are taking any other medicines, or have recently taken any. This includes medicines you bought without a prescription. Some other medicines may affect the way that Quixidar works or be affected by Quixidar.

Pregnancy and breast feeding
Quixidar should not be prescribed to pregnant women unless clearly necessary. Breast-feeding is not recommended during treatment with Quixidar. If you are **pregnant**, think you might be, or if you are **breast feeding:**
→ **tell your doctor or pharmacist.**

Important information about some of the ingredients of Quixidar
This medicinal product contains less than 23 mg of sodium in each dose and therefore is essentially sodium-free.

3. HOW TO USE QUIXIDAR

Always use Quixidar exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is 2.5 mg once a day, injected at about the same time each day.

If you have kidney disease, the dose may be reduced to 1.5 mg once a day.

How is Quixidar given
- Quixidar is given by injection under the skin (*subcutaneously*) into a skin fold of the lower abdominal area. The syringes are pre-filled with the exact dose you need. There are different syringes for the 2.5 mg and 1.5 mg doses. **For step-by-step instructions please see over the page**
- Do **not** inject Quixidar into muscle.

How long should Quixidar be taken for
You should continue Quixidar treatment for as long as your doctor has told you, since Quixidar prevents development of a serious condition.

If you inject too much Quixidar
Contact your doctor or pharmacist for advice as soon as possible because of the increased risk of bleeding.

If you forget to take Quixidar
- **Take the dose as soon as you remember. Do not inject a double dose to make up for a forgotten dose**.
- **If you are not sure what to do**, ask your doctor or pharmacist.

Don't stop using Quixidar without advice
If you stop the treatment before your doctor told you to, you are at risk of developing a blood clot in a vein of your leg or lung. **Contact your doctor or pharmacist before stopping.**

If you have any further questions about how to use this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Quixidar can cause side effects, although not everybody gets them.

Common side effects
These may affect **more than 1 in 100 people** treated with Quixidar.
- **bleeding** (for example from an operation site, an existing stomach ulcer, nosebleed, gums)
- **anaemia** (a reduction in the number of red blood cells).

Uncommon side effects
These may affect **up to 1 in 100 people** treated with Quixidar.
- bruising or swelling (*oedema*)
- feeling sick or being sick (*nausea or vomiting*)
- chest pain
- breathlessness
- rash or itchy skin
- oozing from operation wound site
- fever
- reduction or increase in the number of platelets (blood cells necessary for blood clotting)
- increase in some chemicals (*enzymes*) produced by the liver.

Rare side effects
These may affect **up to 1 in every 1000 people** treated with Quixidar.
- allergic reaction
- internal bleeding in the brain or abdomen
- anxiety or confusion
- headache
- fainting or dizziness, low blood pressure
- drowsiness or tiredness
- flushing
- coughing
- leg pain or stomach pain
- diarrhoea or constipation
- indigestion
- wound infection
- increase in bilirubin (a substance produced by the liver) in the blood
- reduction in potassium in your blood.

If you get side effects
→ **Tell your doctor or pharmacist if any of the side effects gets severe or troublesome**, or if you notice any side effects not listed in this leaflet.

5. HOW TO STORE QUIXIDAR

- Keep out of the reach and sight of children
- Do not freeze
- Quixidar does not need to be kept in the fridge.

Do not use Quixidar:
- after the expiry date stated on the label and carton

- if you notice any particles in the solution, or if the solution is discoloured
- if you notice that the syringe is damaged
- if you have opened a syringe and you do not use it straightaway.

Disposal of syringes
Medicines and syringes should **not** be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Quixidar contains
- The active substance is 1.5 mg fondaparinux sodium in 0.3 ml solution for injection

- The other ingredient(s) are sodium chloride, water for injections, and hydrochloric acid and/or sodium hydroxide to adjust the pH.

Quixidar does not contain any animal products.

What Quixidar looks like and contents of the pack
Quixidar is a clear and colourless solution for injection. It is supplied in a pre-filled, single-use syringe fitted with an automatic safety system to help prevent needle stick injuries after use. It is available in packs of 2, 7, 10 and 20 pre-filled syringes (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer

Marketing Authorization Holder:
Glaxo Group Ltd, Greenford, Middlesex, UB6 0NN, United Kingdom

Manufacturer:
Glaxo Wellcome Production, 1 rue de l'Abbaye, F-76960 Notre Dame de Bondeville, France.

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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customercontactuk@gsk.com

Parts of the safety syringe

① Rigid needle guard

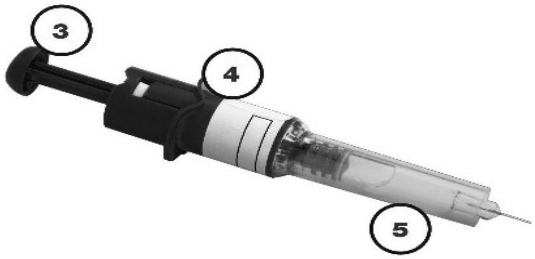
② Cap

③ Plunger

④ Finger-grip

⑤ Security sleeve

Syringe BEFORE USE



Syringe AFTER USE

STEP BY STEP GUIDE TO USING QUIXIDAR

Instructions for use

1. **Wash your hands thoroughly** with soap and water and dry them with a towel.

2. **Remove the syringe from the carton and check that:**
   - the expiry date has not passed
   - the solution is clear and colourless and doesn't contain particles
   - the syringe has not been opened or damaged

3. Sit or lie down in a comfortable position.
Choose a place in the lower abdominal (tummy) area, at least 5 cm below your belly button (picture **A**).
Alternate the left and right side of the lower abdominal area at each injection. This will help to reduce the discomfort at the injection site.
If injecting in the lower abdominal area is not possible, ask your nurse or doctor for advice.

Picture A

4. Clean the injection area with an alcohol wipe.

5. Hold the body of the syringe firmly in one hand.
Remove the cap that protects the plunger by pulling it off (picture **B**).
Discard the plunger cap.

Picture B

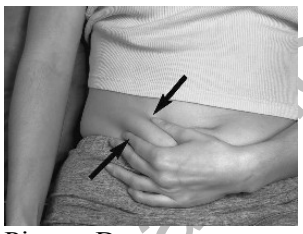
6. Remove the needle guard, by first twisting it and then pulling it in a straight line away from the body of the syringe (picture **C**).
Discard the needle guard.


Picture C

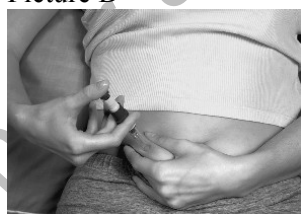
Important note

- **Do not touch the needle** or allow it to touch any surface before the injection.
- It is normal to see a small air bubble in this syringe. **Do not try to remove this air bubble before making the injection** - you may lose some of the medicine if you do.

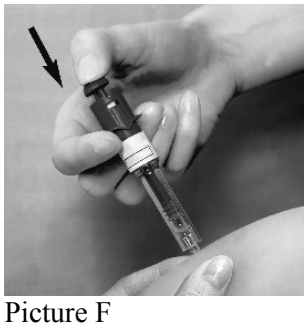
7. Gently pinch the skin that has been cleaned to make a fold. Hold the fold between the thumb and the forefinger during the entire injection (picture **D**).


Picture D

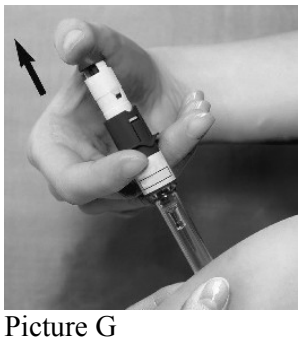
8. Hold the syringe firmly by the finger grip.
Insert the full length of the needle at right angles into the skin fold (picture **E**).


Picture E

9. Inject ALL of the contents of the syringe by pressing down on the plunger as far as it goes. This will activate the automatic needle protection system (picture **F**).


Picture F

10. Release the plunger and the needle will automatically withdraw from the skin and go back into the security sleeve where it will be locked permanently (picture **G**).


Picture G

Do not dispose of the used syringe in the household waste. Dispose of it as your doctor or pharmacist has instructed.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Quixidar 2.5 mg/0.5 ml solution for injection
fondaparinux sodium

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you personally. Do not pass it on to others. It may harm them, even if their symptoms seem to be the same as yours.
- If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT QUIXIDAR IS AND WHAT IT IS USED FOR

Quixidar is a medicine that helps prevent blood clots from forming in the blood vessels (*an antithrombotic agent*).

Quixidar contains a synthetic substance called fondaparinux sodium. This stops a clotting factor Xa ("ten-A") from working in the blood, and so prevents unwanted blood clots (*thromboses*) from forming in the blood vessels.

Quixidar is used to:
- prevent the formation of blood clots in the blood vessels of the legs or lungs after orthopaedic surgery (such as hip or knee surgery) or abdominal surgery
- prevent the formation of blood clots during and shortly after a period of restricted mobility due to acute illness
- treat some types of heart attack and severe angina (pain caused by narrowing of the arteries in the heart).

2. BEFORE YOU USE QUIXIDAR

Do not use Quixidar:
- **if you are allergic** (*hypersensitive*) to fondaparinux sodium or to any of the other ingredients of Quixidar
- **if you are bleeding excessively**
- **if you have a bacterial heart infection**
- **if you have very severe kidney disease**.

→ **Tell your doctor** if you think any of these applies to you. If they do, you must **not** use Quixidar.

Take special care with Quixidar:
Your doctor needs to know before you take Quixidar:

- **if you have a risk of uncontrolled bleeding** (*haemorrhage*) including:
  - **stomach ulcer**
  - **bleeding disorders**
  - recent **bleeding in the brain** (*intracranial bleeding*)
  - **recent surgery** on the brain, spine or eye
- **if you have severe liver disease**
- **if you have kidney disease**
- **if you are 75 years old or older**
- **if you weigh less than 50 kg.**

→ **Tell your doctor** if any of these applies to you.

Children
Quixidar has not been tested in children and adolescents under the age of 17 years.

Using other medicines
Tell your doctor or pharmacist if you are taking any other medicines, or have recently taken any. This includes medicines you bought without a prescription. Some other medicines may affect the way that Quixidar works or be affected by Quixidar.

Pregnancy and breast feeding
Quixidar should not be prescribed to pregnant women unless clearly necessary. Breast-feeding is not recommended during treatment with Quixidar. If you are **pregnant**, think you might be, or if you are **breast-feeding**:
→ **tell your doctor or pharmacist**.

Important information about some of the ingredients of Quixidar
This medicinal product contains less than 23 mg of sodium in each dose and therefore is essentially sodium-free.

3. HOW TO USE QUIXIDAR

Always use Quixidar exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is 2.5 mg once a day, injected at about the same time each day.

If you have kidney disease, the dose may be reduced to 1.5 mg once a day.

How Quixidar is given

- Quixidar is given by injection under the skin (*subcutaneously*) into a skin fold of the lower abdominal area. The syringes are pre-filled with the exact dose you need. There are different syringes for the 2.5 mg and 1.5 mg doses. **For step-by-step instructions please see over the page**. To treat some types of heart attack, a health professional may give the first dose into a vein (*intravenously*).
- Do **not** inject Quixidar into muscle.

How long Quixidar should be taken for
You should continue Quixidar treatment for as long as your doctor has told you, since Quixidar prevents development of a serious condition.

If you inject too much Quixidar
Contact your doctor or pharmacist for advice as soon as possible, because of the increased risk of bleeding.

If you forget to take Quixidar

- **Take the dose as soon as you remember. Do not inject a double dose to make up for a forgotten dose**.
- **If you are not sure what to do**, ask your doctor or pharmacist.

Don't stop using Quixidar without advice

If you stop the treatment before your doctor told you to, you are at risk of developing a blood clot in a vein of your leg or lung. **Contact your doctor or pharmacist before stopping**.

If you have any further questions about how to use this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Quixidar can cause side effects, although not everybody gets them.

Common side effects

These may affect **more than 1 in 100 people** treated with Quixidar.

- **bleeding** (for example from an operation site, an existing stomach ulcer, nosebleed, gums)
- **anaemia** (a reduction in the number of red blood cells)

Uncommon side effects

These may affect **up to 1 in 100 people** treated with Quixidar.

- bruising or swelling (*oedema*)
- feeling sick or being sick (*nausea* or *vomiting*)
- chest pain
- breathlessness
- rash or itchy skin
- oozing from operation wound site
- fever
- reduction or increase in the number of platelets (blood cells necessary for blood clotting)
- increase in some chemicals (*enzymes*) produced by the liver.

Rare side effects

These may affect **up to 1 in 1000 people** treated with Quixidar.

- allergic reaction
- internal bleeding in the brain or abdomen
- anxiety or confusion
- headache
- fainting or dizziness, low blood pressure
- drowsiness or tiredness
- flushing
- coughing
- leg pain or stomach pain
- diarrhoea or constipation
- indigestion
- wound infection
- increase in bilirubin (a substance produced by the liver) in the blood
- reduction in potassium in your blood

If you get side effects

→ **Tell your doctor or pharmacist if any of the side effects gets severe or troublesome**, or if you notice any side effects not listed in this leaflet**.**

5. HOW TO STORE QUIXIDAR

- Keep out of the reach and sight of children
- Do not freeze
- Quixidar does not need to be kept in a fridge.

Do not use Quixidar:
- after the expiry date stated on the label and carton
- if you notice any particles in the solution, or if the solution is discoloured
- if you notice that the syringe is damaged
- if you have opened a syringe and you do not use it straightaway.

Disposal of syringes:
Medicines and syringes should **not** be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Quixidar contains
- The active substance is 2.5 mg fondaparinux sodium in 0.5 ml solution for injection

- The other ingredients are sodium chloride, water for injections, and hydrochloric acid and/or sodium hydroxide to adjust the pH.

Quixidar does not contain any animal products.

What Quixidar looks like and contents of the pack
Quixidar is a clear and colourless solution for injection. It is supplied in a pre-filled, single-use syringe fitted with an automatic safety system to help prevent needle stick injuries after use. It is available in packs of 2, 7, 10 and 20 pre-filled syringes (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer

Marketing Authorization Holder:
Glaxo Group Ltd, Greenford, Middlesex, UB6 0NN, United Kingdom

Manufacturer:
Glaxo Wellcome Production, 1 rue de l'Abbaye, F-76960 Notre Dame de Bondeville, France.

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Parts of the safety syringe

① Rigid needle guard

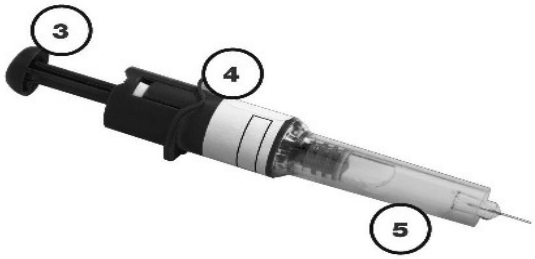
② Cap

③ Plunger

④ Finger-grip

⑤ Security sleeve

Syringe BEFORE USE



Syringe AFTER USE

STEP BY STEP GUIDE TO USING QUIXIDAR

Instructions for use

1. **Wash your hands thoroughly** with soap and water and dry them with a towel.

2. **Remove the syringe from the carton and check that:**
   - the expiry date has not passed
   - the solution is clear and colourless and doesn't contain particles
   - the syringe has not been opened or damaged

3. Sit or lie down in a comfortable position.
Choose a place in the lower abdominal (tummy) area, at least 5 cm below your belly button (picture **A**).
Alternate the left and right side of the lower abdominal area at each injection. This will help to reduce the discomfort at the injection site.
If injecting in the lower abdominal area is not possible, ask your nurse or doctor for advice.

Picture A

4. Clean the injection area with an alcohol wipe.

5. Hold the body of the syringe firmly in one hand.
Remove the cap that protects the plunger by pulling it off (picture **B**).
Discard the plunger cap.

Picture B

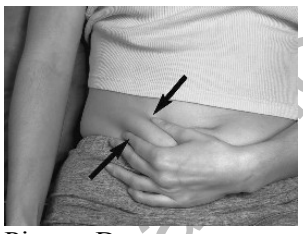
6. Remove the needle guard, by first twisting it and then pulling it in a straight line away from the body of the syringe (picture **C**).
Discard the needle guard.


Picture C

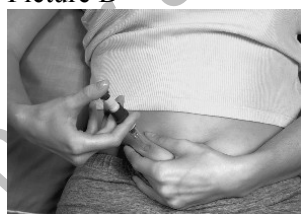
Important note

- **Do not touch the needle** or allow it to touch any surface before the injection.
- It is normal to see a small air bubble in this syringe. **Do not try to remove this air bubble before making the injection** - you may lose some of the medicine if you do.

7. Gently pinch the skin that has been cleaned to make a fold. Hold the fold between the thumb and the forefinger during the entire injection (picture **D**).


Picture D

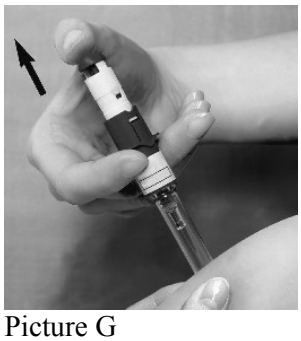
8. Hold the syringe firmly by the finger grip.
Insert the full length of the needle at right angles into the skin fold (picture **E**).


Picture E

9. Inject ALL of the contents of the syringe by pressing down on the plunger as far as it goes. This will activate the automatic needle protection system (picture **F**).


Picture F

10. Release the plunger and the needle will automatically withdraw from the skin and go back into the security sleeve where it will be locked permanently (picture **G**).


Picture G

Do not dispose of the used syringe in the household waste. Dispose of it as your doctor or pharmacist has instructed.

PACKAGE LEAFLET

Quixidar 5 mg/0.4 ml solution for injection.
Quixidar 7.5 mg/0.6 ml solution for injection
Quixidar 10 mg/0.8 ml solution for injection
Fondaparinux sodium

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you personally. Do not pass it on to others. It may harm them, even if their symptoms seem to be the same as yours.
- If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT QUIXIDAR IS AND WHAT IT IS USED FOR

Quixidar is a medicine that treats or helps to prevent blood clots from forming in the blood vessels (*an antithrombotic agent*).

Quixidar contains a synthetic substance called fondaparinux sodium. This stops a clotting factor Xa ("ten-A") from working in the blood, and so prevents unwanted blood clots (*thromboses*) from forming in the blood vessels.

Quixidar is used to treat patients with a blood clot in the blood vessels of their legs (*deep vein thrombosis*) **and/or lungs** (*pulmonary embolism*).

2. BEFORE YOU USE QUIXIDAR

Do not use Quixidar:
- **if you are allergic** (*hypersensitive*) to fondaparinux sodium or to any of the other ingredients of Quixidar
- **if you are bleeding excessively**
- **if you have a bacterial heart infection**
- **if you have severe kidney disease**.

→ **Tell your doctor** if you think any of these applies to you. If they do, you must **not** use Quixidar.

Take special care with Quixidar:
Your doctor needs to know before you take Quixidar:
- **if you have a risk uncontrolled bleeding** (*haemorrhage*) including:
  - **stomach ulcer**
  - **bleeding disorders**
  - recent **bleeding into the brain** (*intracranial bleeding*)
  - **recent surgery** on the brain, spine or eye
- **if you have severe liver disease**
- **if you have kidney disease**

- **if you are 75 years old or older.**

→ **Tell your doctor** if any of these applies to you.

Children
Quixidar has not been tested in children and adolescents under the age of 17 years.

Using other medicines
Tell your doctor or pharmacist if you are taking any other medicines, or have recently taken any. This includes medicines you bought without a prescription. Some other medicines may affect the way that Quixidar works or be affected by Quixidar.

Pregnancy and breast feeding
Quixidar should not be prescribed to pregnant women unless clearly necessary. Breast-feeding is not recommended during treatment with Quixidar. If you are **pregnant**, think you might be, or if you are **breast feeding:**
→ **tell your doctor or pharmacist.**

Important information about some of the ingredients of Quixidar
This medicinal product contains less than 23 mg of sodium in each dose and therefore is essentially sodium-free.

3. HOW TO USE QUIXIDAR

Always use Quixidar exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your weight	**Usual dose**
Below 50 kg	5 mg once a day
Between 50 kg and 100 kg	7.5 mg once a day
Over 100 kg	10 mg once a day. This dose may be reduced to 7.5 mg once a day if you have moderate kidney disease.

You should inject at about the same time each day.

How Quixidar is given
- Quixidar is given by injection under the skin (*subcutaneously*) into a skin fold of the lower abdominal area. They syringes are pre-filled with the exact dose you need. There are different syringes for the 5 mg, 7.5 mg and 10 mg doses. **For step-by-step instructions please see over the page**.
- Do **not** inject Quixidar into muscle.

How long should Quixidar be taken for
You should continue Quixidar treatment for as long as your doctor has told you, since Quixidar prevents development of a serious condition.

If you inject too much Quixidar
Contact your doctor or pharmacist for advice as soon as possible, because of the increased risk of bleeding.

If you forget to take Quixidar
- **Take the dose as soon as you remember. Do not inject a double dose to make up for a forgotten dos**e.
- **If you are not sure what to do**, ask your doctor or pharmacist.

Don't stop using Quixidar without advice
If you stop the treatment before your doctor told you to, the blood clot may not be treated properly and you may also be at risk of developing a new blood clot in a vein of your leg or in the lung. **Contact your doctor or pharmacist before stopping**.

If you have any further questions about how to use this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Quixidar can cause side effects, although not everybody gets them.

Common side effects
These may affect **more than 1 in 100 people** treated with Quixidar.
- **bleeding** (for example from an operation site, an existing stomach ulcer, nosebleed, bruising)

Uncommon side effects
These may affect **up to 1 in 100 people** treated with Quixidar.
- swelling (*oedema*)
- headache
- pain
- feeling sick or being sick (*nausea or vomiting*)
- low number of red blood cells (*anaemia*)
- low number of platelets (blood cells necessary for blood clotting)
- increase in some chemical (*enzymes*) produced by the liver

Rare side effects
These may affect **up to 1 in every 1000 people** treated with Quixidar.
- allergic reaction
- internal bleeding in the brain, liver or abdomen
- rash
- dizziness
- pain and swelling at injection site
- high number of platelets (blood cells necessary for blood clotting)
- increase in the amount of non-protein nitrogen in the blood

If you get side effects
→ **Tell your doctor or pharmacist if any of the side effects gets severe or troublesome**, or if you notice any side effects not listed in this leaflet.

5. HOW TO STORE QUIXIDAR
- Keep out of the reach and sight of children
- Do not freeze
- Quixidar does not have to be kept in the fridge.

Do not use Quixidar:
- after the expiry date stated on the label and carton
- if you notice any particles in the solution, or if the solution is discoloured
- if you notice that the syringe is damaged
- if you have opened a syringe and you do not use it straightaway.

Disposal of syringes:
Medicines and syringes should **not** be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Quixidar contains
The active substance is:

- 5 mg fondaparinux sodium in 0.4 ml solution for injection
- 7.5 mg fondaparinux sodium in 0.6 ml solution for injection
- 10 mg fondaparinux sodium in 0.8 ml solution for injection

The other ingredient(s) are sodium chloride, water for injections, and hydrochloric acid and/or sodium hydroxide to adjust the pH.

Quixidar does not contain any animal products.

What Quixidar looks like and contents of the pack
Quixidar is a clear and colourless to slightly yellow solution for injection. It is supplied in a pre-filled syringe fitted with an automatic safety system to help prevent needle stick injuries after use.
It is available in packs of 2, 7, 10 and 20 pre-filled syringes (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer

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This leaflet was last approved in

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Parts of the safety syringe

① Rigid needle guard

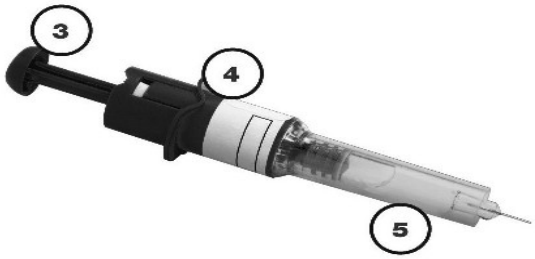
② Cap

③ Plunger

④ Finger-grip

⑤ Security sleeve

Syringe BEFORE USE



Syringe AFTER USE

STEP BY STEP GUIDE TO USING QUIXIDAR

1. **Wash your hands thoroughly** with soap and water and dry them with a towel.

2. **Remove the syringe from the carton and check that:**
   - the expiry date has not passed
   - the solution is clear and colourless to slightly yellow and doesn't contain particles
   - the syringe has not been opened or damaged

3. Sit or lie down in a comfortable position.
Choose a place in the lower abdominal (tummy) area, at least 5 cm below your belly button (picture **A**).
Alternate the left and right side of the lower abdominal area at each injection. This will help to reduce the discomfort at the injection site.
If injecting in the lower abdominal area is not possible, ask your nurse or doctor for advice.

Picture A

4. Clean the injection area with an alcohol wipe.

5. Hold the body of the syringe firmly in one hand.
Remove the cap that protects the plunger by pulling it off (picture **B**).
Discard the plunger cap.

Picture B

6. Remove the needle guard, by first twisting it and then pulling it in a straight line away from the body of the syringe (picture **C**).

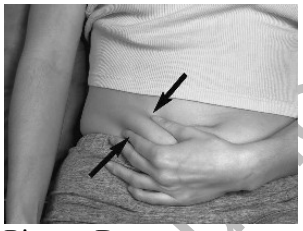
Discard the needle guard.

Important note

- **Do not touch the needle** or allow it to touch any surface before the injection.
- It is normal to see a small air bubble in this syringe. **Do not try to remove this air bubble before making the injection** - you may lose some of the medicine if you do.

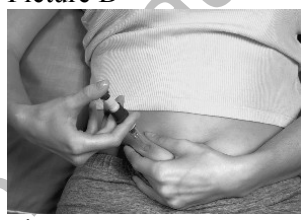
Picture C

7. Gently pinch the skin that has been cleaned to make a fold. Hold the fold between the thumb and the forefinger during the entire injection (picture **D**).



Picture D

8. Hold the syringe firmly by the finger grip.
Insert the full length of the needle at right angles into the skin fold (picture **E**).

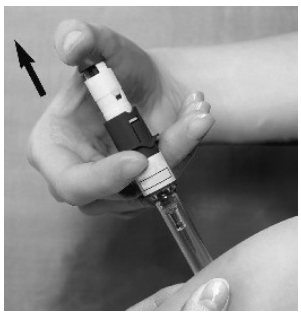


Picture E

9. Inject ALL of the contents of the syringe by pressing down on the plunger as far as it goes. This will activate the automatic needle protection system (picture **F**).

Picture F

10. Release the plunger and the needle will automatically withdraw from the skin and go back into the security sleeve where it will be locked permanently (picture **G**).



Picture G

Do not dispose of the used syringe in the household waste. Dispose of it as your doctor or pharmacist has instructed.