SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Exembol 1 mg/ml Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution for infusion contains 1 mg argatroban monohydrate.

One vial with 50 ml solution for infusion contains 50 mg argatroban monohydrate.

Excipients: 1 ml of solution for infusion contains 4 mg ethanol (0.5% by volume), 3 mg sorbitol (E420 i) and 9 mg sodium chloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion.

Clear colourless to pale yellow solution.

The pH of the intravenous solution is 5.0 – 8.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anticoagulation in adult patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic therapy.

The diagnosis should be confirmed by the HIPAA (heparin induced platelet activation assay) or an equivalent test. However, such confirmation must not delay the start of treatment.

4.2 Posology and method of administration

Paediatric population
Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.
Initial Dosage

Treatment with Exembol should be initiated under the guidance of a physician with experience in coagulation disorders.
The initial dosage in adult patients without hepatic impairment in HIT type II is 2 microgram/kg/min, administered as a continuous infusion (see Method of Administration).
Before Exembol is administered, heparin therapy should be discontinued and a baseline aPTT value obtained.
Standard recommendations
Monitoring:
In general, therapy with Exembol is monitored using the activated partial thromboplastin time (aPTT).
Tests of anticoagulant effects (including the aPTT) attain steady-state levels typically within 1-3 hours following initiation of Exembol.
The target range for steady-state aPTT is 1.5-3.0 times the initial baseline value, but not exceeding 100 seconds.
Dose adjustment may be required to attain the target aPTT (see Dose Modifications). aPTT should be checked two hours after the start of the infusion to confirm that the aPTT is within the desired therapeutic range. Thereafter, the aPTT should be monitored at least once per day.
Dose modifications:
After the initial dose of Exembol, the dose can be adjusted based on the clinical course until the steady-state aPTT is within the desired therapeutic range (1.5 to 3.0 times the initial baseline value but not exceeding 100 seconds). In case of an elevated aPTT (greater than 3 times baseline or 100 seconds), the infusion should be discontinued until the aPTT is within the desired range of 1.5 to 3 times baseline (typically within 2 hours of discontinuation of infusion), and the infusion restarted at one half of the previous infusion rate. The aPTT should be checked again after 2 hours.
The maximum recommended dose is 10 microgram/kg/min. The maximum recommended duration of treatment is 14 days, although there is limited clinical experience of administration for longer periods (see section 5.1).

Standard dosing schedule Initial Infusion Rate 2 mcg/kg/min			**Critically III/Hepatically impaired patients Initial infusion rate 0.5 mcg/kg/min**	
aPTT (s)	**Infusion Rate Change**	**Next aPTT**	**Infusion Rate Change**	**Next aPTT**
< 1.5 times baseline	Increase by 0.5 mcg/kg/min.	2 hours	Increase by 0.1 mcg/kg/min.	4 hours
1.5-3.0 times baseline (not exceeding 100 s)	No change.	2 hours; after 2 consecutive aPTT's within target range, check at least once per day	No change.	4 hours; after 2 consecutive aPTT's within target range, check at least once per day.
> 3.0 times	Stop	2 hours.	Stop infusion	4 hours.

baseline or > 100 s	infusion until the aPTT is 1.5-3.0 times baseline. Resume at half of the previous infusion rate.		until the aPTT is 1.5-3.0 times baseline. Resume at half of the previous infusion rate.	

Method of administration
Exembol is supplied as a 1 mg/ml ready to use solution for intravenous infusion
(50 mg/50 ml (see section 6.6). It is recommended for use with a syringe driver to control the rate of administration.
Standard infusion rates for the 2 microgram/kg/min recommended initial dosage (1 mg/ml concentration) are detailed in the table below. The standard infusion rates for patients with moderate hepatic impairment (Child-Pugh Class B), after cardiac surgery and critically ill patients with a starting infusion rate of 0.5 microgram/kg/min are also detailed in the table below:

Body Weight (kg)	**Infusion Rate (ml/hr)**	
	2 microgram/kg/min	**0.5 microgram/kg/min**
50	6	1.5
60	7	1.8
70	8	2.1
80	10	2.4
90	11	2.7
100	12	3.0
110	13	3.3
120	14	3.6
130	16	3.9
140	17	4.2

Additional Information on Special Populations:
Older people
The standard initial dosage recommendations for use in adults are applicable to elderly patients.
Paediatric population
Limited data from a prospective clinical study in 18 children (neonates to 16 years old) and published data is available. The safe and effective dose or the effective target range for aPTT or activated clotting time (ACT) of Exembol has not been clearly established in this patient population. Currently available data are described in Section 5.1 and 5.2 but no recommendation on a posology can be made.
Renal impairment
The standard initial dosage recommendations for use in adults are applicable to patients with renal impairment (see section 5.2).

Limited data is available from the use of Exembol in haemodialysis. Based on the data, therapy could be initiated with an initial bolus (250 microgram/kg) followed by continuous infusion of 2 microgram/kg/min. The infusion is stopped 1 hour before the end of the procedure. The target ACT range is 170-230 seconds (measured using the Haemotec device).
In patients that are already being treated with Exembol no bolus dose is required. Exembol clearance by high flux membranes used during haemodialysis and continuous venovenous haemofiltration was clinically insignificant.

Hepatic impairment

For patients with moderate hepatic impairment (Child-Pugh Class B), an initial dose of 0.5 microgram/kg/min is recommended (see section 4.4 and section 5.2). The aPTT should be monitored closely and the dosage should be adjusted as indicated clinically. Exembol is contra-indicated in patients with severely impaired liver function.

Patients with HIT Type II after cardiac surgery and critically ill patients

Limited data is available from the use of Exembol in patients with HIT Type II after cardiac surgery and critically ill patients / intensive care unit (ICU) patients with (multiple) organ system failure. Based on the data therapy could be initiated with a starting infusion rate of 0.5 microgram/kg/min (maximum 10 microgram/kg/min) and adjusted to the target aPTT range of 1.5-3.0 times baseline value (not exceeding 100 seconds).
In critically ill/ICU patients with severe (multiple) organ failure (as assessed by SOFA-II APACHE-II or comparable scores) a reduced maintenance dose is recommended.
The clinical status of the patient, especially acute changes in hepatic function, should be taken into account and the infusion rate should be carefully adjusted to maintain the aPTT in the desired range.
An increase in the frequency of monitoring is recommended to ensure the target aPTT values are achieved and maintained.

Patients with HIT Type II undergoing percutaneous coronary intervention (PCI)

Limited data is available from the use of Exembol in patients with HIT Type II undergoing percutaneous coronary intervention. Based on the data, when there is no alternative, therapy could be initiated with a bolus dose of 350 microgram/kg over 3 to 5 minutes followed by an infusion dose of 25 microgram/kg/min. ACT should be checked 5 to 10 minutes after the bolus dose is completed. The procedure may proceed if the ACT is greater than 300 sec. If the ACT is below 300 sec, an additional bolus dose of 150 microgram/kg should be administered, the infusion rate be increased to 30 microgram/kg/min, and the ACT should be checked 5 to 10 minutes later. If the ACT is higher than 450 sec, the infusion rate should be decreased to 15 microgram/kg/min and ACT values be checked 5 to 10 minutes later. Once a therapeutic ACT between 300 to 450 sec has been achieved, the infusion dose should be continued for the duration of the procedure. ACT measurements were recorded using both Haemotec and Haemochrom devices.
The efficacy and safety of Exembol use in combination with GPIIb/IIIa inhibitors has not been established.

Body Weight (kg)	For ACT 300-450 seconds Initial Dosage 25 mcg/kg/min			If ACT <300 seconds Dosage Adjustment† 30 mcg/kg/min			If ACT >450 seconds Dosage Adjustment 15 mcg/kg/min	
	Bolus Dose (mcg)	Infusion Dose (mcg/min)	Infusion Rate (ml/hr)	Bolus Dose (mcg)	Infusion Dose (mcg/min)	Infusion Rate (ml/hr)	Infusion Dose (mcg/min)	Infusion Rate (ml/hr)
50	17500	1250	75	7500	1500	90	750	45
60	21000	1500	90	9000	1800	108	900	54
70	24500	1750	105	10500	2100	126	1050	63
80	28000	2000	120	12000	2400	144	1200	72
90	31500	2250	135	13500	2700	162	1350	81
100	35000	2500	150	15000	3000	180	1500	90
110	38500	2750	165	16500	3300	198	1650	99
120	42000	3000	180	18000	3600	216	1800	108
130	45500	3250	195	19500	3900	234	1950	117
140	49000	3500	210	21000	4200	252	2100	126

NOTE: 1 mg/ml = 1000 microgram (mcg)/ml

† Additional IV bolus dose of 150 mcg/kg should be administered if ACT <300 seconds.

Specific dosing information on patients with hepatic impairment undergoing PCI is not available. Therefore, the use of Exembol for treatment of patients with hepatic impairment requiring PCI is not recommended.

<u>Recommendations for use in patients scheduled for a conversion to oral anticoagulation</u>

Use of oral anticoagulants (of the coumarin type) should be delayed until substantial resolution of thrombocytopaenia (e.g. platelets >100 x 10^9/l) to avoid coumarin associated microvascular thrombosis and venous limb gangrene**.** The intended maintenance dose should be started with no loading dose.

Quick type PT assay	**Owren type PT assay**
In a Quick type PT assay the recommendations below should be considered: Co-administration of Exembol and oral anticoagulants of the coumarin type produces an additive effect on the INR when the Quick type PT assay is used. The INR depends on both the dose of Exembol and the International Sensitivity Index (ISI) of the thromboplastin reagent used. In general, with doses of Exembol up to 2 microgram/kg/min, Exembol can be discontinued when the INR reaches a minimum of 4 on combined therapy.	When an Owren PT type assay is used the plasma samples is considerably diluted prior to analysis and the recommendations below should be considered: *In vitro* tests indicate there is no clinically significant effect of Exembol on the INR value at a typical plasma concentration arising from a dose of around 2 microgram/kg/min. However, higher concentrations of Exembol may result in an increase of the INR values. The target value for INR on co-therapy should be as recommended for the oral anticoagulant alone i.e. 2-3.

For both the Quick and Owren type PT assays;

Co-therapy of Exembol and oral anticoagulants (of the coumarin type) is recommended for a minimum of 5 days. INR should be measured daily while Exembol and oral anticoagulants are co-administered. On co-therapy the target value for INR should be within the therapeutic range according to the type of assay used (see above) for at least 2 days before Exembol is discontinued.

The INR measurement should be repeated 4-6 hours after discontinuation of Exembol. If the repeat INR is below the desired therapeutic range, the infusion of Exembol should be resumed and the procedure repeated daily until the desired therapeutic range on oral anticoagulants alone is reached.

For doses greater than 2 microgram/kg/min, the relationship between INR on oral anticoagulants alone or INR on oral anticoagulants plus Exembol is less predictable. With such higher doses, the dose of Exembol should be temporarily reduced to 2 microgram/kg/min in order to improve the prediction of INR on oral anticoagulants alone (see above). The INR on Exembol and oral anticoagulants should be measured 4 to 6 hours after reduction of the Exembol dose.

4.3 Contraindications

Exembol is contraindicated in patients with uncontrolled bleeding. Hypersensitivity to argatroban or to any of the excipients. Severe hepatic impairment.

4.4 Special warnings and precautions for use

Exembol causes a generally increased tendency to bleeding. An unexplained fall in haematocrit, fall in blood pressure, or any other unexplained symptom should lead to consideration of a haemorrhagic event.

Exembol should be used with extreme caution in disease states and other circumstances in which there is an increased danger of haemorrhage. These include treatment for severe hypertension; diabetic retinopathy; immediately following lumbar puncture; spinal anaesthesia; major surgery, especially involving the brain, spinal cord, or eye; haematological conditions associated with increased bleeding tendencies such as congenital or acquired bleeding disorders and gastrointestinal lesions such as ulcerations.

Parenteral anticoagulants: All parenteral anticoagulants should be discontinued before administration of Exembol. When Exembol is to be started after cessation of heparin therapy, sufficient time should be allowed for the effect of heparin on the aPTT to decrease prior to start of Exembol therapy (about 1-2 hours).

Hepatic Impairment: Caution should be exercised when administering Exembol to patients with hepatic disease, by starting with a lower dose and carefully titrating until the desired level of anticoagulation is achieved (see section 4.2). Also, upon cessation of Exembol infusion in the hepatically-impaired patient, full reversal of anticoagulant effects may require longer than 4 hours due to decreased clearance of argatroban.

Laboratory Tests: Measurements of aPTT are recommended for monitoring the infusion. Although other plasma coagulation tests including prothrombin time (PT, expressed for example as the International Normalized Ratio (INR)), the activated clotting time (ACT) and thrombin time (TT) are affected by Exembol; the therapeutic ranges for these tests have not been defined. Plasma argatroban concentrations also correlate well with the anticoagulant effects.

The concomitant use of Exembol and oral anticoagulants may result in prolongation of the PT (INR) beyond that produced by oral anticoagulants alone. Refer to section 4.2 for alternative approaches for monitoring concurrent Exembol and oral anticoagulants therapy.

Ethanol: Exembol contains ethanol. A 70kg patient administered the maximum recommended daily dose (10 microgram/kg/min) would receive a dose of approximately 4g ethanol per day.

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use this medicinal product.

There is no specific antidote to Exembol.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with antiplatelet agents, thrombolytics, and other anticoagulants may increase the risk of bleeding.

*Oral anticoagulant agent*s: Pharmacokinetic drug interactions between Exembol and warfarin (7.5 mg single oral dose) have not been demonstrated. However, the concomitant use of Exembol and warfarin (5-7.5 mg initial oral dose followed by 2.5-6 mg/day orally for 6-10 days) results in an increase of the International Normalized Ratio (INR). Refer to section 4.2 for recommendations for managing the switch from Exembol to oral anticoagulation.

Thrombolytics, anti-platelet and other agents: The safety and effectiveness of Exembol with thrombolytic agents have not been established.

The risks for interaction with argatroban have not been evaluated. Caution is needed when concomitant medicinal products are commenced.

As Exembol contains ethanol, an interaction with metronidazole or disulfiram cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Exembol in pregnant women. Animal studies are insufficient with respect to reproductive toxicity, as technical issues have limited systemic exposure (see section 5.3 for results of animal studies). The increased bleeding risk with Exembol may constitute a risk in treatment during pregnancy. Exembol contains ethanol. A 70kg patient administered the maximum recommended daily dose (10 microgram/kg/min) would receive a dose of approximately 4g ethanol per day.

Exembol should be used during pregnancy only if treatment is clearly necessary.

Lactation

It is unknown whether argatroban/metabolites are excreted in human milk. Animal studies using radiolabelled argatroban have shown that radioactivity reaches greater levels in breast milk than in maternal blood. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Exembol therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on potential effects of Exembol on fertility.

4.7 Effects on ability to drive and use machines

In theory, the presence of ethanol in the formulation (200 mg per vial) may impair the patient's ability to drive or operate machinery. However, this is unlikely to be of clinical relevance in patients receiving Exembol.

4.8 Undesirable effects

Bleeding complications, as is to be expected given the pharmacological properties, constitute the main adverse events. In the clinical trials involving patients with HIT type II anticoagulated with Exembol, the incidence of major bleeds was 31/568 (5.5%) and minor bleeds 221/568 (38.9%). The incidence of major bleeds was almost three times higher in those patients in whom the aPTT level exceeded more than three times the baseline value than in those whose aPTT was within the therapeutic range. Dosage of Exembol should be adjusted to achieve a target aPTT level of 1.5-3.0 x baseline not exceeding 100 seconds (see section 4.2).

The incidence of adverse reactions in clinical trials (568 patients with HIT Type II) which are considered to be possibly related to Exembol is stated below.

Organ system	**Common (≥1/100, ≤1/10)**	**Uncommon (≥1/1000, ≤1/100)**	**Not Known (frequency cannot be estimated from the available data)**
Infections and infestations		Infection, urinary tract infection	
Blood and lymphatic system disorders	Anaemia	Coagulopathy, thrombocytopenia, leukopenia	Cerebral haemorrhage
Metabolism and nutrition disorders		Anorexia, hypoglycaemia, hyponatraemia	
Psychiatric disorders		Confusional state	
Nervous system disorders		Dizziness, headache, syncope, cerebrovascular accident, hypotonia, speech disorder	
Eye disorders		Visual disturbance	
Ear and labyrinth disorders		Deafness	
Cardiac disorders		Atrial fibrillation, tachycardia, cardiac arrest, myocardial infarction, arrhythmia supraventricular, pericardial effusion, ventricular tachycardia, hypertension, hypotension,	
Vascular disorders	Deep vein thrombosis, haemorrhage	Thrombosis, phlebitis, thrombophlebitis, thrombophlebitis leg superficial, shock, peripheral ischaemia, peripheral embolism	
Respiratory, thoracic and mediastinal disorders		Hypoxia, pulmonary embolism, dyspnoea, pulmonary haemorrhage, pleural effusion, hiccups	
Gastrointestinal disorders	Nausea	Vomiting, constipation, diarrhoea, gastritis, gastrointestinal haemorrhage, melaena, dysphagia, tongue disorder	

Organ system	Common (≥1/100, ≤1/10)	Uncommon (≥1/1000, ≤1/100)	Not Known (frequency cannot be estimated from the available data)
Hepatobiliary disorders		Hepatic function abnormal, hyperbilirubinaemia, hepatic failure, hepatomegaly, jaundice	
Skin and subcutaneous tissue disorders	Purpura	Rash, sweating increased, dermatitis bullous, alopecia, skin disorder, urticaria	
Musculoskeletal and connective tissue disorders		Muscular weakness, myalgia	
Renal and urinary disorders		Haematuria, renal insufficiency	
General disorders and administration site conditions		Pyrexia, pain, fatigue, application site reaction, injection site reaction, oedema peripheral	
Investigations		Prothrombin complex level decreased, coagulation factor decreased, coagulation time prolonged, aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased	
Injury and poisoning and procedural complications		Wound secretion	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing Exembol or by decreasing the infusion rate. In clinical studies, anticoagulation parameters return to baseline generally within 2 to 4 hours after discontinuation of Exembol. Reversal of anticoagulant effect may take longer in patients with hepatic impairment.

No specific antidote to Exembol is available. If life-threatening bleeding occurs and excessive plasma levels of argatroban are suspected, Exembol should be discontinued immediately and aPTT and other coagulation tests should be performed**.** Symptomatic and supportive therapy should be provided to the patient.

Lethal single intravenous doses of argatroban for mice, rats, rabbits, and dogs were 200, 124, 150, and 200 mg/kg respectively. The symptoms of acute toxicity were loss of righting reflex, tremors, clonic convulsions, paralysis of hind limbs, and coma.

Each vial contains 200 mg ethanol.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct thrombin inhibitors.

ATC code: B01AE03.

Mechanism of Action

Argatroban, a synthetic L-arginine derivative, is a direct thrombin inhibitor (molecular weight 526.65) that binds reversibly to thrombin. Argatroban exerts its anticoagulant effect independently of antithrombin III and inhibits fibrin formation; activation of coagulation factors V, VIII and XIII; activation of protein C; and platelet aggregation.

Pharmacodynamic effects

Argatroban is highly selective for thrombin; inhibitory constant (Ki) values in studies *in vitro* with synthetic tripeptides ranged from 5 to 39 nM.

Argatroban is capable of inhibiting the action of both free and clot-associated thrombin. It does not interact with heparin-induced antibodies. There was no evidence of formation of antibodies against argatroban in patients who received multiple doses of argatroban.

Clinical efficacy and safety

Evidence of the efficacy of Exembol in HIT type II derives from data from two studies where a total of 568 adult patients were treated with Exembol. The average treatment duration employed in these clinical studies was 6 days with a maximum of 14 days. In the first prospective trial, an improvement in the composite outcome at 37 days (death, amputation, new thrombosis) was observed in the Exembol group versus the historical controls (n=46) The reduction of the incidence of the primary endpoint was consistent in the subgroups of patients having HIT type II without thromboembolic complications (25.6% vs 38.8%), p=0.014 by categorical analysis;

p=0.007 by time-to-event analysis) and HIT type II with thromboembolic complications (43.8% vs 56.5%, p=0.131 by categorical analysis; p=0.018 by time-to event analysis).

The studies were not statistically powered for individual endpoints. However, in the first prospective study, the reduction of the incidence of individual endpoints for patients having HIT type II without and with thromboembolic complications respectively was as follows: mortality (16.9 vs 21.8%, *n.s*) and (18.1 vs 28.3%, *n.s*), amputation (1.9 vs 2.0%, *n.s*) and (11.1 vs 8.7%, *n.s*), new thromboses (6.9 vs 15%, p=0.027) and (14.6 vs 19.6%, *n.s*).

In the second follow-on study, similar outcomes were observed.

Paediatric population

The efficacy and safety of the use of Exembol in patients under 18 years of age has not been established. However, limited results from a prospective clinical study conducted in the USA in 18 seriously ill paediatric patients with (suspected) HIT Type II requiring an alternative to heparin anticoagulation are available.

The age range of the patients participating in this study were less than six months (8 patients), six months to less than 8 years (6 patients) and 8 to 16 years (4 patients). All patients had serious underlying conditions and were receiving multiple concomitant medications.

Thirteen patients received Exembol solely as a continuous infusion (no bolus dose). In the majority of these 13 patients dosing was initiated at 1 microgram/kg/min to achieve an aPTT of 1.5 to 3 times the baseline value (not exceeding 100 seconds). Most patients required multiple dose adjustments to maintain anticoagulation parameters within the desired range.

During the 30-day study period thrombotic events occurred during Exembol administration in two patients and following Exembol discontinuation in three other patients. Major bleeding occurred among two patients; one patient experienced an intracranial haemorrhage after 4 days of Exembol therapy in the setting of sepsis and thromobocytopenia. Another patient completed 14 days of treatment but experienced an intracranial haemorrhage while receiving Exembol following completion of the study treatment period.

As only limited data are available, an initial continuous infusion rate of 0.75 microgram/kg/min has been suggested in seriously ill paediatric patients with normal hepatic function. A reduced starting dose of 0.2 microgram/kg/min would be suggested in seriously ill paediatric patients with impaired hepatic function (see Section 5.2). The dose should be adjusted to achieve target aPTT 1.5-3 times the baseline value, not exceeding 100 seconds.

5.2 Pharmacokinetic properties

Absorption

Steady-state levels of both argatroban and anticoagulant effect are typically attained within 1-3 hours and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state plasma argatroban concentrations increase proportionally with dose (for infusion doses up to 40 microgram/kg/min in healthy subjects) and are well correlated with steady-state anticoagulant effects. For infusion doses up to 40 microgram/kg/min, argatroban increases, in a dose-dependent fashion, the

activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the International Normalized Ratio (INR) and the thrombin time (TT) in healthy volunteers and cardiac patients.

Distribution

Argatroban distributes mainly in the extra-cellular fluid. The volume of distribution (Vdβ) was 391 ± 155 ml/kg (mean ± SD). Argatroban is 54% bound in human serum proteins, with binding to albumin and α_1-acid glycoprotein being 20% and 34% respectively.

Biotransformation

The metabolism of argatroban has not yet been fully characterized. The metabolites identified (M-1, M-2, and M-3) are formed by hydroxylation and aromatization of the 3-methyltetrahydroquinoline ring in the liver. The formation of the metabolites is catalysed *in vitro* by cytochrome P450 enzymes CYP3A4/5, but this is not a major path of elimination *in vivo*. The primary metabolite (M1) exerts 40-fold weaker antithrombin effect than argatroban. Metabolites M-1, M-2 and M-3 were detected in the urine, and M-1 was detected in plasma and faeces.

There is no interconversion of the 21-(R) and 21-(S) diastereoisomers. The ratio of diastereoisomers is unchanged by metabolism or hepatic impairment, remaining constant at 65:35 (±2%).

Elimination

On termination of the infusion, the concentration of argatroban decreased rapidly. The apparent terminal elimination half life (mean ± SD) is 52 ± 16 min. Clearance (mean ± SD) was 5.2 ± 1.3 ml/kg/min.

Argatroban is excreted mainly in the faeces, presumably through biliary secretion. Following intravenous infusion of ^{14}C-radiolabelled argatroban 21.8 ± 5.8% of the dose was excreted in urine and 65.4 ± 7.1% in the faeces.

Special populations

Older people: clearance is approximately 15% lower then in younger persons. No age related dose adjustment is necessary.

Renal impairment: compared with patients with normal renal function (creatinine clearance ≥ 80ml/min) who had a terminal half-life of 47±22 min, patients with severely impaired renal function (creatinine clearance ≤ 29ml/min) had only slight prolongation of this value (65±35 min). No initial dose regimen adjustment with respect to renal function is necessary.

Hepatic impairment: in patients with hepatic impairment (Child Pugh score 7 to 11) clearance was 26% of that of healthy volunteers. Initial dose reduction is required in patients with moderate hepatic impairment. Exembol is contraindicated in patients with severe hepatic impairment.

Paediatric patients: argatroban clearance is decreased in seriously ill paediatric patients. Based on population pharmacokinetic modelling, clearance in paediatric patients (0.17 L/hr/kg) was 50% lower compared to healthy adults (0.31 L/hr/kg). Population pharmacokinetic data also indicate that the infusion rate should be adjusted according to body weight.

Other special populations: Based on population pharmacokinetic modelling, patients with elevated bilirubin (secondary to cardiac complications or hepatic impairment) had, on average, 80% lower clearance (0.03 L/hr/kg) when compared to paediatric patients with normal bilirubin levels.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity. Toxicity studies with continuous intravenous infusions and reproduction toxicity studies using daily intravenous bolus injections achieved only limited systemic exposure to argatroban (2 times the exposure seen in humans). Although these studies do not suggest any particular risk to humans, their value is limited by the low systemic exposure realised.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E 420 i)

Sodium chloride

Anhydrous ethanol

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Shelf life as packaged for sale: 48 months

Shelf life after first opening: The product should be used immediately.

6.4 Special precautions for storage

Keep vial in the outer carton in order to protect from light.

In use, the solution should not be exposed to direct sunlight.

Do not refrigerate or freeze.

6.5 Nature and contents of container

Clear 50 ml glass vial sealed with an ethylene tetrafluorethylene (ETFE)-coated chlorobutyl rubber stopper and aluminium crimp-seal with a polypropylene flip-off cap. Each vial contains 50 ml of solution for infusion.

Vials are supplied in cardboard cartons of 4 or 12 vials. Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

Exembol 1 mg/ml Solution for Infusion is ready to use and requires no dilution before administration.

The drug product is unpreserved and intended for single use only. The solution should be used immediately after opening. Any unused solution should be discarded.

The solution should be inspected visually prior to use. Only clear solutions without visible particles should be used.

Light resisting measures such as foil protection for intravenous lines are not necessary. No significant potency losses have been noted following simulated delivery of the solution through intravenous tubing.

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

7 MARKETING AUTHORISATION HOLDER

Ethypharm,
194, Bureaux de la Colline,
Bâtiment D,
92213
Saint-Cloud cedex,
France.

8 MARKETING AUTHORISATION NUMBER(S)

PL 06934/0254

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/12/2015

10 DATE OF REVISION OF THE TEXT

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