SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Exembol Multidose 100 mg/ml concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains argatroban as 100 mg argatroban monohydrate.

1 Vial with 2.5 ml concentrate for solution for infusion contains argatroban as 250 mg argatroban monohydrate. Final concentration after dilution as recommended is 1 mg/ml (see section 6.6).

Excipients: 1 ml solution contains 400 mg ethanol (50% by volume) and 300 mg sorbitol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for Infusion.

Clear colourless to pale yellow solution.

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

Initial Dosage

Treatment with Exembol Multidose 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 Multidose is administered, heparin therapy should be discontinued and a baseline aPTT value obtained.

Standard recommendations
Monitoring:
In general, therapy with Exembol Multidose 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 Multidose.
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 Multidose, 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 Ill/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 baseline or > 100 s	Stop infusion until the aPTT is 1.5-3.0 times baseline; Resume at half of the previous	2 hours	Stop infusion until the aPTT is 1.5-3.0 times baseline; Resume at half of the previous	4 hours

	infusion rate		infusion rate	

Method of administration
Exembol Multidose is supplied as a concentrate (250 mg/2.5 ml) which must be diluted 100-fold prior to infusion to a final concentration of 1 mg/ml (see section 6.6).
Standard infusion rates for the 2 microgram/kg/min recommended initial dosage (1 mg/ml final 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:
Elderly patients
The standard initial dosage recommendations for use in adults are applicable to elderly patients.
Children and adolescents (<18 years)
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 Multidose has not been clearly established in this patient population (see Section 5.1 and 5.2).
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 Multidose 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 Multidose no bolus dose is required.

Exembol Multidose 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 Multidose 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 Multidose 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.

<u>Patients with HIT Type II undergoing percutaneous coronary intervention (PCI)</u>

Limited data is available from the use of Exembol Multidose 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 min 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 Multidose 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	**Infusion Dose**	**Infusion Rate**	**Bolus Dose**	**Infusion Dose**	**Infusion Rate**	**Infusion Dose**	**Infusion Rate**

	(mcg)	(mcg/min)	(ml/hr)	(mcg)	(mcg/ • min)	(ml/hr)	(mcg/min)	(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: Exembol Multidose concentrate is diluted before use to 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 Multidose for treatment of patients with hepatic impairment requiring PCI is not recommended.

Recommendations for use in patients scheduled for a conversion to oral anticoagulation:

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 Multidose 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 Multidose and the International Sensitivity Index (ISI) of the thromboplastin reagent used. In general, with doses of Exembol Multidose up to 2 microgram/kg/min, Exembol Multidose can be discontinued when the INR reaches up to 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 Multidose on the INR value at a typical plasma concentration arising from a dose of around 2 microgram/kg/min. However, higher concentrations of Exembol Multidose 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 Multidose and oral anticoagulants (of the coumarin type) is recommended for a minimum of 5 days. INR should be measured daily while Exembol Multidose 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 Multidose is discontinued.
The INR measurement should be repeated 4-6 hours after discontinuation of Exembol Multidose. If the repeat INR is below the desired therapeutic range, the infusion of Exembol Multidose 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 Multidose is less predictable. With such higher doses, the dose of Exembol Multidose 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 Multidose and oral anticoagulants should be measured 4 to 6 hours after reduction of the Exembol Multidose dose.

4.3 Contraindications

Exembol Multidose 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 Multidose 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 Multidose 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 Multidose. When Exembol Multidose 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 Multidose therapy (about 1-2 hours).

Hepatic Impairment: Caution should be exercised when administering Exembol Multidose 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 Multidose 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 Multidose; the therapeutic ranges for these tests have not been defined (with the exception of ACT) Plasma argatroban concentrations also correlate well with the anticoagulant effects.
The concomitant use of Exembol Multidose and oral anticoagulants of the coumarin type 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 Multidose and oral anticoagulants therapy.

This medicinal product contains ethanol. The maximum recommended daily dose (10 microgram/kg/min) of this medicine administered to an adult weighing 70 kg would result in exposure to 57.6 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 9.6 mg/100 ml. Because this medicine is usually given slowly over several hours, the effects of alcohol may be reduced.

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 Multidose.

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 Multidose and warfarin (7.5 mg single oral dose) have not been demonstrated. However, the concomitant use of Exembol Multidose 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 Multidose to oral anticoagulation.

Thrombolytics, anti-platelet and other agents: The safety and effectiveness of Exembol Multidose 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 Multidose contains ethanol, an interaction with metronidazole or disulfiram cannot be excluded.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of Exembol Multidose in pregnant women. The effect of argatroban on reproduction has been incompletely studied in animal experiments, as technical issues have limited systemic exposure (see section 5.3 for results of animal studies). The increased bleeding risk with Exembol Multidose may constitute a risk in treatment during pregnancy. Exembol Multidose contains ethanol. A 70kg patient administered the maximum recommended daily dose (10µg/kg/min) would receive a dose of approximately 4g ethanol per day. Exembol Multidose should be used during pregnancy only if treatment is clearly necessary.

Information concerning the passage of argatroban into human milk is not available. Animal studies using radiolabelled argatroban have shown that radioactivity reaches greater levels in breast milk than in maternal blood. Breast feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

In theory, the presence of ethanol in the formulation (1g 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 Multidose.

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 Multidose, 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 Multidose 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 Multidose is stated below.

Organ system	**Common** **(≥1/100, ≤1/10)**	**Uncommon** **(≥1/1000, ≤1/100)**
Infections and infestations		Infection, urinary tract infection
Blood and lymphatic system disorders	Anaemia	Coagulopathy, thrombocytopenia, leukopenia
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,

Organ system	Common (≥1/100, ≤1/10)	Uncommon (≥1/1000, ≤1/100)
		pleural effusion, hiccups
Gastrointestinal disorders	Nausea	Vomiting, constipation, diarrhoea, gastritis, gastrointestinal haemorrhage, melaena, dysphagia, tongue disorder
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 Multidose or by decreasing the infusion rate. In clinical

studies, anticoagulation parameters return to baseline generally within 2 to 4 hours after discontinuation of Exembol Multidose. Reversal of anticoagulant effect may take longer in patients with hepatic impairment.

No specific antidote to Exembol Multidose is available. If life-threatening bleeding occurs and excessive plasma levels of argatroban are suspected, Exembol Multidose 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 1g ethanol.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct thrombin inhibitors.

ATC code: B01AE03.

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.

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.

Evidence of the efficacy of argatroban in HIT type II derives from data from two studies where a total of 568 adult patients were treated with argatroban. 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 argatroban 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 the 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.

The efficacy and safety of the use of Exembol Multidose 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 argatroban 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 argatroban administration in two patients and following argatroban discontinuation in three other patients. Major bleeding occurred among two patients; one patient experienced an intracranial haemorrhage after 4 days of argatroban therapy in the setting of sepsis and thromobocytopenia. Another patient completed 14 days of treatment but experienced an intracranial haemorrhage while receiving argatroban following completion of the study treatment period.

As only limited data is 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 adjusted to achieve target aPTT 1.5 -3 times the baseline value, not exceeding 100 seconds.

5.2 Pharmacokinetic properties

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 ($V_{d\beta}$) 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.

Metabolism

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%).

Excretion

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

Elderly patients: clearance is approximately 15% lower than 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 Multidose 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.

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 420i)

Anhydrous ethanol

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial before opening

4 years (see Section 6.4)

After opening before dilution

Chemical and physical stability has been demonstrated in use following multiple needle entries and product withdrawal for 28 days at both 25ºC and at 2 to 8ºC.

After dilution

Diluted solution: chemical and physical in-use stability has been demonstrated for up to 14 days at 25ºC and 2 to 8ºC in sodium chloride 9 mg/ml (0.9%) solution for infusion, glucose 50 mg/ml (5%) solution for infusion, or Sodium Lactate Intravenous Infusion Compound (see Section 6.6).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8 ºC unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Vial before opening

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

Do not refrigerate or freeze.

Vial after first opening
Keep vial in the outer carton in order to protect from light.
Do not refrigerate or freeze.

After dilution
Diluted solutions should not be exposed to direct sunlight.

6.5 Nature and contents of container

Clear 5 mL type I glass vial sealed with a teflon-coated chlorobutylrubber stopper and an aluminium crimp-seal with a polypropylene flip-off cap. Each vial contains 2.5 ml of concentrate for solution for infusion.

Vials are supplied in cardboard cartons of 1 or 6 vials. Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

Exembol Multidose should be diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion, glucose 50 mg/ml (5%) solution for infusion, or Sodium Lactate Intravenous Infusion Compound to a final concentration of 1 mg/ml. If the solution is cloudy, or if an insoluble precipitate is noted, the vial should be discarded.

Following multiple needle entries and product withdrawals, the vials maintain microbial, chemical and physical stability for up to 28 days at 25ºC and at 2 to 8ºC. Other in-use storage times and conditions are the responsibility of the user.

The 100 mg/ml concentrate for solution for infusion should be diluted 100-fold by mixing with diluent. For a starting infusion rate of 0.5 microgram/kg/min, use 50 mg (0.5 ml) concentrate for solution for infusion per 50 ml of diluent.
The constituted solution must be mixed by repeated inversion of the diluent bag or bottle for one minute. The diluted solution should be clear and practically free from visible particles. Upon preparation, the solution may show slight but brief haziness due to the formation of microprecipitates that rapidly dissolve upon mixing. The pH of the intravenous solution prepared as recommended is 3.2-7.5.
Multiple use of Exembol Multidose applies to the 100 mg/ml concentrate for solution for infusion in its original container. The diluted solution should be used immediately. Any unused solution should be discarded.
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 06934/0253

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2013

10 DATE OF REVISION OF THE TEXT

31/10/2024