

Public Assessment Report

Scientific discussion

Novastan (argatroban monohydrate)

SE/H/483/04/DC

This module reflects the scientific discussion for the approval of Novastan. The procedure was finalised on 2015-12-07. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Mitsubishi Tanabe Pharma Europe Ltd has applied for a marketing authorisation for Novastan, 1 mg/ml, solution for infusion. The active substance argatroban monohydrate is the same as in Novastan, concentrate for infusion, 100 mg/ml, marketed by Mitsubishi Tanabe Pharma Europe Ltd since 2004. No PAR has been prepared for the previously approved product Novastan, concentrate for solution for infusion, 100 mg/ml.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The application for approval of Novastan 1 mg/ml was not accompanied by any new nonclinical data and no studies are required. The data presented in this report refers to the first approval of Novastan.

III.2 Pharmacology

Argatroban is a relatively potent and apparently selective inhibitor of thrombin (K_i values in the nM range and low affinity to a number of other serine proteases). It was found that the 21-S diastereoisomer of argatroban was a somewhat more potent thrombin inhibitor than the R-form. Unlike heparin, argatroban has been shown to inhibit both the amidolytic and platelet activating activities of clot-associated thrombin. Antithrombotic activity has been clearly demonstrated in a number of in vivo models of venous and arterial thrombosis. At clinically relevant iv doses, argatroban was shown to inhibit venous thrombus formation whereas considerably higher doses were needed to inhibit the extension of already established thrombosis. Moreover, the doses required to inhibit arterial thrombosis were higher than those needed to inhibit venous thrombosis. The concomitant administration of argatroban with aspirin, indomethacin, sulfinpyrazone, quinidine, ouabain, tolbutamide, clofibrate, furosemide or ticlopidine did not affect the anticoagulant properties of argatroban in the rat.

III.3 Toxicology

Single dose administration of high iv bolus doses of argatroban affected CNS, cardiovascular, respiratory, and digestive systems and caused bleedings. These effects were transient and probably related to high peak plasma levels.

Very few symptoms related to argatroban were observed in repeat dose studies in rats and dogs (iv infusion as well as iv bolus administration). However, in the repeat dose studies it was only possible to obtain plasma levels ≤ 2 times higher than in humans at the highest recommended dose.

Reproduction studies were conducted in rats and rabbits with iv bolus administration of argatroban at doses of up to 27 mg/kg/d and 10.8 mg/kg/d, respectively. Plasma levels were not determined, but, due to the mode of administration, it can be anticipated that the parent animals were exposed to high levels during a relatively short period. These studies revealed no effect on fertility and reproduction performance in rats and no embryotoxic or teratogenic effect was observed in rats and rabbits. No adverse effects of argatroban on the peri- and postnatal development in rats were reported. It was concluded that the experimental design of the reproduction studies (iv bolus) does not allow an adequate evaluation. However, owing to the difficulties in performing continuous infusion studies in pregnant animals and low exposure to the foetus, no further reproduction studies were required, provided that a warning in the SPC was included.

Argatroban did not show any genotoxic effect in *in vitro* and *in vivo* standard tests. However, the systemic exposure of mice in the micronucleus test was not determined and no other pharmacokinetic information in mice is available. In spite of this deficiency in the study design it may be anticipated that the bone marrow was exposed to high levels of argatroban for a short time period during two consecutive days (27 mg/kg iv bolus for 2 days). Carcinogenicity studies with argatroban have not been performed and are not required due to the short duration of clinical therapy

III.4 Ecotoxicity/environmental risk assessment

Argatroban is not considered to be of any concern for the environment.

III.5 Discussion on the non-clinical aspects

No special hazard for humans was indicated in non-clinical safety pharmacology and genotoxicity studies performed. However, in general, the toxicity studies performed using continuous intravenous infusions and reproduction toxicity studies using daily intravenous bolus injections is limited by the low systemic exposure obtained (2 times the exposure seen in humans). This is reflected in the SmPC where adequate warnings and information have been included in the text

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The application for Novastan 1 mg/ml is not accompanied by any new pharmacokinetic data. No studies are required since the applied product is a new solution for infusion with identical qualitative and quantitative composition as the already marketed Novastan concentrate at the time of administration.

IV.2 Pharmacodynamics

The preclinical studies characterised argatroban as a selective thrombin inhibitor with anticoagulant properties, both *in vitro* and *in vivo*. Its activity does not depend upon the presence of antithrombin III. Argatroban inhibits both the amidolytic and platelet-activating activities of free and clot-associated thrombin. Pharmacological studies showed that argatroban is an active antithrombotic agent when administered as an intravenous infusion in a wide variety of animal models of thrombosis.

IV.3 Clinical efficacy and safety

Argatroban monohydrate is a synthetic, low molecular weight, direct thrombin inhibitor that selectively and reversibly binds to free and clot-associated thrombin. No new data has been submitted, which is accepted for this application. Argatroban monohydrate is currently approved in 12 countries in Europe/European Economic Area, as well as in USA, Canada, Japan, South Korea, and China. Argatroban monohydrate

100 mg/mL concentrate for solution for infusion has been registered in the EU/EEA since 2004.

The efficacy and safety of argatroban monohydrate as an anticoagulant in patients with HIT type II have been extensively evaluated for the marketing authorisation of argatroban monohydrate 100 mg/mL concentrate for solution for infusion (European Procedure Number. SE/H/483/01/01). As the propose drug product argatroban monohydrate 1 mg/mL solution for infusion is qualitatively and quantitatively identical to the currently authorised argatroban monohydrate 100 mg/mL concentrate for solution for infusion, when diluted to 1 mg/mL with 0.9% w/v saline, additional clinical studies on efficacy and safety are not considered necessary.

IV.4 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Novastan.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none">• Haemorrhage• Abnormal hepatic function• Cerebral haemorrhage
Important potential risk	<u>Related to 'Ready to use' formulation</u> <ul style="list-style-type: none">• Medication error – under dosing
Missing information	<ul style="list-style-type: none">• Pregnant patients• Breastfeeding patients• Paediatric patients

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Haemorrhage	Listed in SmPC sections 4.3 contraindication, section 4.4 special warnings and precautions regarding bleeding section 4.5 concurrent use with anticoagulants, thrombolytics and anti-platelet agents increase the risk of bleeding and section 4.2 treatment with argatroban to be initiated under guidance of a physician with experience in coagulation disorder	None proposed
Abnormal hepatic function	Listed in SmPC section 4.3 contraindication Section 4.4 special warnings and precautions regarding use in hepatic impairment Section 5.2 slow clearance of argatroban in presence of hepatic impairment and listed in section 4.2 dose reduction for hepatic impaired patients	None proposed
Cerebral haemorrhage	Listed in SmPC section 4.4 special warnings and precautions regarding bleeding including post-operative and section 4.5 concurrent use with anticoagulants, thrombolytics and anti-platelet agents increase the risk of bleeding	None proposed
Pregnant and breast feeding	Listed in SmPC section 4.6 regarding use during pregnancy and 'breastfeeding not recommended during treatment'	None proposed

Safety concerns identified for the “ready to use” formulation:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Medication error (under dosing)	Update in SmPC	1. Two different formulations will be differentiated by; <ul style="list-style-type: none"> o Brand name o Pack colour (carton, label and Flip-Off® seal) o Vial size (2.5 ml vs 50 ml) o Specific labelling to differentiate the strength and concentration (1mg/ml
		vs 100mg/ml) <ul style="list-style-type: none"> o Package Insert describing 'ready to use' formulation 1mg/ml which does not need dilution prior to administration o External carton size 2. Healthcare professional education programme

Summary of the RMP

The RMP is approved.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Novastan Multidos 100 mg/mL Concentrate for Solution for Infusion, SE/H/483/02/MR. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Novastan, 1 mg/ml, solution for infusion is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

Area¹	Description
Quality	<p>A commitment is provided to complete all on-going stability studies and to notify the Competent Authority immediately if test results show that the product will not meet the proposed shelf life. The Applicant also commits to notifying the Authorities in case unexpected results are obtained in the stability studies.</p> <p>The Applicant also commits to placing the first three commercial scale batches on 6 months accelerated (40°C/75% RH) and long term (25°C/60% RH) stability. Samples from one commercial-scale product batch per year will be placed on stability storage at 25°C/60% RH (ICH long-term storage condition). Vials will be placed on stability in both the upright and inverted position.</p>

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Novastan, 1 mg/ml, solution for infusion was positively finalised on 2015-12-07.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)