LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Novastan Multidos
(argatroban monohydrate)

SE/H/483/02/E04

This module reflects the scientific discussion for the approval of Novastan Multidos. The procedure was finalised at 2013-09-10. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Mitsubishi Pharma Europe Ltd has applied for a marketing authorisation for Novastan Multidos, concentrate for solution for infusion, 100 mg/ml. The active substance argatroban monohydrate is the same as in Novastan (SE/H/483/01), concentrate for solution for infusion, 100 mg/ml, marketed by Mitsubishi Pharma Europe Ltd since 2004-10-15. This PAR has been prepared following the fourth Repeat Use procedure. No PAR has been prepared for the previously approved product Novastan (SE/H/483/01), concentrate for solution for infusion, 100 mg/ml.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Novastan Multidos is presented in the form a concentrate for solution for infusion containing 100 mg/ml argatroban monohydrate (corresponding to 96.6 mg/ml argatroban) filled in glass vials. The excipients are D-sorbitol, anhydrous ethanol and water for injections.

II.2 Drug Substance

Argatroban monohydrate does not have a monograph in the Ph Eur.

Argatroban monohydrate is a white, crystalline powder which is very slightly soluble in water, freely soluble in glacial acetic acid, slightly soluble in ethanol, and practically insoluble in ether and acetone.
The structure of argatroban monohydrate has been adequately proven and its physico-chemical properties sufficiently described. Argatroban is a chiral substance present as a mixture of two diastereoisomers. Relevant information on chirality and polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Novastan Multidos 100 mg/ml concentrate for solution for infusion is formulated using excipients described in the current Ph Eur. All raw materials used in the product are in compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as its stability characteristics and poor aqueous solubility.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The approval of the multi-dose vial of Novastan was not accompanied by any new nonclinical data. 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 (Ki values in the nM range and low affinity to a number of other serine proteases). It was found that the 21-S diasterioisomer 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, oubain, 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

An environmental risk assessment was submitted. 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 toxicicity 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 approval of the multi-dose vial of Novastan was not accompanied by any new pharmacokinetic data. The data presented in this report refers to the first approval of Novastan.

The pharmacokinetics of argatroban are linear: steady-state concentrations obtained at the end of infusions are proportional to the dose (1.25 to 40 μg/kg/min). The elimination half-life is short, around 55 min, and does not depend on infusion rate or dose. The pharmacokinetics of the two diastereoisomers of argatroban are similar and their ratio in plasma is the same as in the injected solution. There is no evidence of time dependent changes in argatroban pharmacokinetics.

The small changes in argatroban pharmacokinetics in elderly volunteers are not judged to be clinically significant and the recommendation of no dosage reduction is agreed with. Argatroban clearance, steady-state volume of distribution or elimination half-life were not significantly different between the normal and renal impairment groups studied, thus the recommendation of no dosage reduction for these patients is also appropriate.

With respect to hepatic impairment, C_{max} was doubled and the mean argatroban clearance was 26% that of healthy volunteers, resulting in higher plasma drug concentrations at the same infusion dosage. The mean elimination half-life of argatroban in hepatic subjects was over twice that of healthy subjects. The main elimination pathway of argatroban are via hepatic

metabolism, and so caution should be used when administering argatroban to hepatically impaired subjects. A 50% reduction of the initial dose is proposed for patients with moderate hepatic impairment, the drug should not be used in patients with severe hepatic impairment.

With respect to drug/drug interactions, there is a clear positive interaction with heparin and argatroban on aPTT and CaTT. This fact should be considered when argatroban treatment immediately follows heparin. Argatroban does not modify the kinetics of heparin or digoxin and aspirin or erythromycin pretreatment did not have a significant effect on argatroban pharmacokinetics.

Argatroban is predominantly eliminated by metabolism and *in vitro* results indicated that CYP3A4 was the main enzyme. However, erythromycin (moderate CYP3A4-inhibitor) had no effect on argatroban pharmacokinetics. Further interaction studies with inducers (CYP3A4 and CYP3A5) and inhibitors (CYP3A5) of these enzymes are missing. Given these results the catalysing enzyme(s) has not been defined, which is considered a deficiency. Caution should be exercised when initiating treatment with other medicinal products. About 30% appears to be eliminated unchanged (in urine and faeces).

The potential of argatroban to inhibit the activity of CYP-enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) was investigated in an *in vitro*-study. Inhibition was less than 20% at concentrations 50 times above steady-state plasma concentrations.

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

The claim of efficacy in the indication sought is based on a pivotal, open, historically controlled study (ARG 911). A supportive follow-on study (ARG 915) is also included in the application where the outcome for argatroban-treated patients with HIT-type II are compared with the group of historical controls used in study 911.

IV.4 Clinical safety

Overall, 5586 patients and volunteer subjects (including 193 historical controls) were assessed for safety in 70 studies, of which 3882 (69%) received argatroban. Nineteen percent of the total number of patients and volunteers receiving argatroban had HIT type II. The 312 volunteers included 289 healthy volunteers, 18 subjects with renal and 5 with hepatic impairment. In summary the provided clinical studies together with rather extensive post-marketing experience is judged to sufficiently documents the efficacy and safety of argatroban for anticoagulation in patients with HIT type II.

IV.5 Clinical efficacy and safety regarding new information since last MRP procedure

To the additional analyses of the clinical trials conducted as part of the 1st repeat wave MRP, additional studies have been added in the following special patient populations (with these data being submitted and approved as part of the 2nd repeat wave MRP in Spain and France):
• Patients undergoing percutaneous coronary intervention (PCI)
• Patients post cardiac surgery
• Patients who are critically ill/intensive care unit (ICU) patients with organ system failure, including patients requiring renal replacement therapy
• Patients with HIT type II with a need for renal replacement therapy (investigations not specifically including critically ill patients)
• Seriously ill paediatric patients
The results showed that administration of argatroban by intravenous (IV) infusion, its short half-life, the predominantly hepatic elimination, ease of monitoring, and its safety profile make it advantageous for critically ill patients, i.e., those treated in ICUs. These account for two thirds of HIT patients in some studies. The SmPC was revised following a variation in 2010 to update the dosing information for the above patient populations.

A prospective, uncontrolled clinical study in 20 patients has also been conducted in France in 11 major clinical centres (Study ARG-E07).This study was designed to collect data on the clinical management of argatroban in subjects with HIT type II who require parenteral antithrombotic therapy in France. The inclusion and exclusion criteria were based on the SmPC, reflecting the target patient population once argatroban is marketed. Preliminary data indicate that argatroban increased mean platelet counts in all subjects and quickly achieved anti-coagulation levels that were easily monitored via activated thromboplastin time (aPTT) values.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Thrombin inhibition may be regarded as an attractive pharmacodynamic concept for treatment of thromboembolism in HIT-type II.
Essentially two requirements must be fulfilled for the approval of a new agent for treatment of thromboembolism in HIT-type II:
→ The efficacy and safety of the agent for treatment of thromboembolism must be demonstrated.
→ The agent must not continue to trigger the immunologic process resulting in the clinical picture of HIT type II.
These aspects were sufficiently covered. The gathered clinical experience (nearly 300 HITTS patients treated prospectively in clinical studies) is sufficient from a safety aspect.
There are patients with HIT type II that cannot be treated with the currently approved agents (due to e.g. immunological intolerance, renal impairment or immunological cross-reactivity) and especially for such patients argatroban could be a valuable treatment alternative.

Since last MRP procedure (SE/H/483/02/MR, concluded July 2010) there is post-marketing data that does not reveal any new safety concerns. Otherwise, no new clinical data has been submitted.
The risk-benefit balance is regarded as positive.

User consultation
The user testing was assessed and accepted in the previous MRP SE/H/483/02/MR. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Novastan Multidos, concentrate for solution for infusion, 100 mg/ml is recommended for approval.

Follow-up measures

- Submission of a variation application to include an RMP in the dossier. The variation should be submitted within two months after the end of the Repeat Use procedure.
- Submission of a variation application to update the product information in accordance with comments raised during the Repeat Use procedure. The variation should be submitted within two months after the end of the Repeat Use procedure.

VI. APPROVAL

Novastan Multidos, concentrate for solution for infusion, 100 mg/ml was approved in the national procedure on 2009-09-18.

The subsequent Mutual recognition/Repeat Use procedure, SE/H/483/02/E04, for Novastan Multidos, concentrate for solution for infusion, 100 mg/ml was successfully finalised on 2013-09-10.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se