Public Assessment Report

Decentralised Procedure

Tirofiban 50 micrograms/ml solution for infusion

(Tirofiban hydrochloride)

Procedure No: UK/H/6261/001/MR

UK Licence No: PL 35533/0058

Aspire Pharma Limited
LAY SUMMARY

Tirofiban 50 micrograms/ml solution for infusion
(Tirofiban hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Tirofiban 50 micrograms/ml solution for infusion (PL 35533/0058; UK/H/6261/001/DC, formerly PL 43586/0001; PT/H/1301/001/DC). It explains how the application for Tirofiban 50 micrograms/ml solution for infusion was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Tirofiban 50 micrograms/ml solution for infusion.

For practical information about using Tirofiban 50 micrograms/ml solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

Tirofiban 50 micrograms/ml solution for infusion may be referred to as ‘Tirofiban’ in this Lay Summary.

What is Tirofiban and what is it used for?
Tirofiban is a ‘generic medicine’. This means that Tirofiban is similar to a ‘reference medicine’ already authorised in the UK called Aggrastat (50 micrograms/ml) solution for infusion (PL 35173/0002; Correvio (UK) Limited, UK), which was first authorised in the UK on 15 July 1999.

Tirofiban is used to help assist the blood flow to the heart and to help prevent chest pain and heart attacks.

This medicine may also be used in patients whose heart vessels are dilated with a balloon (percutaneous coronary intervention or PCI). This is a procedure, possibly with implantation of a small tube (stent), to improve the blood flow to the heart. Tirofiban is intended for use with aspirin and unfractionated heparin.

How does Tirofiban work?
This medicine contains the active substance, tirofiban (as tirofiban hydrochloride). Tirofiban works by preventing platelets, cells found in the body, from forming blood clots.

How is Tirofiban used?
The pharmaceutical form of this medicine is solution for infusion. This medicine is given to the patient by injection into a vein by a health professional.

The prescribing doctor will decide on the appropriate dose, depending on the patient’s condition and weight.

The use of Tirofiban in children is not recommended.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription. Tirofiban should be prescribed by a qualified doctor who is experienced in the management of heart attacks.
What benefits of tirofiban been shown in studies?
No additional clinical studies were needed as Tirofiban is a generic medicine that is an aqueous solution that is given by injection and contains the same active substance as the reference medicine, Aggrastat (50 micrograms/ml) solution for infusion (Correvio (UK) Limited, UK).

What are the possible side effects of Tirofiban?
Because Tirofiban is a generic medicine and is bioequivalent to the reference medicine, the benefits and possible side effects are taken as being the same as those of the reference medicine.

Below is a list of the very common and common side effects that have occurred in some people following treatment with Tirofiban. The side effects are listed in decreasing order of frequency.

Very common (may affect more than 1 in 10 people):
- bleeding after surgery
- bleeding under the skin at the site of an injection, or into a muscle, causing swelling
- small red bruises on the skin
- invisible blood in urine or stool
- feeling sick
- headache.

Common (may affect up to 1 in 10 people):
- blood in urine
- coughing up of blood
- nose bleeds
- bleeding in the gums and mouth
- bleeding from vessel puncture site
- reduction in red blood cells (reduced haematocrit and haemoglobin)
- decreases in platelet count below 90,000/mm³
- fever.

For the full list of all side effects reported with Tirofiban, see section 4 of the package leaflet.

Also, for the full list of restrictions, see the package leaflet.

Why is Tirofiban approved?
It was concluded that, in accordance with EU requirements, Tirofiban has been shown to have comparable quality and is considered to be bioequivalent to Aggrastat (50 micrograms/ml) solution for infusion (Correvio (UK) Limited, UK). Therefore, the view was that, as for Aggrastat (50 micrograms/ml) solution for infusion (Correvio (UK) Limited, UK), the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Tirofiban?
A Risk Management Plan has been developed to ensure that Tirofiban are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Tirofiban, including the appropriate precautions to be followed by healthcare professionals and patients.
Other information about Tirofiban
Portugal and the UK agreed to grant a Marketing Authorisation for Tirofiban on 15 July 2015. A Marketing Authorisation (PL 43586/0001) was granted in the UK to Juno Pharma UK Limited on 04 August 2015.

Following a change of ownership procedure, Tirofiban (PL 35533/0058) was granted to Aspire Pharma Limited on 07 September 2015.

The full PAR for Tirofiban follows this summary.

For more information about treatment with Tirofiban, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2016.
**SCIENTIFIC DISCUSSION**

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Scientific discussion

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Portugal and the UK considered that the application for Tirofiban 50 micrograms/ml solution for infusion (PL 35533/0058; UK/H/6261/001/DC, formerly PL 43586/0001; PT/H/1301/001/DC) could be approved. This product is a prescription-only medicine (POM) and may be referred to as Tiroban in the remainder of this report.

Tirofiban is indicated for the prevention of early myocardial infarction in adult patients presenting with acute coronary syndromes without ST elevation (NSTEMI) with the last episode of chest pain occurring within 12 hours and with ECG changes and/or elevated cardiac enzymes.

Patients most likely to benefit from Tirofiban treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina symptoms including for instance those that are likely to undergo an early percutaneous coronary intervention (PCI). Tirofiban is also indicated for the reduction of major cardiovascular events in patients with acute myocardial infarction (STEMI) intended for primary PCI (see sections 4.2 and 5.1).

Tirofiban is intended for use with acetylsalicylic acid (ASA) and unfractionated heparin.

The application was submitted using the Decentralised Procedure (DCP), with Portugal as Reference Member State (RMS), and the UK as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Aggrastat (50 micrograms/ml) solution for infusion (PL 35173/0002; Correvio (UK) Limited, UK), which was first authorised in the UK on 15 July 1999. The reference product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

The active substance, tirofiban (as tirofiban hydrochloride), is a synthetic nonpeptide tyrosine derivative. Tirofiban is a platelet glycoprotein (GP IIb/IIIa)-receptor inhibitor. It has a reversible and high specific affinity for the glycoprotein IIb/IIIa receptor. The platelet aggregation inhibition of tirofiban is immediate, extensive and additive to oral treatment with aspirin or clopidogrel.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that have been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product, containing the same active substance as the reference product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’
issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Portugal and the UK considered that the application could be approved at the end of procedure (Day 210) on 15 July 2015. After a subsequent national phase, a licence was granted in the UK for Tirofiban solution for infusion to Juno Pharma UK Limited on 04 August 2015. Following a change of ownership procedure, Tirofiban (PL 35533/0058) was granted to Aspire Pharma Limited on 07 September 2015.

The RMS responsibility for Tirofiban was transferred from Portugal to the UK on 27 January 2016.

II. QUALITY ASPECTS
II.1 INTRODUCTION
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Tirofiban solution for infusion is a clear colourless solution. Each ml of solution for infusion contains 56 micrograms of tirofiban hydrochloride monohydrate which is equivalent to 50 micrograms tirofiban. The solution also contains the excipients sodium dihydrogen phosphate dihydrate, mannitol (E421), sodium chloride, water for injection and sodium hydroxide and/or hydrochloric acid for pH adjustment. Appropriate justification for the inclusion of each excipient has been provided.

Tirofiban solution for infusion is available in a 250 ml flexible plastic IV bag with a twist-off port stopper, colourless, 3-layer polypropylene film. It is packed in a pre-printed foil overpouch.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 DRUG SUBSTANCE
Tirofiban hydrochloride
rINN: Tirofiban hydrochloride
Chemical name(s): N-(butylsulfonyl)-O-[4-(4-piperidiniyl) butyl] -L-tyrosine hydrochloride monohydrate

Structure:

Molecular formula: C_{22}H_{36}N_{2}O_{5}SHCl·H_{2}O
M_r 495.07
Appearance: A white crystalline powder
Solubility: Slightly soluble in water
Stereochemistry: Tirofiban hydrochloride is an optically active amino acid containing one chiral centre
Polymorphism  
Tirofiban hydrochloride exists in two polymorphic forms.

Tirofiban hydrochloride is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3  MEDICINAL PRODUCT
Pharmaceutical Development
The objective of the development programme was to produce a safe, efficacious, stable solution for infusion that was equivalent to the reference product Aggrastat (50 micrograms/ml) solution for infusion (PL 35173/0002; Correvio (UK) Limited, UK). Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution and impurity profiles have been provided for this product and the reference product.

All the excipients comply with their respective European Pharmacopoeia monographs.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months, with the special storage conditions ‘Do not freeze. Keep infusion bag in foil overpouch to protect from light.’ has been accepted.
Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**
A bioequivalence study was not necessary to support this type of application for a parenteral product.

II.4  **Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for Tirofiban.

III.  **NON-CLINICAL ASPECTS**

III.1  **Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of tirofiban are well-known, no new non-clinical data are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  **Pharmacology**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.3  **Pharmacokinetics**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.4  **Toxicology**
No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.5  **Ecotoxicity/Environmental Risk Assessment (ERA)**
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6  **Discussion of the non-clinical aspects**
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV.  **CLINICAL ASPECTS**

IV.1  **Introduction**.
The clinical pharmacology of tirofiban is well-known. No new clinical pharmacology data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for a parenteral product and the applicant submitted none.

According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1, Guideline on the Investigation of Bioequivalence).
All the relevant clinical information provided is literature based. The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**IV.2 Pharmacokinetics**
The pharmacokinetic properties of tirofiban are well known and are adequately described in the applicant’s clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.

**IV.3 Pharmacodynamics**
The clinical pharmacodynamic properties of tirofiban are well-known. No new pharmacodynamics data were submitted and none are required for this type of application.

**IV.4 Clinical Efficacy**
The clinical efficacy of tirofiban is well-known. No new efficacy data are presented for this type of application.

**IV.5 Clinical Safety**
The safety profile of tirofiban is well known. No new safety data have been submitted with this application for the proposed indication and none are required. No new or unexpected safety concerns arose from this application.

**IV.6 Risk Management Plan**
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 Tirofiban 50 micrograms/ml solution for infusion.

The following table lists the summary of safety concerns which have been identified:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tbody>
<tr>
<td>Important identified risks</td>
<td>• Bleeding</td>
</tr>
<tr>
<td></td>
<td>• Acute and severe thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• Severe allergic reactions</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>• No important potential risks identified</td>
</tr>
<tr>
<td>Missing information</td>
<td>• No missing information identified</td>
</tr>
</tbody>
</table>

Appropriate pharmacovigilance and risk minimisation activities have been addressed.

**IV.7 Discussion of the clinical aspects**
It is recommended that a Marketing Authorisation is granted for Tirofiban.

**V. USER CONSULTATION**
A 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 language used for the purpose of user testing the pack leaflet was English.

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.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Tirofiban 50 micrograms/ml solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of tirofiban are well-known, no additional data were required.

No new non-clinical data were submitted and none are required for this type of application.

EFFICACY
No new clinical data were submitted and none were required for this type of application. No bioequivalence studies were submitted or required for this application for a parenteral product.

SAFETY
The safety profile of tirofiban is well-known. No new or unexpected safety issues or concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling text are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tirofiban is considered to have demonstrated the therapeutic value of the compound and bioequivalence to the reference product has been shown. The benefit/risk balance is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and package leaflet is available on the MHRA website. The current labelling is presented below:
Tirofiban 50 micrograms/ml solution for infusion

Do not use Tirofiban solution for infusion if there are visible particles or discolouration of the solution before use. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

MA Holder:
Aspire Pharma Ltd
Bellamy House, Winton Road
Petersfield, Hampshire, GU32 3HA
United Kingdom

POM
PL 35533/0058
1010287-X1.3

Tirofiban 50 micrograms/ml solution for infusion

One millilitre of Tirofiban solution for infusion contains 56 micrograms Tirofiban hydrochloride monohydrate which is equivalent to 50 micrograms Tirofiban hydrochloride.

Excipients: Sodium dihydrogen phosphate dihydrate, mannitol, sodium chloride, water for injection, sodium hydroxide and/or hydrochloric acid.

IV infusion.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not freeze. Keep container in foil overpouch to protect from light.

250ml solution for infusion

Made in India
Code No: DRUGS/AP/01/2008

FLE-031006-00
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update sections 4.2 and 6.5 of the Summary of Product Characteristics (SmPC) to bring in line with the originator product Aggrastat (Tirofiban) 50 microgram/ml solution for infusion. Consequentially the Patient Information Leaflet (PIL) has been updated. In addition, to increase clarity, editorial amendments to the packaging description provided in the SmPC and PIL have been made; no changes have been made to any aspect of the packaging.</td>
<td>UK/H/6261/01/IB/002</td>
<td>SmPC and PIL</td>
<td>02 August 2016</td>
<td>31 August 2016</td>
<td>Approval</td>
<td>Yes (Annex 1.1)</td>
</tr>
</tbody>
</table>
Annex 1.1

Reference: PL 35533/0058, Application 7
Product: Tirofiban 50 micrograms/ml solution for infusion
Marketing Authorisation Holder: Aspire Pharma Limited
Active Ingredient(S): Tirofiban hydrochloride.

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/6261/01/IB/002

Reason:
To update sections 4.2 and 6.5 of the Summary of Product Characteristics (SmPC) to bring in line with the originator product Aggrastat (Tirofiban) 50 microgram/ml solution for infusion. Consequentially the Patient Information Leaflet (PIL) has been updated. In addition, to increase clarity, editorial amendments to the packaging description provided in the SmPC and PIL have been made; no changes have been made to any aspect of the packaging.

Supporting Evidence
Revised SmPC fragments
Revised PIL

Evaluation
The proposed changes to the SmPC and PIL are satisfactory.

Conclusion
The proposed updates are generally in line with the innovator’s product information documents and the Quality Review of Documents (QRD) template. The proposed changes are considered acceptable and there are no objections to approval.

Decision - Approved on 31 August 2016