argatroban, 100mg/ml, concentrate for solution for infusion (Exembol)  
SMC No. (812/12)

Mitsubishi Pharma Europe Ltd

05 October 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**argatroban (Exembol®)** is not recommended for use within NHS Scotland.

**Indication under review:** anticoagulation in adult patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic therapy.

Argatroban produces anticoagulant effects in adults with heparin-induced thrombocytopenia type II and there is limited evidence that it may be associated with a reduction in thrombosis, and deaths due to thrombosis. The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 November 2012
Indication
Anticoagulation in adult patients with heparin-induced thrombocytopenia type II who require parenteral antithrombotic therapy.

Dosing Information
Initially 2 microgram/kg/minute intravenous infusion in adults without hepatic impairment, and 0.5 microgram/kg/minute in adults with moderate hepatic impairment (Child-Pugh Class B) or who are post-cardiac surgery or critically ill. Then adjusted, up to a maximum of 10 microgram/kg/minute, to attain steady-state activated partial thromboplastin time (aPTT) 1.5 to 3 times baseline, but not exceeding 100 seconds. Treatment should be initiated under the guidance of a physician with experience in coagulation disorders.

Product availability date
18 June 2012

Summary of evidence on comparative efficacy
Heparin-induced thrombocytopenia (HIT) type II is an immune-mediated adverse reaction to heparin in which antibodies are produced to the complex of heparin and platelet factor 4 on platelets. It is associated with thrombocytopenia and pro-coagulant changes that can result in thrombosis. Argatroban is a reversible direct thrombin inhibitor that produces anticoagulant effects through inhibition of fibrin formation, activation of coagulation factors V, VIII and XIII, activation of protein C and platelet aggregation.

Two similarly designed open-label, non-randomised, historically-controlled studies (ARG-911 and ARG-915 plus extension ARG-915X) recruited adults with HIT, defined as a platelet count <100 x 10^9/L or a reduction of at least 50% after initiation of heparin with no explanation other than HIT, without thrombosis (the ‘HIT’ group) and with thrombosis (the ‘HITTS’ group). Adults with a previous history of a positive HIT antibody test who required anticoagulation (latent disease) were also recruited and were included in the HIT group. All patients received argatroban intravenous infusion 2 microgram/kg/minute for two hours then titrated to achieve an activated partial thromboplastin time (aPTT) 1.5 to 3 times baseline and continued for up to 14 days or until the underlying condition resolved or anticoagulation with other agents was provided. The same group of historical controls was used for both studies. This included patients treated within the four years before the study began (i.e. from 1991 to 1995) at participating study centres who met the inclusion/exclusion criteria applied to the prospectively treated patients. The primary outcome, rate of death (all causes), amputation (all causes) or new thrombosis at 37 days, was compared primarily by categorical analysis in the intention-to-treat population, which comprised all patients who received argatroban and all patients in the historical control group. In the HIT groups, the primary outcome occurred in 26% (41/160) and 28% (53/189) of argatroban-treated patients in the ARG-911 and ARG-915/915X studies, respectively. This was a significantly lower rate than that in historical controls at 39% (57/147 and 54/139). In the HITTS group, the rate of the primary outcome was lower in patients given argatroban, 44% (63/144) and 42% (95/229) in the respective studies, versus historical controls 56% (26/46), but the differences were not significant. Data on the individual components of the primary outcome are detailed in the table below. In both studies within the HIT and HITTS groups, rates of new thrombosis were lower in argatroban-treated patients compared to historical controls, with significant differences observed except in the HITTS group of study ARG-911. Rates of death due to thrombosis were significantly
lower in the patients given argatroban compared to historical controls within the HIT and HITTS groups of both studies.\textsuperscript{3,7}

**Components of composite endpoint and death due to thrombosis.\textsuperscript{3,4}**

<table>
<thead>
<tr>
<th>HIT</th>
<th>ARG-911</th>
<th>ARG-915/915X</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Argatroban</td>
</tr>
<tr>
<td>N</td>
<td>147</td>
<td>160</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>32 (22)</td>
<td>27 (17)</td>
</tr>
<tr>
<td>Amputation, n (%)</td>
<td>3 (2.0)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>New thrombosis, n (%)</td>
<td>22 (15)</td>
<td>11 (6.9)*</td>
</tr>
<tr>
<td>Death due to thrombosis, n (%)</td>
<td>7 (4.8)</td>
<td>0 (0)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HITTS</th>
<th>ARG-911</th>
<th>ARG-915/915X</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Argatroban</td>
</tr>
<tr>
<td>N</td>
<td>46</td>
<td>144</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>13 (28)</td>
<td>26 (18)</td>
</tr>
<tr>
<td>Amputation, n (%)</td>
<td>4 (9)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>New thrombosis, n (%)</td>
<td>9 (20)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Death due to thrombosis, n (%)</td>
<td>7 (15)</td>
<td>1 (0.7)*</td>
</tr>
</tbody>
</table>

*p <0.05 vs. historical control*

In the HIT and HITTS groups, respectively, mean platelet count increased from baseline to day three in argatroban-treated patients by 54 and 52 in the ARG-911 study and by 42 and 48 in the ARG-915 study, while it decreased by 33 and 21 in the historical controls.\textsuperscript{5,6}

Argatroban demonstrated prompt anticoagulant effects in both studies, with the majority of patients (76% to 81% in the ARG-911 study) achieving target aPTT at first assessment, which generally occurred on average between 3.8 to 4.6 hours after initiation of argatroban infusion.\textsuperscript{5,6}

**Summary of evidence on comparative safety**

The main adverse effects are related to haemorrhage. In the studies that compared argatroban-treated patients with historical controls there were no significant differences between the groups in rates of major and minor bleeds. The incidence of other adverse effects was low.\textsuperscript{3,6}

**Summary of clinical effectiveness issues**

Argatroban is the second direct thrombin inhibitor to be licensed for HIT. However, since lepirudin, the other licensed direct thrombin inhibitor has recently been withdrawn from the market for commercial reasons,\textsuperscript{7} argatroban is currently the only direct thrombin inhibitor available for HIT. The only other medicine licensed for this condition, danaparoid, produces anticoagulant effects mainly via anti-factor Xa activity.\textsuperscript{8} Although danaparoid is therefore now the main alternative treatment, SMC clinical experts have advised that due to ongoing supply issues its availability is unpredictable and that fondaparinux and bivalirudin are sometimes used off-label for HIT. SMC clinical experts identified an unmet need due to limitations with the available treatment options. It was also noted that argatroban may be a useful treatment option for patients with renal impairment, as it is the only licensed treatment option with no specific precautions required in renal impairment, and HIT is often complicated by renal impairment. As argatroban has been licensed in the US since 2000, and in many European countries
for a number of years, there is reasonable body of patient exposure and safety data available. There has been some use of argatroban on a named-patient basis in the UK, according to local treatment protocols in some centres.

The comparator in the key studies was historical controls treated between 1991 and 1995 in the USA when there were no medicines licensed for treatment of HIT. Treatment in the control group varied between centres based on local practice and comprised discontinuation of heparin and/or anticoagulant. The anticoagulant used would have been different from current anticoagulant treatment of HIT in Scotland, which is with danaparoid or occasionally off-label fondaparinux, as neither was commercially available in the USA at that time. The treatment effect of argatroban relative to the historical controls in the studies is unlikely to represent the treatment effect that would be achieved with argatroban versus current treatment of HIT in Scotland today.

There was no formal indirect comparison presented in the submission to the Scottish Medicines Consortium (SMC). Data from the key argatroban studies and data from a separate study of danaparoid were used in the economic analysis. However, there are difficulties in comparing the argatroban studies and the danaparoid study due to differences in study design, and inclusion and exclusion criteria.

In the two main studies, significant treatment effects for the composite primary endpoint were demonstrated in the HIT groups, but not the HITTS groups. The between-treatment differences in the primary composite outcome appear to derive to a large extent from reduction in new thrombosis and these were significant in both HIT and HITTS patients. However, there are a number of issues with the design and conduct of the studies that limit the applicability of these results.

The open-label, non-randomised, historical-control design of the studies allows bias in reporting, e.g. of comorbidities, and between-group baseline differences in demographics, including disease severity, may confound the observed treatment effects. For example, almost 20% of patients in the HIT group argatroban treatment arms had latent disease (a previous history of HIT but no acute symptoms who required anticoagulation), who may be at a lower risk of thrombosis than those with HIT, whereas the control group contained fewer of these patients (5%).

The evidence from the studies indicating that argatroban produces prompt anticoagulant effects is less compromised by the limitations of the study design. In addition, the anticoagulant effects can be monitored by a test (aPTT) that is routinely available in practice.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing argatroban with danaparoid, lepirudin or no treatment. The comparison with danaparoid is the most relevant as this is the only other treatment licensed for the treatment of HIT type II in the UK. A decision-tree model was used to capture the outcomes following each treatment, where patients were at risk of experiencing a new thrombosis, amputation or death. Patients were also at risk of major or minor bleeds. A lifetime horizon was used in the analysis.

The source of the clinical data in the argatroban arm of the model was a pooled analysis of the two open-label, non-randomised, historically-controlled studies. For the danaparoid arm, a retrospective study comparing danaparoid with historical controls was selected as being the most appropriate data source. For the no further treatment arm, the efficacy data were based on the historical controls from the argatroban studies.
The utility values were taken from a published cost-effectiveness analysis of the management of suspected HIT where a number of different quality of life data sources were used. The utility value for amputation was estimated to be 0.734 based on a weighted average of a range of published utility values. A utility value for thrombosis was not identified. Instead, the company used the utility value associated with stroke (0.7) on the basis that stroke is one of the major of consequences of thrombosis. Resource use relating to the management of thrombocytopenia, thrombosis and bleeding were taken from NHS reference costs.

The company presented the results of the economic analysis in the form of cost per quality adjusted life year (QALY) for each arm of the model individually instead of in the form of an incremental cost-effectiveness ratio (ICER). This is not appropriate as the key information that SMC needs in order to make a decision is the ICER i.e. the extra benefits the new treatment provides over alternative treatments compared to the additional costs associated with the new treatment. However, the ICERs can be calculated based on the information provided by the company and are indicated in the table below.

<table>
<thead>
<tr>
<th>Argatroban versus</th>
<th>Incremental cost</th>
<th>Incremental QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid</td>
<td>£119</td>
<td>0.8</td>
<td>£149</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>-£791</td>
<td>0.9</td>
<td>dominant</td>
</tr>
<tr>
<td>No other anti-coagulation</td>
<td>£1,117</td>
<td>0.9</td>
<td>£1,241</td>
</tr>
</tbody>
</table>

The company has since provided revised results, which corrected for some errors identified in the original model, and this indicated that argatroban would dominate danaparoid based on a cost-saving of £379 and a QALY gain of 0.07.

The following limitations were noted:

- A formal indirect comparison was not provided. Instead, the company used the individual arms of the argatroban and danaparoid studies and assumed the results could be compared. The company acknowledged that there were important differences in the inclusion criteria and design of the studies. Therefore, the effectiveness estimates used in the model were uncertain.

- The model results lack face validity. The drug cost of argatroban is between £700 and £6,000 more than danaparoid and the clinical data used in the model indicated argatroban is associated with a risk of death which is 10% higher than the danaparoid arm (19.7% vs 9.7%) and almost as high as the ‘no treatment’ arm of the model (22.7%). While the efficacy of argatroban is estimated to be better based on the other outcome measures, such as new thrombosis and major bleeds, it is surprising that the model estimates a QALY gain with argatroban given the higher rate of death in this group relative to the comparators. However, as noted above, the clinical data used in the model are uncertain as they are based on a naive indirect comparison and therefore the differences between the treatments may partly reflect the differences between the studies.

- The model structure may not be appropriate. It is assumed in the model that, following treatment, patients remain in the same health state for the remainder of the model time horizon without any change in quality of life over time. This seems unlikely. In addition, it appears that the model structure does not appropriately account for patients who have died, which raises questions about the validity of the modelling approach.

- The utility value applied to thrombosis may be too low, as a utility value for stroke was used as a proxy. This effectively assumes that all new thromboses result in stroke and patients remain in this health state for the duration of the model. This is particularly important given that the efficacy estimates used in the model indicate that the proportion of patients who experience a new thrombosis is lowest in the argatroban arm. The company provided a sensitivity analysis using a utility value for new thrombosis of 0.82 (instead of 0.7) and this resulted in a cost...
saving with argatroban compared with danaparoid of £198, but also showed argatroban was less effective with a QALY loss of 0.06.

- The cost of argatroban may have been underestimated as no drug wastage was included on the basis that there would be vial sharing. However, given the nature of this treatment it is unlikely vial sharing would happen in practice. The cost of argatroban included in the model was £1,200 per course based on 6 days treatment but this would increase to £1,490 per course when wastage is factored in, which would have a detrimental impact on the results.
- There were a number of errors in the presentation and interpretation of the sensitivity analysis. Additional sensitivity analysis was requested to test the ICER but again this contained some errors.
- SMC clinical experts considered that there may be a role for this treatment in patients with renal impairment but this patient group was not specifically considered in the economic model. The economic analysis submitted by the company did not therefore include any potential additional costs or benefits of this treatment in patients with renal impairment.

Due to the significant weaknesses outlined above, the economic case has not been demonstrated.

**Summary of patient and public involvement**

A Patient Interest Group Submission was not made.

**Additional information: guidelines and protocols**

In December 2010 the Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 122 on the prevention and management of venous thromboembolism. It recommends that whether or not there is evidence of a new thrombotic episode related to HIT, patients should receive therapeutic, as opposed to prophylactic, doses of lepirudin or danaparoid. Where warfarin therapy is proposed it should not be introduced until the platelet count has risen to greater than 100 x 10^9/L. When warfarin therapy is introduced it should be at a low dose (5mg daily) and lepirudin or danaparoid should be withdrawn only after INR has been >2 on two consecutive days. The guideline predates the availability of argatroban for use in this indication.

**Additional information: comparators**

Danaparoid is the main licensed comparator. SMC clinical experts have advised that fondaparinux and bivalirudin are occasionally used off-label for this condition.
Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>2 to 10 microgram/kg/minute intravenous infusion</td>
<td>1,740 to 6,958</td>
</tr>
<tr>
<td>Bivalirudin*</td>
<td>0.15 to 0.20 mg/kg/hour intravenous infusion</td>
<td>2,170 to 2,917</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>2,500 units, then 400 units/hour for 2 hours, then 300 units/hour for 2 hours then 200 units/hour intravenous infusion for 5 days</td>
<td>1,014</td>
</tr>
<tr>
<td>Fondaparinux*</td>
<td>7.5mg subcutaneous injection once daily</td>
<td>82</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Doses calculated for body weight of 70kg. *Bivalirudin and fondaparinux are not licensed for treatment of HIT and doses have been taken from ACCP guidelines. Duration of treatment is variable and an average of 7 days was used to calculate costs for argatroban, bivalirudin and fondaparinux. The SPC states that danaparoid should be used for 5 days and the cost reflects this. Costs from eVadis on 23 July 2012, except for bivalirudin and danaparoid, which are from the British National Formulary number 63, March 2012.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 417 in all 5 years with an estimated uptake rate of 100% in year 1 and 50% in year 5. The gross impact on the medicines budget was estimated to be £518k in year 1 and £259k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to result in savings of £6k in year 1 and £3k in year 5. It should be noted that these estimates assume some displacement of lepirudin which gives rise to the estimated cost savings. However, lepirudin has recently been withdrawn from use and thus these savings are unlikely to be realised.
References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.


5. US Food and Drug Administration. Medical review of argatroban.


11. Lubenow N et al. Results of a systematic evaluation of treatment outcomes for heparin-induced thrombocytopenia in patients receiving danaparoid, ancrod, and/or coumarin explain the rapid shift in clinical practice during the 1990s. Thrombosis Research 2006; 117: 507-15.


This assessment is based on data submitted by the applicant company up to and including 14 September 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.
**Advice context:**

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.