Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

argatroban, 100mg/ml, concentrate for solution for infusion (Exembol®)

SMC No. (812/12)

Mitsubishi Pharma Europe Ltd

05 July 2013

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 Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

argatroban (Exembol®) is accepted 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. However there is limited evidence that the anticoagulant effects are associated with a reduction in thrombosis and deaths due to thrombosis.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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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 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.

The maximum recommended duration of treatment is 14 days, although there is limited clinical experience of administration for longer periods.

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.[1] 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.[2]

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 $<100 \times 10^9$/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).[3,4] 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 but the ARG-915 plus extension study excluded eight patients with a remote rather than immediate history of HIT from its control group. 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 was a composite of rate of death (all causes), amputation (all causes) or new thrombosis at 37 days and 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 with 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 with historical controls within the HIT and HITTS groups of both studies.[3-6]

Table 1 Components of composite endpoint and death due to thrombosis:[3-6]

HIT				
	ARG-911		ARG-915/915X	
	Control	Argatroban	Control	Argatroban
N	147	160	139	189
Death, n (%)	32 (22)	27 (17)	29 (21)	36 (19)
Amputation, n (%)	3 (2.0)	3 (1.9)	4 (2.9)	8 (4.2)
New thrombosis, n (%)	22 (15)	11 (6.9)*	32 (23)	11 (5.8)*
Death due to thrombosis	7 (4.8)	0 (0)*	6 (4.3)	1 (0.5)*
HITTS				
	ARG-911		ARG-915/915X	
	Control	Argatroban	Control	Argatroban
N	46	144	46	229
Death, n (%)	13 (28)	26 (18)	13 (28)	53 (23)
Amputation, n (%)	4 (9)	16 (11)	5 (11)	34 (15)
New thrombosis, n (%)	9 (20)	21 (15)	16 (35)	30 (13)*
Death due to thrombosis, n (%)	7 (15)	1 (0.7)*	7 (15)	6 (2.6)*

*p<0.05 versus 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.[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.[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.[3-6]

Summary of clinical effectiveness issues

Argatroban is the only direct thrombin inhibitor available for anticoagulation in patients with HIT type II who require parenteral anti-thrombotic therapy. The only other medicine licensed for this condition, danaparoid, produces anticoagulant effects mainly via anti-factor Xa activity.[7] According to clinical experts consulted by SMC there continue to be supply issues with danaparoid. The off-label use of fondaparinux has also been recommended as a treatment option by the British Committee for Standards in Haematology. As argatroban has been licensed in the USA 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 in the UK, according to local treatment protocols in some centres.

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.[3-6]

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 treatment with a non-heparin anticoagulant.[4-6] 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 the time of the studies.[8,9] 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.

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%).[3-6]

The British Committee for Standards in Haematology 2012 guideline notes that the quality of the argatroban studies was compromised because approximately one third of patients included in the analysis were found to be HIT antibody negative on retrospective testing and because some of the patients included had a remote rather than an immediate history of HIT.[10]

There are no head to head studies comparing argatroban with the most relevant comparator, danaparoid. The submitting company presented an indirect comparison using the Bucher method that compared data from the HITTS subgroup in the pivotal argatroban studies with another non-randomised, historically controlled study including danaparoid.[11] The Bucher method is not appropriate in this instance as it depends on the exchangeability of controls which requires randomised studies. There was a high level of heterogeneity in baseline disease

characteristics and in control treatments and the Bucher method does not allow for this. Other limitations of the indirect comparison were the use of a variety of historical control treatments, (including some that were unknown), that would not be currently used for this indication and the use of several different danaparoid dosing regimens. The indirect comparison is not considered to be robust. It should also be noted that a significant improvement over historical control was found for danaparoid but not for argatroban, yet the submitting company reached a conclusion of equivalence. In addition to the limitations noted above, although the indirect comparison showed no significant difference between argatroban and danaparoid, the patient numbers were small and the odds ratio confidence intervals were very wide; therefore, the conclusion that the two drugs are equivalent is not deemed to be valid.

Argatroban produces prompt anticoagulant effects that can be monitored by a test (aPTT) that is routinely available in practice compared with danaparoid which is monitored using an anti-factor Xa test which has limited availability, and a longer time to receive results.[3-7] Argatroban may be a useful treatment option for patients with renal impairment, which often accompanies HIT, as it is eliminated hepatically and is the only licensed treatment option with no specific precautions required in renal impairment. However, there are limited data available for use in patients undergoing haemodialysis. Argatroban has a relatively short half-life.[2] Clinical experts consulted by SMC have noted this is useful in the management of HIT type II.

A panel of European experts published a consensus statement on the use of argatroban in patients with HIT requiring antithrombotic therapy. It noted that argatroban's route of administration (continuous intravenous infusion) can be detrimental in patients after the very acute phase of HIT as they should be mobilised.[12]

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing argatroban with danaparoid in patients with HIT type II who require parenteral antithrombotic therapy. SMC clinical experts have confirmed that danaparoid is an appropriate comparator. The results of the economic analysis were presented separately for patients with and without renal impairment. The submitting company stated that argatroban may have advantages in patients with renal impairment as, unlike the comparator danaparoid, there are no specific precautions when using argatroban in these patients. The time horizon of the analysis was 10 days.

The clinical data which underpin the assumption of comparable efficacy between argatroban and danaparoid were based on an indirect comparison using the Bucher method. A literature search was conducted which identified two argatroban studies and one danaparoid study to be used in the indirect comparison. The results indicated there was a numerical advantage in favour of danaparoid but, as the confidence intervals overlapped, the conclusion of no significant difference between the treatments was reached.

The analysis included drug acquisition and monitoring costs of argatroban and danaparoid. It was assumed there would be no difference in administration costs and therefore a cost was not included in the model. No other resource use was included. Monitoring for patients on argatroban requires a daily aPTT test. The monitoring of danaparoid was more complicated as it involves a daily anti-Xa test, but only for patients with renal impairment. As not all hospitals can perform an anti-Xa test, the cost of transportation of the samples to test centres was also included. This was estimated to be £110 per test and was assumed to apply to all patients.

For patients without renal impairment, the company estimated that argatroban treatment would result in an increased cost of £755. This is due to an increased drug cost with argatroban and no monitoring requirements with danaparoid if patients do not have renal impairment.

For patients with renal impairment, the company estimated that argatroban treatment would be associated with savings of £945 per patient. In this analysis, the increased drug acquisition cost of argatroban is offset by the increased monitoring costs in the danaparoid arm when used in patients with renal impairment. Reducing the length of treatment to 7 days in the argatroban arm and 5 days in the danaparoid arm reduced the cost saving to £20 in this subgroup.

The following weaknesses were noted:

- Due to weaknesses with the indirect comparison the conclusion of comparable efficacy between argatroban and danaparoid which underpins the cost-minimisation analysis is uncertain.
- The base case analysis assumes all anti-Xa tests would require transportation to a test centre at a cost of £110 per test. This is not appropriate as some patients will be treated in hospitals where the test can be carried out. When the transportation cost was removed argatroban treatment was associated with an incremental cost of £155 in patients with renal impairment. Threshold analysis from the company indicated that at least 14% of patients would require tests to be sent away for analysis for argatroban to be at least cost-neutral. SMC clinical experts were asked to comment on the relevant figure for NHS Scotland and a figure of 25% was suggested as being an appropriate estimate for transportation for tests.
- The aPTT test, anti-Xa test and transportation cost estimates were based on clinical opinion. Sensitivity analysis indicated that if the anti-Xa test cost and transport costs fell to £50 and £80 respectively, the cost saving for argatroban fell to £545. SMC clinical experts were asked to comment on the relevant costs currently incurred and responses suggest that the cost used by the company in the base case may be relatively high.
- The combined uncertainty from varying the assumed test/ transport costs and the number of tests requiring transportation was not investigated however additional analysis was provided by the company to address this.

The Committee acknowledged the limitations in the clinical evidence base that impacted on the economic analysis as well as the unmet need, identified by SMC clinical experts, for a treatment for HIT that may be used in patients with renal impairment. On balance the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology (BCSH) "Guidelines on the diagnosis and management of heparin induced thrombocytopenia: second edition" published in 2012 recommend the use of argatroban, danaparoid or (off-label) fondaparinux.[10] Bivalirudin is suggested as an alternative where urgent surgery is required and is recommended In patients with previous or present HIT who require coronary intervention including angiography and percutaneous coronary intervention. The initial anticoagulant treatment of HIT should be the same whether or not it is already complicated by thrombosis at the time of diagnosis.

In December 2010 the Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 122 on the prevention and management of venous thromboembolism.[13] 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. Bivalirudin has not been included in the cost table because BCSH guidelines recommend a narrower indication than that under review, (see above).

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Argatroban	**2 to 5 micrograms/kg/minute intravenous infusion[#]**	**1,740 to 4,970**
Danaparoid	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	1,014
Fondaparinux*	7.5mg subcutaneous injection once daily	82

Doses are for general comparison and do not imply therapeutic equivalence.
Doses calculated for body weight of 70kg. [#]Lower initial dose required if hepatic impairment, post-cardiac surgery or critically ill. *Fondaparinux is not licensed for treatment of HIT and doses have been taken from BCSH guidelines. Duration of treatment is variable and an average of 7 days was used to calculate costs for argatroban and fondaparinux. The SPC states that danaparoid should be used for 5 days plus four hours and the cost reflects this. Cost of fondaparinux from eVadis on 25.04.13. Costs of argatroban and danaparoid from MIMS on 01.05.13.

Additional information: budget impact

The submitting company presented two scenarios covering patients with and without renal impairment.

Scenario 1- patients without renal impairment
The submitting company estimated the population eligible for treatment to be 39 in all 5 years with an estimated uptake rate of 25% each year.

The gross impact on the medicines budget was estimated to be £24.2k in years 1 to 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £6.3k per year.

Scenario 2- patients with renal impairment
The submitting company estimated the population eligible for treatment to be 39 in all 5 years with an estimated uptake rate of 75% each year.

The gross impact on the medicines budget was estimated to be £72.7k per year. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £18.9k in year 1 per year.

References

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

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2. Mitsubishi. Summary of product characteristics for Exembol (argatroban).
3. Lewis BE et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 2001; 103: 1838-43.
4. Lewis BE et al. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 2003; 163: 1849-56.
5. US Food and Drug Administration. Medical review of argatroban.
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7. Merck Sharp Dohme. Summary of product characteristics for Orgaran (danaparoid).
8.. US Food and Drug Administration. Review of danaparoid.
9.. US Food and Drug Administration. Review of Atrixa (fondaparinux).
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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.
12. Alatri A, Armstrong AE, Greinacher A et al. Results of a consensus meeting on the use of argatroban in patients with heparin-induced thrombocytopenia requiring antithrombotic therapy – An European Perspective Thromb Res (2012), doi:10.1016/j.thromres.2011.11.041
13. Scottish Intercollegiate Guidelines Network. Guideline number 122: Prevention and management of venous thromboembolism, December 2010.

This assessment is based on data submitted by the applicant company up to and including 14 June 2013.

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.