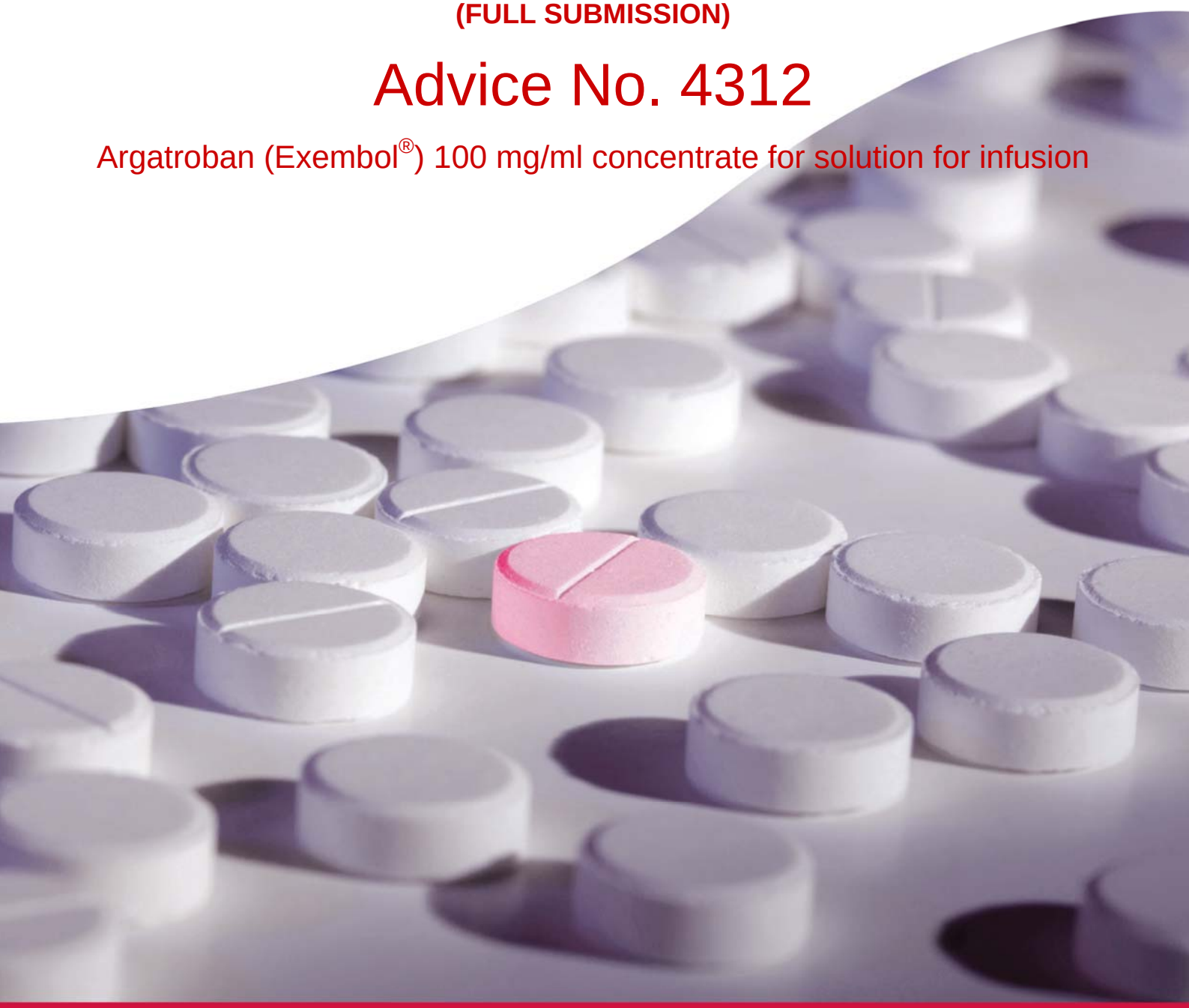
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 4312

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



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 4312
Argatroban (Exembol®) 100 mg/ml concentrate for solution for infusion

This assessment report is based on evidence submitted by Mitsubishi Pharma Europe Ltd on 23 July 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Argatroban (Exembol®) is indicated for anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II who require parenteral antithrombotic therapy. The diagnosis should be confirmed by the heparin induced platelet activation assay or an equivalent test. However, such confirmation must not delay the start of treatment[2].
Dosing	The initial dosage of argatroban in adult patients without hepatic impairment in HIT type II is 2 microgram/kg/min administered as a continuous infusion. Refer to the Summary of Product Characteristics (SPC) for further information regarding dose adjustments during treatment and dose modifications in special populations[2].
Marketing authorisation date	11 May 2012[1,2].

2.0 DECISION CONTEXT

2.1 Background

Heparin-induced thrombocytopenia (HIT)[*] is a serious complication of heparin therapy that can lead to the formation of arterial or venous thromboses, following treatment with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Most HIT patients develop thrombocytopenia five or more days after the first treatment with heparin; one-half to two-thirds of these patients will experience a thrombotic event, referred to as HIT with thrombosis syndrome (HITTS)[4]. Common resulting complications of HITTS are deep vein thrombosis, pulmonary embolism, limb artery thrombosis, thrombotic stroke and myocardial infarction[5].

The paradoxical association of a fall in platelet count with acute thrombotic events is the result of a heparin-driven immune response[6,7]. The development of heparin-dependent immunoglobulin G antibodies (HIT antibodies) and their binding to platelet factor 4, a procoagulant protein that promotes platelet aggregation and activation, leads to the formation of platelet-derived microparticles, which are thought to trigger the thromboses associated with HIT[6].

[*]Historically, an early onset, nonimmune fall in platelet count was designated as HIT type I, with later onset, immune mediated thrombocytopenia classified as HIT type II[3]. However, in practice this terminology is infrequently used; HIT usually refers specifically to HIT type II[3]. This report will follow convention and use HIT as synonymous with HIT type II.

Standard HIT treatment is the discontinuation of heparin, followed by initiation of an alternative anticoagulant that will not cross-react with HIT antibodies[5,8]. Argatroban is a synthetic direct-acting anticoagulant; its mechanism of action is thrombin inhibition and it is active against both soluble and clot-bound thrombii[9]. The only other available treatment option in the UK is danaparoid (Orgaran®). Lepirudin (Refludan®), another anticoagulant used to treat HIT, was permanently discontinued in April 2012 and the marketing authorisation subsequently withdrawn[10].

Reported estimates of the incidence of HIT vary between 0.5% and 5.0% of heparin-treated patients; factors that may influence the risk of HIT include the type of heparin used, its method of administration and the duration of heparin therapy[11,12]. The risk of HIT has been shown to be lower with LMWH than with UFH[13], although the quality of the evidence to support this is low[14].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was danaparoid.

2.3 Guidance and related advice

- British Committee for Standards in Haematology (Haemostasis and Thrombosis Task Force). Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition (2012)[8].
- Aneurin Bevan Health Board guidance for management of patients with heparin induced thrombocytopenia (2011)[15].
- American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia (2012)[5].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

In support of clinical efficacy and safety, the company submission provides evidence from two prospective, non-randomised, open-label studies, ARG-911 and ARG-915, both of which compared argatroban-treated patients with a historical control group[1,4,9].

3.1 Study design

3.1.1 ARG-911: Design

ARG-911 was conducted at 86 centres in the USA. Patients eligible for ARG-911 were men and non-pregnant, non-breastfeeding women aged 18–80 years, with thrombocytopenia (defined as a platelet count < 100 × 10^9/l, or a 50% reduction in platelet count after heparin therapy) with no explanation besides HIT. Patients were excluded if they had an unexplained activated partial thromboplastin time* (aPTT) greater than two times the control value at baseline, a lumbar puncture within the past seven days, any documented coagulation disorder or bleeding diathesis unrelated to HIT, or a history of previous aneurysm, haemorrhagic stroke or recent (within past six months) thrombotic stroke[1,9].

All patients enrolled in ARG-911 (n = 304) received argatroban as an intravenous (IV) infusion at a starting dose of 2 micrograms/kg/min. After two hours aPTT was determined and the dose adjusted until aPTT was between 1.5 and 3 times the baseline value (dose not to exceed 10 micrograms/kg/min; aPTT not to exceed 100 seconds). Treatment continued for a maximum of 14 days, but was stopped if the

*A measurement of the rate of blood coagulation, commonly used in the monitoring of heparin therapy.

clinical condition resolved or appropriate anticoagulation was provided by another agent. Patients were followed up for an additional 30 days after treatment cessation[1,9].

A historical control group (n = 193) was used for comparison with argatroban, due to the lack of any approved active comparator at the time of study initiation (1996), and the ethical issues associated with administering placebo to HIT patients. Control subjects were identified from patient records at participating centres, using the inclusion/exclusion criteria already described. Typically, suitable control subjects had been seen within the four years prior to initiation of ARG-911. Treatment was according to local standard practice at each study centre, typically heparin discontinuation and/or administration of oral anticoagulation (the agent given was not specified). Patients were followed up for 37 days from baseline[1,9].

The primary efficacy endpoint was a composite of all-cause death, all-cause amputation or new thrombosis, within 37 days of baseline. Between-treatment analysis was performed using both categorical and time-to-event methods. Secondary endpoints included each of the individual components of the composite endpoint, death caused by thrombosis, any new thrombosis, and resolution of thrombocytopenia (see Table 1 for endpoint definitions). The argatroban and control groups were both subdivided according to whether their HIT was complicated by thrombosis (HITTS arm) or not (HIT arm) and data presented separately for each arm[1,9].

3.1.2 ARG-915: Design

ARG-915 was a follow-on study to ARG-911, conducted at many of the same centres. The design of ARG-915 was largely as described for ARG-911. Inclusion/exclusion criteria differed slightly in that no upper age limit was applied for inclusion. A total of 418 patients were treated with argatroban; the historical control group consisted of the same patients as ARG-911, although the number of patients included for analysis differed slightly (n = 185)[1,4]. Some endpoints measured for ARG-911 were not reported for ARG-915.

3.2 ARG-911 and ARG-915: Efficacy results

Outcomes of ARG-911 and ARG-915 are presented in Table 1 and Table 2, respectively. Only endpoints for which data were available for both the argatroban and control groups are shown. All results are for the intent-to-treat (ITT) populations.

In ARG-911, the incidence of the composite primary endpoint was statistically significantly reduced in argatroban-treated patients compared to controls with HIT (p = 0.014); incidence was also reduced in argatroban-treated HITTS patients compared to controls, but the difference was not statistically significant (p = 0.131)[1,9]. By time-to-event analysis, the difference between treatment groups significantly favoured argatroban over the control group in both the HIT (hazard ratio [HR] = 0.60, 95% confidence interval [CI]: 0.40, 0.89, p = 0.010) and HITTS arms (HR = 0.57, 95% CI: 0.36, 0.90)[1,9]. The same pattern of results was seen in ARG-915 for the primary endpoint; categorical analysis showed a statistically significant difference between argatroban and controls only in HIT patients, but time-to-event analysis favoured argatroban over controls in both the HIT (HR = 0.64, 95% CI: 0.43, 0.93, p = 0.02) and HITTS arms (HR = 0.56, 95% CI: 0.36, 0.87, p = 0.008)[1,4].

Table 1. Primary and secondary outcomes from ARG-911 (ITT population)[1,9]

	HIT arm, n (%)			HITTS arm, n (%)		
	Argatroban (n = 160)	Controls (n = 147)	p value	Argatroban (n = 144)	Controls (n = 46)	p value
Composite primary endpoint	41 (25.6)	57 (38.8)	0.014	63 (43.8)	26 (56.5)	0.131
Death (all causes)*	27 (16.9)	32 (21.8)	0.311	26 (18.1)	13 (28.3)	0.146
Amputation (all causes)*	3 (1.9)	3 (2.0)	1.0	16 (11.1)	4 (8.7)	0.787
New thrombosis*	11 (6.9)	22 (15.0)	0.027	21 (14.6)	9 (19.6)	0.486
Any new thrombosis	13 (8.1)	33 (22.4)	< 0.001	28 (19.4)	16 (34.8)	0.044
Death caused by thrombosis	0 (0.0)	7 (4.8)	0.005	1 (0.7)	7 (15.2)	< 0.001
Resolution of thrombocytopenia†	104/129§ (81)	57/139§ (41)	-	100 (69)	23 (50)	-

* Components of primary endpoint. Most severe event counted; only one event counted per patient (severity ranking death > amputation > new thrombosis).
† Thrombocytopenia was defined as resolved if at any time during argatroban infusion (or within 7 days of baseline for control subjects) a baseline platelet count < 100 × 10^9/l increased to ≥ 100 × 10^9/l, or if a baseline platelet count of ≥ 100 × 10^9/l remained at the same level or increased during treatment.
§ Patients with latent disease were excluded from the analysis.

In both studies, incidence of new thrombosis (where this was the most severe event reported) was lower in the argatroban group than in the control group, although the difference was not statistically significant for HITTS patients in ARG-911. There was no significant difference in incidence of all-cause amputation or all-cause death between treatment groups. Across all populations in the two studies, incidence of death caused by thrombosis was significantly lower for argatroban-treated patients compared to controls[1,4,9].

Table 2. Primary and secondary outcomes from ARG-915 (ITT population)[1,4]

	HIT arm, n (%)			HITTS arm, n (%)		
	Argatroban (n = 189)	Controls (n = 139)	p value	Argatroban (n = 229)	Controls (n = 46)	p value
Composite primary endpoint	53 (28.0)	54 (38.8)	0.04	95 (41.5)	26 (56.5)	0.07
Death (all causes)*	36 (19.0)	29 (20.9)	0.78	53 (23.1)	13 (28.3)	0.45
Amputation (all causes)*	8 (4.2)	4 (2.9)	0.57	34 (14.8)	5 (10.9)	0.64
New thrombosis*	11 (5.8)	32 (23.0)	< 0.001	30 (13.1)	16 (34.8)	< 0.001
Death caused by thrombosis	1 (0.5)	6 (4.3)	0.04	6 (2.6)	7 (15.2)	0.002

* Components of primary endpoint. Most severe event counted; only one event counted per patient (severity ranking: death > amputation > new thrombosis).

3.3 Safety

3.3.1 ARG-911 and ARG-915

The incidence of major and minor bleeding was measured as a safety outcome in ARG-911 and ARG-915; results are presented in the company submission as a joint analysis (combining HIT and HITTS patients) from both studies[1]. For the combined argatroban-treated population from the two studies (n = 722), the number of patients with major or minor bleed events was 45 (6.2%) and 270 (37.4%), respectively; the equivalent results for the historical control group (n = 193) were 13 (6.7%) and 79 (40.9%)[1]. Adverse events were reported by body system; for the combined argatroban-treated population, the most commonly affected systems were the cardiovascular system, gastro-intestinal system, body as a whole and respiratory

system[1,4,9]. Treatment-emergent adverse events reported in ARG-911 and ARG-915 were in line with the safety profile described in the SPC[1,2,4,9].

3.3.2 Post-marketing experience

Argatroban has been licensed for treatment of HIT in other countries for several years and the safety profile is therefore informed by post-marketing experience. The company submission notes that since the SPC was first approved in Europe in 2004, there have been no updates related to safety[1].

3.4 Comparative clinical effectiveness of argatroban and danaparoid

No formal comparison of argatroban and danaparoid was included in the company submission; there are no head-to-head trials comparing the two treatments. As evidence for the effectiveness of danaparoid, the submission presents data from one study (Lubenow et al) which compared danaparoid (± coumarin) with a control group for the treatment of HIT[16]. This was a retrospective, non-randomised cohort study, conducted at 15 centres in Canada and Germany between 1986 and 1999. Patients included in the study had serological confirmation of HIT, a platelet count < 150 × 10^9/ml and a clinical requirement for further anticoagulation. The majority (89%) of patients had HITTS at study entry. Patients in the danaparoid arm (n = 62) received danaparoid either alone or in combination with coumarin (53/62 received coumarin in addition to danaparoid); control patients (n = 53) received ancrod ± coumarin, or coumarin alone. The primary endpoint was a composite of new, recurrent or progressive thrombosis, thrombotic death or limb amputation (maximum of one event per patient) at day seven[16]. Results of the study are summarised in Table 3.

Table 3. Primary and secondary outcomes from a study comparing danaparoid and controls for the treatment of HIT[1,16]

	Danaparoid (n = 62)	Controls (n = 56)	p value
Incidence of composite endpoint* at day 7 (primary endpoint)	8 (12.9%)	22 (39.3%)	0.001
Incidence of composite endpoint at day 35	12 (19.4%)	24 (42.9%)	0.009
New, recurrent or progressive thrombosis by day 35	11 (17.7%)	24 (42.9%)	0.004
Thrombotic death by day 35	2 (3.2%)	3 (5.4%)	0.667
Major bleed by day 35	8 (12.9%)	19 (33.9%)	0.008
* New, recurrent or progressive thrombosis, thrombotic death, limb amputation (max. 1 event per patient).			

Several other sources of evidence are briefly discussed in the company submission, but the study by Lubenow et al has been selected by the company as the most appropriate as it uses the most similar design to ARG-911/915. In the absence of any formal comparison of clinical effectiveness, the submission includes a crude, unadjusted comparison of outcomes from Lubenow et al with ARG-911 and ARG-915[1]. Results from ARG-911 and ARG-915 have been discussed in Sections 3.2 and 3.3 of this report; results of the study by Lubenow et al are summarised in Table 3. The company conclude that the evidence provided demonstrates that the safety and efficacy of both argatroban and danaparoid have been proven, but the lack of any head-to-head comparison does not allow for definitive conclusions on the comparative clinical effectiveness of the two treatments[1].

3.5 AWTTC critique

- At the time of request for the submission (January 2012), the licensed options for the treatment of HIT were danaparoid and lepirudin. However, in April 2012

the marketing authorisation for lepirudin was withdrawn and supply of this medicine was discontinued.

- There are no clinical trials directly comparing the clinical effectiveness of argatroban and danaparoid. Furthermore, the company state that the low incidence and pharmacological difference between treatments, combined with differences in design and inclusion/exclusion criteria for the available studies, makes comparison of treatments problematic. Analysis is therefore limited to the presentation of studies comparing each individual medicine against historical controls.
- All the clinical trials discussed have limitations. Comparison of argatroban and danaparoid with historical controls, instead of a prospective placebo- or active-controlled patient group, may introduce bias due to, for example, differences in diagnosis, treatment and dosing at the time when control patients were treated. In the study by Lubenow et al, the same limitations apply to the danaparoid treatment arm, where treatment was also retrospective. ARG-911 and ARG-915 both used a prospective argatroban treatment arm. However, since all eligible patients received argatroban, there was no randomisation or blinding of patients or investigators. Nevertheless, it is acknowledged that many of these limitations are unavoidable, given the urgency of treatment required by HIT patients, the limited other treatment options available when these trials were carried out, and the unacceptable nature of treating HIT patients with placebo.
- Argatroban is the only anticoagulant that can be used without dose adjustment in renal impairment, a common comorbidity in HIT patients[2]. Danaparoid can be used with caution in patients with moderate renal impairment, but is contraindicated in patients with severe renal impairment[17].
- Argatroban has a rapid onset of action and a short half-life (52 ± 16 minutes, compared to 25 hours for danaparoid[2,17]). The rapidly reversible nature of argatroban treatment may be advantageous for patients who are critically ill, require surgery or who experience bleeding. Antidotes are not available for either argatroban or danaparoid.
- Argatroban does not cross-react with HIT antibodies (a disadvantage of danaparoid) or induce formation of antibodies that alter its clearance[9,18].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis of argatroban compared to danaparoid, lepirudin and a 'no alternative anti-coagulation' treatment strategy for the treatment of adult patients with HIT who require parenteral antithrombotic therapy[1]. The analysis is based on a decision analytic model, which considers the clinical outcomes of death, new thrombosis or amputation in patients who cease heparin and commence the alternative anticoagulant strategy. Other treatment outcomes, such as major and minor bleedings, were considered as adverse events. In the absence of direct comparative data, unadjusted indirect comparisons are made between outcome data derived from the ARG-911[9] and ARG-915[4] studies of argatroban, and indirect comparisons of lepirudin versus danaparoid[19] and argatroban versus lepirudin[20]. Utility values are derived from a published cost-effectiveness analysis of HIT treatment strategies. The company reports that the model uses time horizons of 37 days for argatroban and 35 days for danaparoid.

4.1.2 Results

Cost-effectiveness estimates provided by the company, in response to queries raised by AWTTC, indicated that argatroban is less effective and more costly than danaparoid (see Table 4). This is due to higher mortality figures reported in historical control studies of agratroban and danaparoid[4,9].

Table 4. Company-reported results of the base case cost-utility analysis of argatroban versus danaparoid for the antithrombotic treatment in adult patients with HIT

Base case	Argatroban	Danaparoid	Difference
Cost of treatment including treatment of adverse events	£13,869	£13,659	£210
Total QALYs gained	10.03	11.20	-1.17
ICER	Argatroban dominated*		
* Argatroban estimated to be less effective and more costly than danaparoid. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

The company provided an alternative estimate of cost-effectiveness derived from an indirect comparison of lepirudin versus danaparoid[19] and argatroban versus lepirudin (unpublished study)[20]. This analysis produced marginally higher quality-adjusted life-years (QALYs) (11.78 versus 11.74) and marginally lower costs (£13,818 versus £13,858) for argatroban compared to danaparoid.

The company also presented the results of two-way sensitivity analyses of argatroban versus danaparoid, assuming simultaneous variation in the probabilities of: new thrombosis and amputation; death and new thrombosis; death and amputation. Sensitivity analyses of historical control studies confirm that argatroban remains dominated despite the probabilities of new thrombosis, amputation and deaths being covaried in two-way sensitivity analyses.

4.1.3 AWTTC critique

There are several areas of weakness and limitations to the economic evidence submitted by the company, relating to both the available data to parameterise the model and the methodological approaches to the modelling of costs and outcomes. Collectively, the results of the cost-utility analysis presented by the company are unreliable.

Key limitations and weaknesses include:

- Results of cost-effectiveness analysis based on published evidence suggest that argatroban is more expensive and less effective than dapanaroid in the treatment of patients with HIT. The results of indirect comparisons, suggesting that argatroban may be a cost-effective option, are based on unpublished data which cannot be verified.
- Although the company suggests a time horizon of 35–37 days, QALY estimates in the model relate to lifetime health states based on life expectancies of 15 years for the modelled cohort. However, costs are effectively limited to those accrued in the first 35–37 days of treatment, rather than considering costs over a lifetime.
- Due to different treatment regimens and individual dose adjustments for argatroban and danaparoid, there is uncertainty surrounding the drug acquisition costs included in the model. It is unclear whether all relevant short-term costs have been appropriately considered; for those experiencing

death, this is assumed to occur instantly and to be associated with no further resource use or costs.

- Sensitivity analyses presented by the company produced negative incremental cost-effectiveness ratios (ICERs). Although it is not clear from the company submission whether these ICERs arise from negative incremental costs or negative incremental QALYs, sensitivity analyses around the base case values at least suggest argatroban remains dominated.
- No scenario analyses have been conducted to assess the impact of the use of argatroban in specific subgroups, such as those with or without prior thromboses at initiation of treatment, or critically ill patients in whom a reduced initiation dose of argatroban is recommended.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches did not identify any published studies on the cost-effectiveness of argatroban versus danaparoid for the treatment of adult patients with HIT who require parenteral antithrombotic therapy.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on the rates of cardiothoracic and orthopaedic surgery in the UK, the company estimates that there are 92,276 patients who require antithrombotic therapy each year in Wales. It is assumed that 75% of these patients are treated with heparin: 10% (6,921 patients) with UFH and 90% (62,287 patients) with low molecular weight heparin LMWH. By applying HIT incidence rates of 2.6% and 0.2% to the number of patients treated with UFH and LMWH respectively, the company estimates that the total number of patients who may develop HIT every year in Wales would be 305. It is anticipated that this number will remain constant over the next five years. The analysis considers 100% market uptake for argatroban, starting from the first year following its introduction.

5.1.2 Results of company budget impact analysis

The company-reported number of patients eligible for treatment with argatroban, and the associated costs over the five-year period are summarised in Table 5. According to company estimates, treatment with argatroban would cost £1,200 per 75 kg patient, compared to £992 for danaparoid. The total cost of treating patients with argatroban is estimated to be £2,463,973 in year one, as per the resource use and costs assumed in the economic model, rising to £2,813,589 in year five (£13,199,095 over the period of five years). Assuming that all patients with HIT are currently treated with danaparoid, the company anticipates an annual saving of £74,514 due to the displacement of danaparoid by argatroban.

Table 5. Company-reported costs associated with the use of argatroban for the treatment of adult patients with HIT who require parenteral antithrombotic therapy

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	305	305	305	305	305
Uptake	100%	100%	100%	100%	100%
Number of treated patients	305	305	305	305	305
Argatroban administration and monitoring costs	£396,500	£396,500	£396,500	£396,500	£396,500
Other treatment costs	£2,067,473	£2,153,712	£2,242,970	£2,335,351	£2,417,089
Total cost	**£2,463,973**	**£2,550,212**	**£2,639,470**	**£2,731,851**	**£2,813,589**

5.1.3 AWTTC critique of the budget impact analysis

- Although the company provided new estimates of cost-effectiveness for argatroban in response to queries raised by AWTTC, resource use and costs included in the budget impact analysis are based on the original submission, and may therefore have limited relevance to the current submission.
- Estimation of eligible patient numbers is based on use in cardiothoracic and orthopaedic surgery patients only. As other uses are not considered, eligible patient numbers appear subject to uncertainty.
- Due to complex dosing schedules and dose adjustments for argatroban and danaparoid sodium, there is uncertainty around drug acquisition costs.
- Collectively, the company's estimates of cost savings associated with the use of argatroban in Wales should be treated with caution.

5.2 Comparative unit costs

Comparison of unit costs for argatroban and danaparoid is problematic due to individual dosing schedules and dose adjustments. Table 6 provides indicative comparative costs based on recommended doses[2,17] assuming a 75 kg patient, a treatment duration of approximately five days and rounding up to nearest whole vial. For more details on dosing schedules please refer to the relevant SPCs[2,17].

Table 6. Examples of drug acquisition costs for the treatment of adult patients with HIT who require parenteral antithrombotic therapy

Drug	Example regimen	Cost of five-day treatment*
Argatroban (Exembol®) 250 mg/2.5 ml concentrate for solution for infusion	2 microgram/kg/min by continuous infusion	£1,243
Danaparoid (Orgaran®) 750 units/0.6 ml solution for injection/infusion	2,500 units by bolus intravenous injection followed by 400 units/hour by intravenous infusion for 2 hours, then by 300 units/hour for 2 hours, then by maintenance dose of 200 units/hour for five days	£1,013

* Costs are based on MIMS[21] list prices as of 28 August 2012, assuming rounding up to nearest whole vial. See relevant SPCs for full dosing details[2,17].
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, argatroban is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 25 June 2012.
Date range of evidence search: No date limits were applied to searches.

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