HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 November 2011

ARGANOVA 100 mg/ml, concentrate for solution for infusion

B/1 vial of 2.5 ml (CIP 416 968-7)

B/6 vials of 2.5 ml (CIP 416 969-3)

Applicant: LFB BIOMEDICAMENTS

Argatroban monohydrate

ATC Code: B01AE03

Medicine for hospital prescription only.

Date of Marketing Authorisation: 21 June 2011
(European Marketing Authorisation by mutual understanding; reporting country: Sweden)

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Argatroban monohydrate

1.2. Background

Argatroban is a synthetic derivative of L-arginine. It is a reversible direct thrombin inhibitor. Argatroban's anticoagulant effect is independent of that of antithrombin; it does not interact with heparin induced antibodies.

1.3. Indication

"ARGANOVA 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 HIPAA (heparin induced platelet activation assay) or an equivalent test. However, such confirmation must not delay the start of treatment."

1.4. Dosage

"Treatment with ARGANOVA should be initiated under the guidance of a physician with experience in coagulation disorders. The initial dosage in adult patients without hepatic impairment in HIT type II is 2 microgram/kg/min, administered as a continuous infusion. Before being administered, heparin therapy should be discontinued and a baseline aPTT value obtained.

- Monitoring*:* In general, it is monitored using the activated partial thromboplastin time (aPTT). Tests of anticoagulant effects (including the aPTT) attain steady-state levels typically within 1-3 hours following initiation of treatment with ARGANOVA. The target range for steady-state aPTT is 1.5-3.0 times the initial baseline value, but not exceeding 100 seconds. Dose adjustment may be required to attain the target aPTT (see Dose Modifications). aPTT should be checked two hours after the start of the infusion to confirm that the aPTT is within the desired therapeutic range. Thereafter, the aPTT should be monitored at least once per day.
- Dose modifications: the dose can be adjusted based on the clinical course until the steady-state aPTT is within the desired therapeutic range (1.5 to 3.0 times the initial baseline value but not exceeding 100 seconds). In case of an elevated aPTT (greater than 3 times baseline or 100 seconds), the infusion should be discontinued until the aPTT is within the desired range of 1.5 to 3 times baseline (typically within 2 hours of discontinuation of infusion). The infusion will then be restarted at one half of the previous infusion rate. The aPTT should be checked again after 2 hours. The maximum recommended dose is 10 microgram/kg/min. The maximum recommended duration of treatment is 14 days, although there is limited clinical experience of administration for longer periods."

<u>Special/populations situations</u>

- Elderly patients: the standard initial dosage recommendations for use in adults are applicable to elderly patients.
- Renal impairment: "The standard initial dosage recommendations for use in adults are applicable to patients with renal impairment. Limited data is available from the use of ARGANOVA in haemodialysis. Based on the data, therapy could be initiated with an initial bolus (250 microgram/kg) followed by continuous infusion of 2 microgram/kg/min.

The infusion is stopped 1 hour before the end of the procedure. The target Activated Clotting Time ACT range is 170-230 seconds (measured using the Haemotec device).

In patients that are already being treated with ARGANOVA, no bolus dose is required. ARGANOVA clearance by high flux membranes used during haemodialysis and continuous veno-venous haemofiltration was clinically insignificant.

- Hepatic impairment: "For patients with moderate hepatic impairment (Child-Pugh Class B), an initial dose of 0.5 microgram/kg/min is recommended. The aPTT should be monitored closely and the dosage should be adjusted as indicated clinically. ARGANOVA is contra-indicated in patients with severely impaired liver function.
- Paediatric population: limited published data are available. Data from a prospective clinical study in 18 children (neonates to 16 years old) are available. Neither the safe and effective dose of ARGANOVA, nor the effective target range for aPTT nor the activated clotting time (ACT) have been clearly established in this patient population.
- Patients with HIT Type II after cardiac surgery and critically ill patients: limited data are available on the use of ARGANOVA in patients with HIT Type II after cardiac surgery and critically ill patients (intensive care unit (ICU) patients with (multiple) organ system failure). Based on available data, therapy could be initiated with a starting infusion rate of 0.5 microgram/kg/min (maximum 10 microgram/kg/min) and adjusted to the target aPTT range of 1.5-3.0 times baseline value (not exceeding 100 seconds).
  In critically ill/ICU patients with severe (multiple) organ failure (as assessed by SOFA, APACHE-II or comparable scores) a reduced maintenance dose is recommended. The clinical status of the patient, especially acute changes in hepatic function, should be taken into account and the infusion rate should be carefully adjusted to maintain the aPTT in the desired range.
  An increase in the frequency of monitoring is recommended to ensure the target aPTT values are achieved and maintained.
- Patients with HIT Type II undergoing percutaneous coronary intervention (PCI): limited data are available from the use of ARGANOVA in patients with HIT Type II and undergoing concomitant percutaneous coronary intervention. Based on the data, therapy could be initiated with a bolus dose of 350 microgram/kg over 3 to 5 minutes followed by an infusion dose of 25 microgram/kg/min. Activated coagulation time (ACT) should be checked 5 to 10 minutes after the bolus dose is completed. The procedure may proceed if the activated coagulation time (ACT) is greater than 300 seconds. If the activated clotting time (ACT) is below 300 seconds, an additional bolus dose of 150 microgram/kg should be administered. The infusion rate may be increased to 30 microgram/kg/min, and the activated clotting time (ACT) should be checked 5 to 10 minutes later. If the activated coagulation time (ACT) is higher than 450 seconds, the infusion rate should be decreased to 15 microgram/kg/min and ACT values be checked 5 to 10 minutes later. Once a therapeutic ACT between 300 to 450 seconds has been achieved, the infusion dose should be continued for the duration of the procedure. Activated coagulation time (ACT) measurements were recorded using both Haemotec and Haemochrom devices. The efficacy and safety of ARGANOVA use in combination with GPIIb/IIIa inhibitors have not been established.

  Specific dosing information on patients with hepatic impairment undergoing PCI is not available. Therefore the use of ARGANOVA for treatment of patients with hepatic impairment requiring PCI is not recommended.

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2010)

B	Blood and blood-forming organs
B01A	Antithrombitic agents
B01AE	Direct thrombin inhibitors
B01AE03	Argatroban

2.2 Medicines in the same therapeutic category

Other direct thrombin inhibitors:

- lepirudin[1]: REFLUDAN 50 mg, lyophilised powder for solution for injection.

For the indication: "Anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II and thromboembolic disease mandating parenteral antithrombotic therapy."

2.3 Medicines with a similar therapeutic aim

Factor IIA and XA inhibitor:

- danaparoid sodium: ORGARAN 750 IU anti-Xa/0.6 ml, solution for injection.

Particularly indicated for:
"- Prevention of thrombo-embolic disorders in patients with acute heparin-induced thrombocytopenia (HIT) type II with no thrombo-embolic complications, or with documented history of HIT type II, who require urgent parenteral anti-thrombotic because of a history of HIT type II.
- Treatment of thrombo-embolic disorders in patients who require parenteral anti-thrombotic because of the development or documented history of heparin-induced thrombocytopenia (HIT)."

This medicinal product is included on the list for reimbursement at a rate of 100% for the two indications.

1 Lepirudin is a recombinant hirudin derived from yeast cells. It is a direct and specific thrombin inhibitor.

3. ANALYSIS OF AVAILABLE DATA

Argatroban obtained initial Marketing Authorisation in 1990 in Japan for the treatment of chronic occlusive arterial disease. Then, from 2000, argatroban was marketed in the United States and Canada for anticoagulation treatment of patients with heparin-induced thrombocytopenia (HIT) type II.[2] In Europe, it a obtained Marketing Authorisation for HIT in Sweden in October 2004, then, through the mutual understandings procedure, subsequently in Germany, the Netherlands, Austria, Italy, Norway, Denmark and Iceland. From 2010, this proprietary medicinal product had a Marketing Authorisation in France and in Spain.

In France, argatroban has been available since 2009 through a nominative TAU, under the ARGATRA brand, and the responsibility of MITSUBISHI PHARMA EUROPE. The initial TAU dated July 2008: within the context of stock availability issues for ORGARAN, 35 patients were treated with argatroban for HIT with the understanding that they could not also receive REFLUDAN. Then 19 patients also benefited from this procedure in March 2009 for the same reasons. Since then, 15 patients with HIT were treated with argatroban in 2010 and 7 in 2011: these patients were not able to receive ORGARAN or REFLUDAN.

Evaluation of the clinical efficacy of argatroban (ARGANOVA) is based on the results from two comparative clinical studies versus a historical control group (studies ARG-911 and 915).

3.1. Efficacy data

3.1.1. ARG-911 Study [3]

The aim of this study was to evaluate the efficacy and tolerance of argatroban in the prevention of thromboses in patients with HIT and in the treatment of thromboses in patients with heparin-induced thrombocytopenia type II thrombosis (HITT).

Methodology:

A prospective, non-randomised, open-label, multi-centred study with a historical control group (retrospective) of patients also with HIT. The studies comprised of one HIT arm and one HITT arm.

Patients in the control group had thrombocytopenia and met the same inclusion and exclusion criteria as the patients being treated. These patients were seen in the clinical study centres in the four years prior to the start of the study. They were identified through a subsequent review of patient files. They were treated using standard therapies in place at the time: stopping heparin combined with or without oral anticoagulant treatment. A centre had to include a maximum of three control patients, identified chronologically, per patient included in the prospective study: 193 patients were eligible to be part of the control group (147 in the HIT and 46 in the HITT arm).

The patients were monitored from Day 0 up to the end of treatment, and then for 30 days after treatment had stopped. The control patients were monitored 37 days after Day 0.

Inclusion criteria:
- Aged 18 to 80 years inclusive;
- Documented heparin-induced thrombocytopenia, defined by a platelet count of <100 x 109/l or a reduction of 50% in platelet count with heparin due to no other possible cause;

[2] The term heparin-induced thrombocytopenia is used to qualify thrombocytopenia type II which occurs with unfractionated heparin or LMWH. Thrombocytopenia type II is a potentially serious, immunologically based condition and generally has a delayed onset. Thrombocytopenia type I is benign, non-immune based and with early onset with no thrombotic complications which regress despite continuation of heparin treatment.

[3] Lewis B.E. et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 2001; 103 (14): 1838-43.

- Previous medical history of HIT documented by the presence of antibodies and requiring anticoagulation treatment.

A list of non-inclusion criteria:
- Unexplained aPTT > 2 times the reference at Day 0;
- Documented coagulation issues or haemorrhagic diathesis not linked to HITT;
- Lumbar puncture in the seven days prior to inclusion;
- Previous medical history of aneurysm, recent haemorrhagic cerebral vascular accident (CVA) or thrombotic CVA (in the past six months) not linked to HITT;
- Prothrombin time greater than 16 seconds in the absence of warfarin;
- Clinical haemorrhagic episode in a known location (such as gastrointestinal bleeding, haematuria, a haemorrhagic CVA, a retroperitoneal haematoma, diabetic retinopathy, a haemorrhagic pericardial effusion and a haemorrhagic pleural effusion);
- Concomitant use of cimetidine.

Exclusion criteria:
- Interruption in the infusion of argatroban of more than 24 hours consecutively;
- Inter-current illness affecting the assessment of the patient's clinical state, according to the clinical investigator;
- Non-compliance.

Argatroban dosage:
After stopping heparin, the patients received argatroban at a dosage of 2 µg/kg/minute to obtain a sustained aPTT of between 1.5 and 3 times that of the reference (not exceeding 100 seconds). Administration was continued until the initial indication for anticoagulant treatment disappeared, or until appropriate anticoagulation was achieved through other anticoagulants and in other cases for 14 days.

Primary efficacy endpoint:
The primary efficacy endpoint involved the occurrence, up to Day 37, of at least one of the following events: death from any cause, amputation or a new thrombosis.

The occurrence of a primary efficacy endpoint with no treatment was estimated at between 30 to 50% for patients with either HIT or HITT. So as to show a difference in efficacy of 20% with an α risk of 1% and a β risk of 10%, it was estimated that 150 patients would be needed per treatment arm, and at least 60 control patients with HIT and 50 control patients with HITT.

Secondary endpoints (up to Day 37):
- each component of the primary efficacy endpoint to be treated separately (death from any cause, amputations and new thromboses);
- correction of thrombocytopenia;
- effective anticoagulation (i.e. an aPTT > 1.5 times the value on Day 0).

Results

Characteristics of the population evaluated: the two groups were of a different age, with patients being younger in the argatroban group. In the HIT group, a difference between the control group and the group treated with argatroban in terms of gender and the number of patients with a positive antibody test was seen (see table 1).

After stopping heparin, 304 patients with HIT received argatroban (n = 160 in the HIT arm and n = 144 in the HITT arm). These 304 patients were compared with 193 patients from the historical reference group (n = 147 in the HIT arm and n = 46 in the HITT arm).

Table 1 - Demographic characteristics at inclusion

	HIT arm		**HITT arm**	
	Argatroban n = 160	**Control n = 147**	**Argatroban n = 144**	**Control n = 46**
Age, years (mean ± standard deviation)	61.3 ± 13.5*	66.1 ± 12.3	61.5 ± 12.7*	65.7 ± 10.9
Gender, number (%)				
Male	68 (43)*	83 (56)	72 (50)	28 (61)
Female	92 (57)*	64 (44)	72 (50)	18 (39)
Weight, kg (mean ± standard deviation)	78.9 ±18.6	80.0 ± 22.8	83.0 ± 20.5	83.8 ± 24.7
Positive test, † number (%)	80 (50)*	119 (81)	94 (65)	30 (65)
Platelet count, x 10^9/l				
Median	82	111	66	94
Inter-quartile range	51 – 145	79 – 159	36 – 112	57 – 225
Vascular disease	160 (100)	126 (86)	142 (99)	43 (94)

*$p \leq 0.05$ *vs.* control group.
† Positive platelet function test or serotonin release test. Results for the other patients were either negative or not determined.

In the HIT arm, 31 out of 160 patients (19.4%) from the argatroban group and 8 out of 147 patients (5.4%) of the control group had a proven medical history of HIT (with a positive antibody test) without thrombocytopenia at inclusion and requiring anticoagulation treatment: they had therefore not reached the acute stage of HIT.
The mean argatroban dosage was 2.0 ± 0.1 µg/kg/min in the HIT group and 1.9 ± 0.1 µg/kg/min in the HITT group. The mean treatment duration was 5.3 ± 0.3 days in the HIT group and 5.9 ± 0.2 days in the HITT group.

From the 304 patients treated with argatroban:
- 252 (83%) continued with treatment throughout the specified period;
- 30 (10%) stopped treatment prematurely: 6 due to a surgical procedure, 3 at the request of the patient and 21 for other reasons, such as an increase in aPTT, a positive blood culture result, or a decision to stop treatment.

The efficacy results were obtained from the intention-to-treat population. The comparison between the group treated with argatroban and the historical control group for the primary efficacy endpoint was made through the analysis of category data and the analysis of the delay in the occurrence of an event.

Primary efficacy endpoint:

In the HIT arm, a reduction was observed in the incidence of the primary efficacy endpoint in the group treated with argatroban compared with the reference group: 25.6% of patients treated with argatroban developed one of the events from the primary endpoint (death, amputation or new thrombosis) versus 38.8% of patients from the reference group (p = 0.014).

Based on the estimated relative risk (1.84; 95% CI [1.13 – 2.99]), in the control group there is an additional risk of 84% of death, an amputation or a new thrombosis occurring compared with the group treated with argatroban.

In the HITT arm, there was no difference in the incidence of the primary endpoint between the group treated with argatroban and the reference group (43.8% versus 56.5%, p = 0.131).

Analysis of the delay in the occurrence of one of the three events of the primary efficacy endpoint was in favour of patients in the group treated with argatroban in the HIT arm (HR = 1.725, 95% CI [1.154 - 2.579] p = 0.0067) and in the HITT arm (HR = 1.710, 95% CI [1.082 - 2.702] p = 0.0181).

Secondary endpoints:

A decrease in the number of patients with new thromboses was observed in the group treated with argatroban compared with the reference group (8.1% versus 22.4% p < 0.001 in the HIT arm and 19.4% versus 34.8% p = 0.044 in the HITT arm). A difference was not observed between the two groups concerning the occurrence of death and the occurrence of an amputation (Table 2).

Table 2: Efficacy results for the primary and secondary endpoints

Endpoints	**HIT arm**			**HITT arm**		
	Argatroban (n = 160)	**Control (n = 147)**	***p***	**Argatroban (n = 144)**	**Control (n = 46)**	***p***
Primary efficacy endpoint*	41 (25.6)	57 (38.8)	0.014	63 (43.8)	26 (56.5)	0.131
	odds ratio = 1.84 (95% CI [1.13 – 2.99])			odds ratio = 1.67 (95% CI [0.86 - 3.26])		
Endpoints, by severity†						
Death from any cause	27 (16.9)	32 (21.8)	0.311	26 (18.1)	13 (28.3)	0.146
Amputation (any cause)	3 (1.9)	3 (2.0)	1.000	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

Numerical values (%).

* Death (from any cause) or amputation (from any cause), or a new thrombosis during the study (37 days).

† Severity classification: death (from any cause) > amputation (from any cause) > new thrombosis; patients with several events were only counted once.

‡ Concerns any new thrombosis without referring to severity classification. Patients were only counted once.

Thrombocytopenia was corrected for 69% to 81% of patients treated with argatroban and for 41% to 50% of reference patients. At Day 3, thrombocytopenia was corrected for more than 50% of patients treated with argatroban (Table 3).

*Table 3 : Correction of thrombocytopenia**

	HIT arm		HITT arm	
	Argatroban	**Control**	**Argatroban**	**Control**
During treatment†	104 / 129 (81)	57 / 139 (41)	100 / 144 (69)	23 / 46 (50)
In the 3 days after Day 0 ‡	56 /105 (53)	…	61 / 105 (58)	…

The values correspond to the number of people achieving correction of thrombocytopenia (%).

* See Methodology for the definitions.

† The patients in the HIT arm with a previous history of HIT were excluded; patients with missing data were considered as study failures.

‡ Analysis was only carried out on the group treated with argatroban; patients with missing data were excluded. 95% CI: HIT, 44% to 64%; HITT, 48% to 68%.

Effective anticoagulation with argatroban was achieved in more than 83% of patients during the study and in the majority of cases in the 4 to 5 hours following the start of treatment. The median aPTT increased from 29.9 seconds on Day 0 to 60.4 seconds (inter-quartile range: 51.0 to 71.8) in the HIT arm and 67.5 seconds (inter-quartile range: 53.9 to 83.4) in the HITT arm, in the 12 hours after the start of treatment with argatroban. During infusion, the aPTT remained stable with daily median values of 52.2 to 62.6 seconds in the HIT arm and 52.4 to 68.0 seconds in the HITT arm (Table 4).

Table 4: Patients treated with argatroban achieving effective anticoagulation (aPTT of ≥ 1.5 the aPTT value on Day 0)

	HIT arm		HITT arm	
	Number	**%**	**Number**	**%**
During study †	133 /160	83	135 / 144	94
After first sample ‡	106 / 139	76	104 / 129	81

† Patients with missing data were considered as treatment failures.

‡ For patients with available data and an initial dose of 2 µg/kg/min. HIT, 95% CI [68%-83%]; HITT, 95% CI [73%-87%]. Average delay (median) for the first sample for those that achieved effective anticoagulation: HIT, 4.6 (2.9) hours; HITT, 3.9 (2.9) hours.

3.1.2. ARG-915 Study [4]

The aim of this study was to evaluate the efficacy and tolerance of argatroban in patients with heparin-induced thrombocytopenia type II, with or without thrombosis, requiring anticoagulation treatment.

The methodology for this study was similar to that of the ARG-911 study:
The reference group is a historical group of patients with HIT type II, identical to that in the ARG 911 study. In this study, the necessary number of patients was not calculated. The patients previously included in the ARG-911 study were eligible to be included in this study. In addition, patients included in the ARG-915 study were able to be re-included in the study if treatment was necessary again. These patients were noted as being "repeat" patients. Given the study methodology, the results are presented for information only.
After stopping heparin, patients with HIT received argatroban at a dose of 2 µg/kg/minute adjusted to obtain a sustained aPTT of between 1.5 and 3 times that of the reference (not exceeding 100 seconds). A lower initial dosage was authorised based on evidence of a concomitant disease (such as hepatic impairment).
Patients in the control group met the same eligibility criteria as those patients in the study and were treated in accordance with local hospital practices, i.e. stopping heparin in

4 Lewis B.E. et al. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 2003; 163: 1849-56.

combination with an oral anticoagulation treatment or not. Patients received argatroban until the initial indication for anticoagulant treatment disappeared, or until appropriate anticoagulation was achieved through other anticoagulants, or in other cases, treatment with argatroban was continued for 14 days. Patients were monitored from Day 0 up to the end of treatment, and then for 30 days after treatment had stopped. The control patients were monitored for 37 days after Day 0.

The primary efficacy endpoint was made up of different components, including death from any cause, amputation and new thromboses.

The secondary endpoints were:
- each component of the primary efficacy endpoint to be treated separately (death from any cause, amputation from any cause and new thromboses during the monitoring period);
- correction of thrombocytopenia at Day 3;
- anticoagulant effect of argatroban measured using the activated partial thromboplastin time (aPTT).

Results

The treated and reference patient groups were comparable in terms of demographic and baseline characteristics in the HIT and HITT groups.

A total of 291 patients received treatment with argatroban. Among these, 27 patients were considered as "repeat" patients (previously included in the ARG-911 study or included more than once in the ARG-915 study). These "repeat" patients were excluded from any analyses: the intention-to-treat population and analysis therefore includes a total of 264 patients.

The mean argatroban dosage was:
- In the HIT arm: 1.8 ± 0.1 µg/kg/minute over a mean duration of 5.1 ± 0.4 days.
- In the HITT arm: 1.9 ± 0.1 µg/kg/minute over a mean duration of 7.2 ± 0.6 days.

Among the 125 patients treated with argatroban in the HIT arm:
- 99 patients (79%) continued with treatment throughout the period specified in the protocol;
- 15 patients (12%) stopped treatment prematurely due to surgery (n = 2), non-compliance with protocol (n = 1), at the request of the patient or their family (n = 1), an intercurrent illness (n = 2), or for other reasons (n = 9).

Among the 139 patients treated with argatroban in the HITT arm:
- 109 (78%) completed the treatment period specified in the protocol;
- 12 (9%) needed to stop the infusion prematurely due to surgery in three cases, a lack of efficacy of the medicinal product in one case, due to an intercurrent illness in two cases, or for other reasons in six cases.

Primary efficacy endpoint:

The comparison between the group treated with argatroban and the control group for the primary efficacy endpoint was made through the analysis of category data and the analysis of the delay in the occurrence of an event.

In the HIT arm, a difference in favour of treatment with argatroban was observed in the incidence of the primary efficacy endpoint between the group treated with argatroban and the control group: 26% of patients treated with argatroban had one of the events from the primary efficacy endpoint versus 39% of patients from the reference group (p = 0.021).

In the HITT arm, there was no difference between the two arms (41% versus 57%, p = 0.067).
Analysis of the delay in the occurrence of one of the three events of the primary efficacy endpoint was in favour of patients in the group treated with argatroban in the HIT arm (HR = 1.646, 95% CI [1.067 - 2.539] p = 0.0217) and in the HITT arm (HR = 1.778, 95% CI [1.116 - 2.831] p = 0.0124).

Secondary endpoints:

In the group treated with argatroban, a decrease in the number of patients reporting a new thrombosis was reported, compared with the reference group in the HIT arm (4.0% versus 15.0%, p = 0.004) and in the HITT arm (4.3% versus 19.6%, p = 0.003). No difference was observed between the two patient groups treated with argatroban and the control group on the "death from any cause" and the occurrence of an amputation endpoints (table 5).

*Table 5: Efficacy results for the group of patients treated with argatroban and the control group for each arm**

Event	HIT alone			HITT		
	Argatroban group n = 125 N (%)	Control group n = 147 N (%)	*p*	Argatroban group n = 139 N (%)	Control group n = 46 N (%)	*p*
Primary efficacy endpoint†	32 (25.6)	57 (38.8)	0.021	57 (41.0)	26 (56.5)	0.067
Death from any cause‡	21 (16.8)	32 (21.8)	0.357	35 (25.2)	13 (28.3)	0.700
Amputation from any cause‡	6 (4.8)	3 (2.0)	0.309	16 (11.5)	4 (8.7)	0.786
New thrombosis‡	5 (4.0)	22 (15.0)	0.004	6 (4.3)	9 (19.6)	0.003

*Data is expressed numerically (percentage).

† Death from any cause, or an amputation from any cause, or a new thrombosis during the 37 days of the study.

‡ Severity classification: death (from any cause) > amputation (from any cause) > new thrombosis; patients with several events were only counted once.

Administration of argatroban was associated with an increase in platelet count on the third day of treatment above the threshold value of 100 x 10^9/l (table 6).

Table 6: Changes in platelet count after administration of argatroban between Day 0 and Day 3

	HIT arm		HITT arm	
	Argatroban	Control	Argatroban	Control
Platelet count on Day 0†	(n = 123) 99.21 ± 67.84	(n = 129) 124.79 ± 80.72	(n = 137) 85.02 ± 76.20	(n = 39) 103.16 ± 81.43
Changes in platelet count between Day 0 and Day 3	(n = 85) +42.32 ± 55.72	(n = 97) -32.61 ± 93.80	(n = 109) +47.83 ± 82.32	(n = 33) -13.40 ± 107.73

† units: x 10^9/l

An increase in aPTT was observed after argatroban administration in the HIT and HITT arms. The mean aPTT values increased from 38.8 seconds at Hour 0 to 69.2 seconds at Hour 12 in the HIT arm and from 37.0 seconds to 69.3 seconds in the HITT arm. These results remained stable during the three day monitoring period.

3.1.3 ARG-915 + ARG-915X Study

Inclusion in the ARG-915 study closed in October 1997. The inclusion period was extended (ARG-915X study). Data from the ARG-915 and ARG-915X studies were gathered and published.[4] Patients were included between 1 November 1996 and 31 August 1998 at the ARG-915 clinical study centres.

Methodology: it is identical to that of the ARG-915 study.

- The baseline characteristics of the two groups of patients (receiving argatroban and the historical control) were comparable except for the platelet count, which was lower for the group treated with argatroban than for the control group in the HIT arm (p<0.001).
- A total of 418 patients with HIT (189 with HIT alone and 229 with HITT) received argatroban. The reference group included 185 patients (139 with HIT alone and 46 with HITT).
- The mean argatroban dosage was:
    - in the HIT arm 1.7 (± 1.0) µg/kg/minute over a mean duration of 5.1 (± 4.2) days;
    - in the HITT arm 1.9 (± 1.1) µg/kg/minute over a mean duration of 7.1 (± 6.5) days.
- Among the 418 patients treated with argatroban:
    - 317 patients (76%) continued with treatment throughout the period specified in the protocol;
    - 54 patients (13%) stopped treatment prematurely due to surgery (n = 12), due to a significant increase in aPTT or INR (n = 10), a negative HIT antibody result after starting treatment (n = 9), transfer to a different study evaluating argatroban during coronary procedures (n = 8), at the request of the patient or their family (n = 4), an intercurrent illness (n = 4), or due to other reasons (n = 7);

Results:

Primary efficacy endpoint:

In the HIT arm, a reduction in the incidence of the primary efficacy endpoint was observed in the group treated with argatroban compared with the reference group (odds ratio = 0.61; 95% CI [0.39-0.98]; p = 0.04): 28.0% of patients treated with argatroban had one of the events of the primary efficacy endpoint (death, amputation, new thrombosis) versus 38.8% of patients in the control group (p = 0.04).

In the HITT arm, no difference between the two groups was observed concerning the incidence of primary efficacy endpoint events (41.5% vs. 56.5%, odds ratio = 0.55; 95% CI [0.29-1.03]; p = 0.07).

Analysis of the delay in the occurrence of one of the three events of the primary efficacy endpoint was in favour of patients in the group treated with argatroban in the HIT arm (odds ratio = 0.64; 95% CI [0.43-0.93]; p = 0.02) and in the HITT arm (odds ratio = 0.56; 95% CI [0.36-0.87]; p = 0.008).

Secondary endpoints:

*Table 7: Efficacy results for the group of patients treated with argatroban and the control group for each arm (HIT and HITT)**

	HIT alone			**HITT**		
Event	**Argatroban group n = 189 (%)**	**Control group n = 139 (%)**	***p***	**Argatroban group n = 229 (%)**	**Control group n = 46 (%)**	***p***
Primary efficacy endpoint†	53 (28.0)	54 (38.8)	0.04	95 (41.5)	26 (56.5)	0.07
Death from any cause‡	36 (19.0)	29 (20.9)	0.78	53 (23.1)	13 (28.3)	0.45
Death due to thrombosis	1 (0.5)	6 (4.3)	0.04	6 (2.6)	7 (15.2)	0.002
Amputation from any cause‡	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

* Data is expressed numerically (percentage). The significance threshold is P < 0.05 for the primary efficacy endpoint (composite) and P < 0.01 for the secondary endpoints (primary efficacy endpoint components and death caused by thrombosis).

† Death from any cause, amputation from any cause, or a new thrombosis during the 37 days of the study.

‡ The categories of events are not mutually exclusive; for a given category, a patient is only counted once, even if more than one event occurred.

In the group treated with argatroban, a significant decrease in the number of patients declaring a new thrombosis was observed, compared with the control group of the HIT arm (5.8% versus 23.0%, p<0.001) and in the HITT arm (13.1% versus 34.8%, p<0.001). No

significant difference was observed between the group of patients treated with argatroban and the reference group for the "death from any cause" and "amputations from cause" endpoints. The number of deaths due to thrombosis was significantly less in the argatroban group than in the reference group in the HIT arm (0.5% versus 4.3%, p = 0.04) and in the HITT arm (2.6% versus 15.2%, p = 0.002). The most common amputation site was the knee, occurring in 28 (6.7%) out of the 418 patients treated with argatroban (of which six patients had a bilateral amputation) and six (3.2%) out of the 185 reference patients (of which two patients had a bilateral amputation).

3.1.4. Summary of the efficacy results

Table 8: Summary of the efficacy results for the ARG-911, ARG-915 and ARG-915+ARG-915X clinical studys

		HIT arm			HITT arm		
ARG-911		**Argatroban**	**Control**		**Argatroban**	**Control**	
	Parameter	(n = 160)	(n = 147)	*P*	(n = 144)	(n = 46)	*p*
	Primary efficacy endpoint*	**41 (25.6)**	**57 (38.8)**	**0.014**	**63 (43.8)**	**26 (56.5)**	**0.131**
	Death (from any cause) †	27 (16.9)	32 (21.8)	0.311	26 (18.1)	13 (28.3)	0.146
	Amputation (from any cause) †	3 (1.9)	3 (2.0)	1.000	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
ARG-915		**HIT arm**			**HITT arm**		
		Argatroban	**Control**		**Argatroban**	**Control**	
	Parameter	(n = 125)	(n = 147)	*P*	(n = 139)	(n = 46)	*p*
	Primary efficacy endpoint*	**32 (25.6)**	**57 (38.8)**	**0.021**	**57 (41.0)**	**26 (56.5)**	**0.067**
	Death (from any cause) †	21 (16.8)	32 (21.8)	0.357	35 (25.2)	13 (28.3)	0.700
	Amputation (from any cause) †	6 (4.8)	3 (2.0)	0.309	16 (11.5)	4 (8.7)	0.786
	New thrombosis†	5 (4.0)	22 (15.0)	0.004	6 (4.3)	9 (19.6)	0.003
ARG-915+ARG-915-X		**HIT arm**			**HITT arm**		
		Argatroban	**Control**		**Argatroban**	**Control**	
	Parameter	(n = 189)	(n = 139)	*P*	(n = 229)	(n = 46)	*p*
	Primary efficacy endpoint*	**53 (28.0)**	**54 (38.8)**	**0.04**	**95 (41.5)**	**26 (56.5)**	**0.07**
	Death (from any cause) ‡	36 (19.0)	29 (20.9)	0.78	53 (23.1)	13 (28.3)	0.45
	Amputation (from any cause) ‡	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 due to thrombosis	1 (0.5)	6 (4.3)	0.04	6 (2.6)	7 (15.2)	0.002

Numerical values (%).

* Death or amputation or a new thrombosis during the clinical study (37 days).

† Severity classification: death (from any cause) > amputation (from any cause) > new thrombosis; patients with several events were only counted once.

‡ Concerns event without referring to severity classification. Patients were only counted once.

3.2. Adverse effects

The assessment of the adverse effects of argatroban is based on the ARG-911, ARG-915 and ARG-915X studys (722 patients) as well as pharmacovigilance data.

3.2.1. Data from ARG 911 study

Twenty-two patients (7%) left the study due to adverse effects. The adverse effects causing the stoppage of treatment for more than one patient were bleeding disorders (two patients), anaemia (two patients), gastro-intestinal haemorrhage (two patients) and a non-specific haemorrhage (three patients).

There was no difference in the incidence of haemorrhaging (major[5] or minor) between the argatroban and the control group.

Table 9: incidence of haemorrhagic events

	HIT arm		**HITT arm**	
	Argatroban n = 160 (%)	**Control n = 147 (%)**	**Argatroban n = 144 (%)**	**Control n = 46 (%)**
Major haemorrhage,* n (%)	5 (3.1)	12 (8.2)	15 (10.4)	1 (2.2)
	p = 0.078		*p* = 0.124	
	Odds ratio = 2.76		Odds ratio = 0.19	
	(95% CI [0.95 – 8.02])		(95% CI [0.02 – 1.49])	
Minor haemorrhage,* n (%)	64 (40.0)	60 (40.8)	60 (41.7)	19 (41.3)

* Patients having more than one event were only counted once.

In patients treated with argatroban in both the HIT and HITT arms, the most common adverse events were diarrhoea (11% of patients) and pain (9% of patients). The most common adverse events considered as being potentially linked to the medicinal product were skin rashes, non-specific haemorrhaging and purpuras for patients in the HIT arm (2% for each) and thrombophlebilitis for patients in the HITT arm (4%).

3.2.2. Data from ARG 915 study

In this study, out of a total of 694 reported adverse events, in 69% (182/263) of patients, the causality of the adverse event linked to argatroban was considered as "certain" in two cases (an increase in coagulation time and pain, both in the HITT group) and "probable" in two cases (increase in coagulation time and hyperbilirubinaemia, both also in the HITT group).

Among the 125 patients treated with argatroban in the HIT arm, 11 patients (9%) left the study due to adverse effects.

Among the 139 patients treated with argatroban in the HITT arm, 18 (13 %) left the study due to adverse effects.

The most commonly encountered adverse events were:
- in the HIT arm: dyspnoea (9% of patients), ventricular tachycardia (7% of patients), nausea (6% of patients), fever (6% of patients) and hypotension (5% of patients).
- in the HITT arm: fever (9% of patients), cardiac arrest (8% of patients), sepsis (8% of patients), hypotension (8% of patients), diarrhoea (7% of patients), peripheral ischaemia (6% of patients), pneumonia (5% of patients), ventricular tachycardia (6% of patients), respiratory failure (6% of patients) and heart failure (5% of patients).

5 A major haemorrhage is defined as any haemorrhage that lowers the haemoglobin level by 2 g/dl or more, or requires a transfusion of 2 units of red blood cells or more, or due to its location (intracranial, retroperitoneal, or at a joint prosthesis). Other haemorrhages are considered as being minor.

There was no difference in the incidence of haemorrhaging (major or minor) between the argatroban and the control group.

*Table 10: incidence of haemorrhagic events**

Event†	HIT alone		HITT	
	Argatroban group (n = 125)	**Control group (n = 147)**	**Argatroban group (n = 139)**	**Control group (n = 46)**
Major haemorrhage n (%)	4 (3.2)	12 (8.2)	6 (4.3)	1 (2.2)
	p=0.119		p=0.683	
Minor haemorrhage n (%)	37 (29.6)	60 (40.8)	60 (43.5)	19 (41.3)

* Data is expressed numerically (percentage).
† Patients having more than one event were only counted once.

Deaths: sixty two (62) patients treated with argatroban died; this occurred in 56 patients (21%) (21 in the HIT arm and 35 in the HITT arm) during the study. Of these 62 deaths, 13 (21%) were due to thrombosis (4 in the HIT arm and 9 in the HITT arm). The link to argatroban was considered by the clinical study investigators as possible for 2 deaths. A total of 45 patients from the control group (23%) (32 in the HIT arm and 13 in the HITT arm) died during the study.

3.2.3. Data from the ARG-915 and ARG-915X studys

- 47 patients (11%) left the study due to adverse effects. Adverse events occurring in more than one patient were gastrointestinal haemorrhaging (n = 5), multi-organ failure resulting in death (n = 3) and thrombocytopenia (n = 2).
- Haemorrhage: there was no difference in the incidence of haemorrhaging (major or minor) between the argatroban and the control group.

*Table 11: incidence of haemorrhagic events**

Event †	HIT alone			HITT		
	Argatroban group n = 189 (%)	**Control group n = 139 (%)**	***p***	**Argatroban group n = 229 (%)**	**Control group n = 46 (%)**	***p***
Major haemorrhage	10 (5.3)	12 (8.6)	0.27 ‡	14 (6.1)	1 (2.2)	0.48 §
Minor haemorrhage	59 (31.2)	57 (41.0)	0.08	87 (38.0)	19 (41.3)	0.74

* Data is expressed numerically (percentage).
† Patients having more than one event were only counted once; patients with both a major and minor haemorrhage were counted as having a major haemorrhage.
‡ Odds ratio, 0.59; 95% Confidence Interval, 0.25 – 1.41.
§ Odds ratio, 2.93; 95% Confidence Interval, 0.38 – 22.8.

3.2.4. Pharmacovigilance data

The latest PSUR covers the period from 1 February 2004 to 31 January 2009. For an exposure of approximately 297,500 patients treated for all indications specified, 157 serious expected and unexpected adverse effects (AE) and 62 non-serious unexpected adverse effects (totalling 219) were reported. Among them, 49 were serious and unexpected for the indication of HIT type II.

Table 12: number of patients treated for HIT type II between 1 February 2004 and 31 January 2009 (excluding Japan)

Country	01/02/2004 to 31/01/2005	01/02/2005 to 31/07/2005	01/08/2005 to 31/01/2006	01/02/2006 to 31/07/2006	01/08/2006 to 31/01/2007	01/02/2007 to 31/07/2007	01/08/2007 to 31/01/2008	01/02/2008 to 31/07/2008	01/08/2008 to 31/01/2009
United States Canada	**16,923**	**7,642**	**10,136**	**11,361**	**12,135**	**10,712**	**13,129**	**12,073**	**14,526**
Europe	**-**	**3**	**357**	**956**	**1,195**	**1,472**	**2,011**	**3,100**	**3,418**
TOTAL	**16,923**	**7,645**	**10,493**	**12,317**	**13,332**	**12,184**	**15,140**	**15,173**	**17,944**

Pharmacovigilance data led to amendments being made to the SPC.
In July 2004, fulmiant hepatitis and jaundice were added to section 4.8 "Adverse Effects" of the product characteristics on the CCDS (Company Core Data Sheet) at the request of the Japanese Ministry for Health (MHLW).
In July 2005, diabetic retinopathy was added, as a condition requiring extreme caution during administration of argatroban, in section 4.4 "Special warnings and precautions for use" on the CCDS.
In July 2008, three other changes were made:

- Information on the indication and the dosage for heparin-induced thrombocytopenia type II in Japan,
- Indication for paediatric patients in the United States,
- Standard guidelines for biological laboratory testing.

3.3. Other data

ORGARAN: In 2009, French hospitals were having difficulties with their supplies of ORGARAN. It was then recommended to "strictly reserve the prescription of ORGARAN to only those patients with acute HIT type II or to patients for whom there was no other satisfactory treatment alternative; limit the quantities ordered to only those who needed it specifically, as described above; or rely on REFLUDAN (lepirudin)".[6] In order to meet the needs of the prescribers, AFSSAPS authorised the marketing of argatroban under a specific TUA.

The SPC states that "generally, at therapeutic doses, danaparoid only has a minor effect in increasing the risk of haemorrhaging. There is a risk of crossed-reactivity of danaparoid and the heparin-induced antibody (between 5% and 10%); this is explained by the absence of the heparin molecule (or one of its fragments) in its composition and its low degree of sulfation, as well as a lower charge density. There is the risk of in vitro crossed-reactivity between danaparoid and plasma in patients with heparin-induced thrombocytopenia (between 5% and 10%). In order to minimise this risk, a platelet aggregation test with danaparoid should be taken, if possible, before starting treatment to check that there is no in vitro crossed-reactivity. However, treatment may be started without waiting for the result of this test. If the test comes back positive, then treatment should be stopped; administration of danaparoid should be carried out with daily monitoring of platelet count; in light of clinical signs (appearance of a new arterial or venous thrombosis or the spreading of a pre-existing thrombosis) and/or biological laboratory testing (aggravation of thrombocytopenia) that could indicate a crossed-reactivity, treatment should be stopped if necessary; if there is any doubt, an in vitro crossed-reactivity test should be performed."

REFLUDAN: the SPC mentions two prospective clinical studies including 198 patients with HIT type II treated with lepirudin. In the indication HIT type II with thromboembolic disease (125 patients), the overall mortality during the study period was approximately 9% while

6 AFSSAPS. Ruptures de stock et arrêts de commercialisation des médicaments ORGARAN 750 U anti Xa / 0,6 ml, solution injectable en ampoule (danaparoïde sodique) (No stock and stopping of marketing of ORGARAN 750 U anti Xa / 0.6 ml, solution for injection in vials (danaparoid sodium)) – Rupture de stock (30/03/2009) - http://www.afssaps.fr/Infos-de-securite/Ruptures-de-stock-et-arrets-de-commercialisation-des-medicaments/ORGARAN-750-U-anti-Xa-0-6-ml-solution-injectable-en-ampoule-danaparoide-sodique-Rupture-de-stock/(language)/fre-FR

amputations and new thromboembolic complications were recorded in 6% and 10%, respectively. A letter to recent prescribers[7] states that "REFLUDAN may cause anaphylactic-type allergic reactions or shock and that fatal anaphylactoid reactions have been reported during re-exposure to REFLUDAN. Before any reintroduction, an alternative therapy should be considered and discussed".

3.4. Conclusion

Efficacy results

The assessment of argatroban (ARGANOVA) is based on two non-comparatives clinical studies, which provide little information especially due to changes in practices.

In one study (ARG-911), argatroban was administered to 304 patients with a previous medical history of HIT, an isolated incident of HIT or with a thrombosis (HITT). These patients were compared to a historical group of 193 patients with HIT type II, treated using standard therapies available at the time (stopping heparin in combination with or without oral anticoagulant treatment). Compared with the reference group, argatroban significantly reduced the number of patients having one of the primary efficacy endpoint events (death, amputation, new thrombosis) in the 37 days after treatment uniquely for patients with HIT but without thrombosis: 5.6% versus 38.8% (p = 0.014). Based on the estimated relative risk (1.84 (95% CI [1.13 – 2.99])), for the reference group there is an additional risk of 84% of death, amputation or a new thrombosis occurring compared with the group treated with argatroban, uniquely for patients with HIT but without thrombosis. Argatroban significantly reduced the delay in the occurrence of one of the three primary efficacy endpoints in the HIT group (p = 0.0067, HR = 1.725, 95% CI [1.154-2.579] and the HITT group (p = 0.0181, HR = 1.710, 95% CI [1.082-2.702]). Based on the estimated relative risk in the HIT and HITT arms, for the reference group, there is an additional risk in the order of 70% compared with the group treated with argatroban of a primary efficacy endpoint occurring, and according to analysis of the secondary endpoints, it is the reduction in the number of new thrombosis cases which is different between the two groups. Thrombocytopenia was corrected with treatment for 69% to 81% of patients treated with argatroban and for 41% to 50% of reference patients. On Day 3, thrombocytopenia was corrected for more than 50% of patients treated with argatroban. Anticoagulation was effective during the study for more than 83% of patients treated with argatroban and in the majority of cases this was achieved four to five hours following the start of treatment.

In the other study, in addition to the methodology issues, there was no calculation made of the number of patients required (ARG 915). These results corroborate the previous results.

There is no study to compare the efficacy of argatroban to that of danaparoid (ORGARAN) or lepirudin (REFLUDAN), two medicinal products indicated for the same clinical situation.

7 AFSSAPS. Communiqués/Points Presse. Refludan et réactions anaphylactiques d'évolution fatale (Press release. Refludan and anaphylactic reactions with fatal developments) [18 January 2011]. http://www.afssaps.fr/Infos-de-securite/Communiques-Points-presse/Refludan-R-et-reactions-anaphylactiques-d-evolution-fatale/(language)/fre-FR.

Adverse effects

Argatroban has been marketed in Japan since 1990, in the United States and Canada since 2000 and in Sweden and Germany since 2004-2005. Tolerance data from the ARG-911 and ARG-915+ARG-915X studies include a total of 722 patients who received argatroban; the pharmocovigilance data is taken from the PSUR covering the period from 1 February 2004 to 31 January 2009 with an estimated exposure for all indications specified in the order of 297,500 patients. There is therefore clinical experience with this medicinal product.

Data taken from the both ARG-911 and ARG-915 studies do not show any statistically significant difference between the argatroban and the historical reference group in terms of the frequency of major or minor haemorrhages. To limit the risk of haemorrhage, the SPC states that the dose of argatroban should be adjusted to obtain a target aPTT of 1.5 to 3 times the initial baseline value, but not exceeding 100 seconds.

The most commonly reported adverse events in the ARG-911 study were diarrhoea (11% of patients) in the HIT arm and pain (9% of patients) in the HITT arm and in the ARG-915 study, dyspnoea (9% of patients) in the HIT arm and fever (9% of patients) in the HITT arm. The SPC states that anaemia, deep vein thrombosis, nausea and purpura are the adverse effects that are commonly considered as being potentially linked to argatroban in the clinical studies.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Heparin-induced thrombocytopenia (HIT) is a rare and serious condition, with a short-term life-threatening prognosis for the patient. This disease often occurs in weak patients, those in ICU and the elderly with a potential modified renal function. HIT exposes the patient to the risk of a haemorrhage (rare) and venous and/or arterial thrombosis (frequent) occurring. In the specific context of the intensive care unit (ICU) or during the post-operative period, the co-existence of other diseases (sepsis, haemorrhaging, large blood transfusions and DIVC) can lead to more severe thrombocytopenia. Thrombocytopenia can be aggravated by disseminated intravascular coagulation (DIVC) and be complicated by venous limb gangrene (rare). Deep vein thrombosis can affect 50% of patients with HIT, with pulmonary embolism occurring in 10 to 25% of cases. Neurological complications (in order of decreasing frequency: ischemic CVA, cerebral venous thrombosis, confusional state or transitory amnesia) and more rarely dermatological complications (skin necrosis at heparin injection sites can be occur, prior to thrombocytopenia) are also possible.

HIT requires the fast and effective substitution of heparin with another anticoagulant. The efficacy/adverse effects ratio for argatroban is considered as high.

In patients with HIT, ARGANOVA (argatroban) is considered as a preventive treatment for those without thromboembolic complications and as a curative treatment for those with thromboembolic complications. This medicinal product is a first-line therapy.

Public health benefit

Heparin-induced thrombocytopenia type II is a serious condition, with a potentially life-threatening prognosis in the absence of treatment, but represents a small burden to public health due to its rarity.

A reduction in the frequency of preventable adverse medicinal product reactions in hospital and outpatient care is a public health need that is already an established priority (Objective 26, 27, 28 of the Law of 9 August 2004 on public health policy).

Given the limitations of the studys presented (how long ago they took place, the historical control group, the absence of a comparison versus an active reference treatment already used, etc.), it is difficult to anticipate the additional impact in terms of morbidity and mortality (prevention and treatment of thromboembolic complications) of ARGANOVA compared with existing treatment alternatives.

ARGANOVA does not appear to provide the additional capacity to meet an identified public health need.

In terms of the organisation of care, making ARGANOVA available is of benefit in easing the potential supply issues of other proprietary medicinal products indicated for HIT.

Finally, given the existing treatments available, it is not expected that ARGANOVA will benefit public health.

Other alternative medicinal products exist: danaparoid (ORGARAN) and lepirudin (REFLUDAN).

In conclusion, the actual benefit of ARGANOVA (argatroban) is substantial.

4.2 Improvement in actual benefit (IAB)

ARGANOVA does not provide an improvement in actual benefit (IAB level V) in the treatment of adult patients with heparin-induced thrombocytopenia (HIT) type II, requiring parenteral anti-thrombotic treatment.

4.3 Therapeutic use

Heparin-induced thrombocytopenia (thrombocytopenia type II, HIT) is a clinical-biological syndrome that is the result of the interaction of factor 4 platelet antibodies (F4P) released by the platelets in the presence of heparin. This interaction leads to intense platelet activation as well as activating coagulation, which may lead to arterial and venous thromboses. HIT has a delayed onset (typically five to eight days, but this delay may be shorter in a patient exposed to heparin previously), and occurs following the administration of unfractionated heparin (UH) or, more rarely, low molecular weight heparin (LMWH). HIT is a rare occurrence. In patients treated with UH, the frequency of HIT varies from 1% in the medical to 3% in the surgical environment (rising to 5% in cardiac or orthopaedic surgery). In patients treated with LMWH, the occurrence HIT is possible, but it is rare, and below 1%.

According to the 2005 HAS report,[8] suspected HIT should be considered in the presence of the following events:

- platelet count < 100 G/l (in the absence of a previous count), and/or a relative drop in platelets across two successive counts (from 30% to 50% according to guidelines) under treatment with heparin;
- venous or arterial thromboses under treatment with heparin;
- resistance to heparin therapy with spreading of the initial thrombotic event;
- even if the patient is no longer on heparin, the presence of thrombosis or thrombocytopenia.

The use of heparins solely for validated indications, using heparins over as short time as possible with early change to AVK and the preferred use of LMWH in the stated indications will reduce the risk of HIT (primary prevention). The creation of a medical certificate to confirm the diagnosis of HIT is necessary (secondary prevention).

The decision to stop heparin and to replace it with a different antithrombotic immediately is taken when HIT is suspected and before confirmation from biological analysis.[9] In France, two medicinal products have Marketing Authorisation: danaparoid (ORGARAN) and lepirudin (REFLUDAN). There have been no clinical studys that have compared these products with each other in terms of either efficacy or tolerance.

8 Haute Autorité de Santé. Recherche d'anticorps potentiellement responsables d'une thrombopénie induite par l'héparine. (Investigation of antibodies potentially responsible for heparin-induced thrombocytopenia) Saint-Denis La Plaine: HAS; 2005. http://www.hassante.fr/portail/upload/docs/application/pdf/rapport_thrombopenie_par_heparine.pdf

9 Thrombopénie induite par l'héparine (Heparin-induced thrombocytopenia). French Society of Anaesthesia and Intensive Care (SFAR), Haemostasis and Thrombosis Study Group of the French Society of Haematology (GEHT), French Society of Cardiology (SFC), Society of Intensive Care Medicine in the French Language (SRLF). Expert conference, 2002. http://www.sfar.org/article/295/thrombopénie-induite-par-l-heparine-de-2002

According to guidelines from an Expert conference, attended by several learned societies (see ref. 8; these guidelines from 2002 are in the process of being updated):

- LMWH is contraindicated and platelet transfusions are not recommended as they can promote the onset of thromboses or the process of disseminated intravascular coagulation.
- Anti-vitamin K oral anticoagulants must never be used on their own in the acute phase of the disease. They can be reintroduced as soon as a rise in platelet count is confirmed.
- The elimination half-life of anti-Xa activity[10] for danaparoid is approximately 25 hours (half-life of anti-IIA activity is approximately 7 hours). There is a risk of crossed-reactivity between danaparoid and plasma in patients with heparin-induced thrombocytopenia (between 5% and 10%), but with only a low frequency of clinical complications. It can be administered subcutaneously (two or three injections per day) or via continuous infusion. It is mainly eliminated by the kidneys. The reduction in dosage in cases of renal impairment should be based on anti-Xa activity measurements.
- With lepirudin, changes to dosage are essential due to the extreme variations in intra and inter-patient anticoagulant action. It is also required in cases of renal impairment. Lepirudin can only be administered via infusion. Given the significance and the difficulties in biological laboratory testing of patients treated with lepirudin, it is recommended that they are transferred to specialist centres who have experience of this treatment. There is a major risk of haemorrhage. It is dependent on the dosage used and the clinical situation: it is higher for renal impairment, for associated thrombolytic treatment, for surgery or for recent catheterisations.
- There are no pharmacological antagonists for these two medicinal products. The major risk with lepirudin is haemorrhage, especially in cases of renal impairment, associated thrombolytic treatment, surgery or recent catheterisation.
- Insertion of an IVC filter may be proposed for pulmonary embolism. Surgical thromboembolectomy is carried out only for cases of ischaemia resulting in functional loss of limb(s) and/or a life-threatening prognosis.

<u>The place of argatroban (ARGANOVA) in the management of HIT</u>

Argatroban represents an alternative to both danaparoid and lepirudin. As it is metabolised by the liver it is of benefit in cases of renal impairment. Its short elimination half-life is of benefit in cases of haemorrhage and in a surgical context.

According to 2008 guidelines from the American College of Chest Physicians,[11] in patients with HIT that is "highly suspected or confirmed, with or without a thrombosis", the three anticoagulants with a Marketing Authorisation in France that can be prescribed are: danaparoid (grade 1B), lepirudin (grade IC) and argatroban (grade IC). In cases of renal impairment, argatroban is a better choice than lepirudin. Danaparoid may also be used with a moderate reduction in its dosage and an increase in coagulation monitoring. In cases of hepatic impairment, the plasma half-life of argatroban is increased. Danaparoid and lepirudin may also be used at reduced doses and with increased monitoring. In patients with thrombocytopenia judged as being at a low risk of HIT, and for those whose indication of anticoagulation therapy is not clearly defined, danaparoid at a low dose appears to be safer.

10 The antithrombotic effect of danaparoid essentially appears to be linked to its anti-Xa activity combined with a low anti-IIa activity.

11 Warkentin TE., Greinacher A., Koster A. et al. Treatment and Prevention of Heparin-Induced Thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 340S-380S.

4.4 Target population

ARGANOVA is indicated for anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II who require parenteral antithrombotic therapy. The target population includes all patients suspected of having HIT.

In France, all suspected HIT cases must be reported to the regional pharmacovigilance centre. According to data from Afssaps, 233 cases of thrombocytopenia were reported in 2004, of which 179 (76.8%) were tested for the antibody potentially responsible for HIT (12 with missing data). These data were subject to reporting bias, as only serious cases of thrombocytopenia with suspected HIT were reported. The significance of this under-reporting cannot be calculated. The figure of 179 is therefore an under-estimation of the target population.[12] According to the estimation made by the laboratory from sales figures for ORGARAN and REFLUDAN in France, the target population would be between 9,000 and 13,500 patients per year. The marketing of new oral anticoagulants, such as PRADAXA and XARELTO, may reduce the use of heparins in certain indications, and thus the occurrence of HIT.

4.5. Conclusion

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services.

12 Haute Autorité de Santé. Biological analysis of haemostasis anomalies. Updating of sub-chapter 5-02 “Haemostasis and coagulation” of the nomenclature of clinical pathology processes. Scoping. Department of Medical and Surgical Procedures Assessment, November 2010.