HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 July 2011

ARTISS, solutions for sealant, deep frozen
B/2 x 1 mL bottles (CIP code: 575 576-6)
B/2 x 2 mL bottles (CIP code: 575 577-2)
B/2 x 5 mL bottles (CIP code: 575 578-9)

Applicant: BAXTER

Component 1: sealer protein solution (human fibrinogen, aprotinin)
Component 2: solution of human thrombin (thrombin, calcium chloride)

ATC codes: B02BC (local haemostatics), V03AK (tissue adhesives)

List I
Medicinal product reserved for hospital use. The use of ARTISS is restricted to experienced physicians and surgeons

Date of Marketing Authorisation (decentralised procedure): 15 September 2009

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

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Component 1: sealer protein solution (human fibrinogen 91 mg/mL, bovine aprotinin 3000 KIU/mL)
Component 2: human thrombin solution (thrombin 4 IU/mL, calcium chloride 40 µmol/mL)

1.2. Background

ARTISS is different from other fibrin sealants in that it has a lower thrombin concentration (4 IU/mL rather than 500-1200 IU/mL), which leads to a longer coagulation time, which facilitates positioning of subcutaneous tissue.

1.3. Indications

"ARTISS is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or adjunct to sutures or staples (see section 5.1 of the SPC). In addition, ARTISS is indicated as an adjunct to haemostasis on subcutaneous tissue surfaces."

1.4. Dosage

"ARTISS is for hospital use only and may only be used by experienced physicians and surgeons.

Dosage
The amount of ARTISS to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.
The dose to be applied is governed by variables including the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.
Application of the product must be individualised by the treating physician. In clinical trials, the individual dosages have ranged from 0.2 to 12 mL. For some procedures (e.g. the sealing of large burned surfaces), larger volumes may be required. ARTISS has not been administered to patients over 65 years old in clinical trials.
The initial amount of the product to be applied area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.
As a guideline, one pack of ARTISS 2 mL (i.e., 1 mL Sealer Protein Solution plus 1 mL Thrombin Solution) will be sufficient for an area of at least 10 cm^2.
To avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of the mixed Sealer Protein/Thrombin Solution or each of the components should be applied.

Method and route of administration
For epilesional (topical) use.
Prepare the solution as described in section 6.6 of the SPC.
Before application, the surface of the wound should be as dry as possible."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

B: Blood and blood forming organs
B02: Antihaemorrhagics
B02B: Vitamin K and other haemostatics
B02BC: Local haemostatics

V: various
V03: All other therapeutic products
V03A: All other therapeutic products
V03AK: Tissue adhesives

2.2. Medicines in the same therapeutic category

Comparator medicines
Other proprietary medicinal products based on fibrinogen and thrombin are not specifically indicated for sealing or haemostasis of subcutaneous tissue or as replacements for conventional methods.

2.3. Medicines with a similar therapeutic aim

Other products based on fibrinogen and thrombin. The indications for these products are different from those for ARTISS:

- Proprietary medicinal products that are indicated in particular for sealing tissue when conventional techniques are inadequate:

BERIPLAST, powders and solvents for sealant
Beriplast can be used locally as supportive treatment where surgical procedures and standard techniques are insufficient:
- for improvement of haemostasis (including endoscopic treatment of bleeding gastroduodenal ulcer)
- to promote adhesion/sealing or as suture support.

TACHOSIL, medicated sponge
Supportive treatment for adults in surgery for improvement of haemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient (see section 5.1 of the SPC).
Note: Under its indication as a tissue sealant, TACHOSIL is used to seal the surfaces of internal organs when standard techniques are insufficient. [1]

- Proprietary medicinal products with indications other than tissue sealing:

EVICEL, solution for sealant
EVICEL is used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis (see section 5.1 of SPC).
EVICEL is also indicated as suture support for haemostasis in vascular surgery.

QUIXIL, solutions for sealant
Quixil is used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis.
Efficacy has been demonstrated in liver surgery and orthopaedic surgery (see section 5.1 of SPC).

TISSUCOLKIT, powders, solutions and solvents for fibrin sealant, for epilesional use
Supportive treatment designed to promote local haemostasis during surgery.

The actual benefit of these proprietary medicinal products is high.

[1] EPAR summary for the public for TACHOSIL
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000505/human_med_001072.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124

3 ANALYSIS OF AVAILABLE DATA

The efficacy and tolerance of ARTISS versus staples have been evaluated for the attachment of autologous skin grafts in burns patients in two randomised open-label studies:
- one phase I/II study,[2] which will not be described here, was an early-phase trial with multiple investigator-evaluated endpoints and involving a product that was slightly different from ARTISS (the manufacturing process involved fewer virus inactivation phases);
- a phase III non-inferiority study.

No clinical studies have been put forward by the applicant for other surgical situations.
No specific studies have been carried out with ARTISS to evaluate its effect on haemostasis of subcutaneous tissue.

3.1. Efficacy

Randomised open-label non-inferiority study[3] evaluating the efficacy of ARTISS in terms of adherence and healing of split-thickness skin grafts in burn patients, in comparison with staples.

Inclusion criteria:
- patients under 65 years of age,
- with burns to ≤ 40% of the total body surface area, using the following as assessment sites:
    - a burn involving 2-8% of the total body surface area, that could be divided into two areas;
    - or two bilateral burns each measuring between 1 and 4% of total body surface area.

Burns to the fingers and genital areas were excluded.

Treatments: each patient was his/her own control, and two comparable sites were identified on each of the 138 patients. On one site, the skin graft was attached using ARTISS that was thawed and then sprayed on (2-4 mL/100 cm^2), and on the other, the graft was attached with staples (control).

Primary efficacy endpoint: complete wound closure by day 28, as assessed by blinded evaluators using photographs, and defined by:
- absence of necrosis and granulation tissue;
- colour of graft is consistent with that of skin;
- a contiguous layer of epithelial cells.

Non-inferiority was assumed if the lower limit of the 97.5% confidence interval for the difference in percentages of complete closure of sites treated with ARTISS and sites treated with staples was greater than -10%.

Secondary endpoints:
- wound closure by days 14 and 28, assessed by planimetry;
- haematoma/seroma on day 1;
- engraftment by day 5;

[2] Gibran, N. et al. Comparison of Fibrin Sealant and Staples for Attaching Split-Thickness Autologous Sheet Grafts in Patients with Deep Partial- or Full-Thickness Burn Wounds: A Phase 1/2 Clinical Study J Burn Care Res. May-Jun. 2007; 28: 401-8.
[3] Foster K et al. Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: Results of a phase 3 clinical study J Burn Care Res Mar. 2008; 29: 293-303.

- scar maturation assessed by assessment of graft pigmentation, vascularity, pliability and height on the Vancouver Scar Scale at months 3, 6, 9 and 12.

Results:
A total of 138 patients were treated with ARTISS and with staples. ITT analysis was performed on 127 patients (106 on PP analysis).
Of the 127 patients for whom assessment was possible, 66.1% were men. Median age was 29 years. Median surface of burns was 11.8% of total body surface area. Median surface area treated with ARTISS and with staples was comparable (1.5%). Test sites were mainly extremities (87%) and torso and neck (13%).

- Primary efficacy endpoint:

Complete wound closure at day 28, assessed by blind evaluators using photographs, was obtained for 43.3% (55/127) of sites treated with ARTISS and 37% (47/127) of stapled sites; 97.5% CI [-2.9%; 15.5%]. Similar results were observed for the per-protocol analysis (45.3% vs 39.6%; 97.5% CI [-4.1%; not provided]).
The lower limit of the 97.5% CI of the difference in percentages of complete wound closure for sites treated with ARTISS and stapled sites was greater than the predetermined limit of -10% (-2.9%).
As a result, ARTISS was demonstrated to be non-inferior to staples in terms of complete wound closure at day 28.

Note: superiority of ARTISS to staples was not demonstrated (on ITT or PP).

- Secondary endpoints (ITT):

Wound closure, assessed using planimetry, was complete for 48.8% (63/129) of sites treated with ARTISS and 42.6% (55/129) of stapled sites at day 14 (at day 28: 70.3% vs 65.8%).

Haematoma or seroma was observed on day 1 in 29.7% (41/138) of sites treated with ARTISS and in 62.3% (86/138) of stapled sites.
Note: In view of the results obtained for the secondary endpoint, the indication in the Marketing Authorisation mentions that ARTISS has additive properties as a sealant as an adjuvant to haemostasis for subcutaneous tissue surfaces.

100% engraftment had occurred at day 5 in 62.3% (86/138) of sites treated with ARTISS and in 55.1% (76/138) of stapled sites.

Scar maturation results, based on pigmentation, vascularity, pliability and height, were evaluated using the Vancouver Scar Scale at 3, 6, 9 and 12 months, and the results were generally similar but involved a restricted number of patients (73 of the 138 patients were evaluated at 12 months).

In addition, ARTISS scored better than staples for criteria that were evaluated openly (such as patient satisfaction, quality of graft adherence as assessed by the investigator, preference for method of fixation, satisfaction with graft fixation, and overall quality of healing).

3.2. Tolerance

In the phase III study, adverse events reported for more than 5% of patients were similar for sites treated with ARTISS and with staples, with the exception of graft complications, which were more common with staples (1.4% or 2/138, versus 10.1% or 14/138). None of these events were classified as serious.

The most common adverse events were: total or partial skin graft failure (25.4% or 35/138 for sites treated with ARTISS and 23.2% or 32/138 for stapled sites), pruritus (20.3% or 28/138 vs 21% or 29/138) and infection (4.3% or 6/138 vs 5.1% or 7/138).

Like any product that contains protein, hypersensitivity allergy-type reactions (urticaria, generalised urticaria, difficulty in breathing, wheezing, hypotension, anaphylaxis) can occur in rare cases. Because of the presence of bovine aprotinin, there is a risk of anaphylaxis.

3.3. Conclusion

The efficacy of ARTISS, a solution based on human fibrinogen and thrombin, was evaluated in burn patients. There are no efficacy data for ARTISS in reconstructive plastic surgery for situations other than burns in adherence of subcutaneous tissue, or as an adjunct to haemostasis for subcutaneous tissue surfaces.

In a comparative study involving 138 burn patients, ARTISS was shown to be non-inferior to staples in the fixation of split-thickness skin grafts in terms of adherence and healing 28 days after the graft on small burned surfaces (median 1.5% of total body surface area).

Rates of the most common adverse events (skin graft failure, pruritus, infection) were similar for ARTISS and staples, with the exception of graft complications, which were more common for staples (1.4% versus 10.1%).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The conditions for which ARTISS is indicated, limited to lesions with small surface area, cause a significant deterioration in the quality of life.

Public health benefit:

As trials have only involved burn patients, the public health benefit can only be assessed in this area.
Serious burns can have significant consequences, and can have physical and psychological sequelae, with major repercussions on individuals and their families. Nevertheless, they represent a minor public health burden given the frequency with which they occur (in 2008, the standardised rate of serious burns was estimated at 0.7 per 100,000 inhabitants, and the number of hospital admissions for burns was around 9,000[4]).
Preventative action to limit avoidable premature mortality caused by accidents is a public health need. Nevertheless, management of serious burns, to which ARTISS could contribute, is not an identified public health priority.
Given the available data, which primarily come from one non-inferiority trial comparing ARTISS with staples in burns surgery, no improvement in graft fixation or healing can be expected from ARTISS. Furthermore, no quality of life data is available. In addition, as with all blood-derived medicinal products, there is a biological hazard, which requires particularly close monitoring and traceability.
There is also no guarantee that these results will be transposed into clinical practice, for the following reasons:
- the patients in the trial were not representative of those seen in practice (age, limited burn surface area, exclusion of zones that were irregular or exposed to movement/rubbing)
- the lack of data about long-term healing.

As a result, ARTISS is not expected to benefit public health.

[4] Annual report on burns epidemiology in mainland France. 2008. F Ravat and the SFETB epidemiology group

The treatment's efficacy has been shown in skin grafts for small surface areas in burns patients. The efficacy/tolerance ratio is moderate in the short term. The efficacy/tolerance ratio in the medium term remains to be determined.

This is intended as a curative treatment.

This proprietary medicinal product is an alternative method of sealing subcutaneous tissue in lesions with a small surface area.

There are non-drug alternatives (staples, sutures).

The actual benefit provided by ARTISS in the sealing of subcutaneous tissue in lesions with a small surface area is moderate.

The Committee is unable to assess the benefit and role of ARTISS in other surgical situations, given the absence of data.

4.2. Improvement in actual benefit (IAB)

In view of the results of the non-inferiority study, ARTISS does not provide an improvement in actual benefit in comparison with staples in the sealing of subcutaneous tissue in lesions with a small surface area.

4.3. Therapeutic use

Initial management of burns involves either chemical or mechanical debridement or excision. After preparation of the underlying connective tissue and granulation, a whole or meshed split-thickness skin graft is placed on the wound bed and held in place by standard methods, which vary depending on the local condition of the burned area (staples, sutures).

Efficacy data for ARTISS applied as a spray are mainly drawn from one randomised open-label study involving the fixation of split-thickness skin grafts in burn patients. No clinical data have been provided for other situations, including the repair of subcutaneous tissue detachment in reconstructive surgery.

In view of the limited data available, which are mainly drawn from one non-inferiority study versus staples in burn surgery, routine use of ARTISS sealant in practice cannot be recommended.
Use of this proprietary medicinal product on limited surface areas appears to be justified in specific situations (in the view of experts), particularly on mobile surfaces such as eyelids and hands, in children and in outpatient settings.

There are no data to support the use of ARTISS:

- as a replacement for skin sutures to close a surgical wound;
- for haemostasis and sealing in situations in which rapid adherence is required. In particular, ARTISS must not be used for cardiovascular operations that require sealing of vascular anastomoses.
- in neurosurgery;
- as suture support for anastomoses in the following areas:
    - gastrointestinal (e.g. in bariatric surgery);
    - vascular (e.g. in breast reconstruction).

In view of these facts ARTISS is an alternative method of sealing subcutaneous tissue in lesions with small surface area.

4.4. Target population

The target population consists of patients needing subcutaneous sealing of a small surface area and for whom the use of a fibrin sealant is necessary in order to achieve adherence.

There is no data in the literature concerning the proportion of burns operations that require the use of a fibrin sealant to achieve adherence of subcutaneous tissue. There is also no data about the proportion of patients who could receive a sealant to seal small areas of subcutaneous tissue.
As the epidemiological data is lacking, data is provided by the PMSI database (programme for clinical information systems).
According to this database, the total population of patients admitted to hospital because of burns was 9341 in 2008.[5] However, data about the proportion of burns patients who required skin grafts is not available.

Against this background, it is difficult to specify the number of patients who could benefit from the use of ARTISS.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services for adherence of subcutaneous tissue in lesions with small surface area.

The Transparency Committee wishes to receive additional data about conditions of use, efficacy and tolerance of ARTISS in normal medical practice in France within the next two years.
In particular, a comprehensive list should be given of the centres in which ARTISS is used (location, specialism, number of cases), and a representative sample of characteristics of patients who undergo surgery using ARTISS (age, gender, comorbidities, type of surgery, surface area and location of lesions) and the conditions in which this proprietary medicinal product is used (e.g. number and content of bottles used, use of antiseptics, use in combination with sutures and/or staples, satisfaction of surgeons with ease of use, etc.).
In addition, data about healing and tolerance outcomes should be provided.

[5] Annual report on burns epidemiology in mainland France. 2008. F Ravat and the SFETB epidemiology group