BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

TISSEEL, human fibrinogen and thrombin-based frozen solution for sealant

No clinical benefit demonstrated for improvement of haemostasis or to support sutures in vascular surgery, where standard surgical techniques are insufficient.

Insufficient actual benefit in the absence of data as a tissue glue to improve wound healing or to support sutures in gastrointestinal anastomoses and to improve adhesion of separated tissues when standard surgical techniques are insufficient.

Main points

- TISSEEL has Marketing Authorisation as supportive treatment where standard surgical techniques appear insufficient:
  - for improvement of haemostasis;
  - as a tissue glue to improve wound healing or to support sutures in vascular surgery and in gastrointestinal anastomoses;
  - for tissue sealing, to improve adhesion of the separated tissue.

- This sealant is intended to replace TISSUCOL KIT although their indications are not identical; TISSUCOL KIT has Marketing Authorisation only as supportive treatment intended to improve local haemostasis during a surgical procedure.

- TISSEEL improves perioperative haemostasis in comparison with manual compression alone, alongside standard methods (that do not use fibrin sealant) during planned hepatic and vascular surgery. However, no contribution towards reducing morbidity and mortality – specifically number of transfusions, repeat surgical procedures, operating time, duration of hospitalisation and death – has been demonstrated.

- In the absence of studies comparing TISSEEL with another fibrin sealant or thrombin-based product, its therapeutic benefit cannot be assessed in relation to the alternatives used in practice.

Therapeutic use

- The quality of haemostasis depends primarily on the quality of the surgical suturing technique. Surgical haemostatic agents cannot replace meticulous haemostasis based on standard methods such as compression, sutures and ligatures and various electrocoagulation techniques.

- The use of surgical haemostatic agents is not recommended if there is no identified bleeding or as an alternative to standard surgical haemostasis methods when there is identified bleeding. Their use should not be systematic. Judicious use, limited to certain salvage situations and to specific cases, is recommended.

- Role of the medicinal product in the therapeutic strategy
  Like other surgical haemostatic agents including fibrin sealants, TISSEEL is an adjuvant treatment of last resort in salvage situations, alongside standard methods, to improve haemostasis when standard surgical techniques are insufficient and to support sutures in vascular surgery.

Clinical data

- During planned hepatic surgery via laparotomy, the perioperative efficacy of TISSEEL was demonstrated in terms of successful perioperative haemostasis (defined as 4 minutes after administration and maintained until surgical closure) versus manual compression alone: 82.9% (29/35) versus 37.1% (13/35), p<0.001.
  The efficacy of TISSEEL versus manual compression alone was demonstrated when supporting sutures in vascular surgery: haemostasis 4 minutes after administration and maintained until surgical closure (the primary
endpoint) was observed in 62.9% of patients in the TISSEEL group (44/70) and in 31.4% in the manual compression group (22/70), p<0.0001.

- During the studies, serious adverse events were reported in more than a quarter of patients. In hepatic surgery, the main adverse events reported more frequently in the TISSEEL group than in the manual compression group were: hypoalbuminaemia, post-operative bile leak, post-operative haematoma and deep vein thrombosis.

In vascular surgery, a surgical site infection was observed in 7 patients in the TISSEEL group (10%) and in 5 in the manual compression group (7.1%); graft occlusion was reported in 5 patients in the TISSEEL group and 8 in the manual compression group (11.4%) during the study. There is a risk of gas embolism associated with spraying fibrin sealants, if there is inappropriate use of spray devices when administering fibrin sealants.

- The relevance and applicability to current surgical practice of the results presented are debatable in view of the choice of control group treatment, the methodological limitations of open-label studies especially when conducted with a small sample size, a primary endpoint that is interim in nature rather than clinical,
- the restrictive nature of the non-inclusion criteria, the short duration of follow-up,
- the fact that the benefit of TISSEEL has not been demonstrated on clinically relevant parameters,
- and the lack of evaluation of a later exposure to a fibrin sealant.

- As no data have been supplied by the pharmaceutical company, the benefit and role of TISSEEL cannot be demonstrated in the other approved Marketing Authorisation indications: as a tissue glue to improve wound healing or to support sutures in gastrointestinal anastomoses; for tissue sealing, to improve adhesion of separated tissues (e.g. tissue flaps, grafts, split skin grafts [mesh grafts]) as supportive treatment, where standard surgical techniques appear insufficient.

Benefit of the medicinal product

- As supportive treatment when standard surgical techniques are insufficient, the actual benefit* of TISSEEL is:
  - substantial for improvement of haemostasis or to support sutures in vascular surgery;
  - insufficient to justify National Health Insurance reimbursement as a tissue glue to improve wound healing or to support sutures in gastrointestinal anastomoses and for tissue sealing, to improve adhesion of separated tissues (e.g. tissue flaps, grafts, split skin grafts [mesh grafts]).

- TISSEEL does not provide clinical added value** (CAV V) in the indication where its actual benefit is substantial.
- Recommends inclusion on the list of reimbursable products for hospital use in the single indication where actual benefit is substantial.

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* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".