BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

RAPLIXA, sealant powder based on human fibrinogen and thrombin

No clinical benefit demonstrated in the current surgical treatment to improve haemostasis in combination with gelatin sponge when standard surgical techniques are inadequate.

Main points

- RAPLIXA has restricted Marketing Authorisation as an adjuvant treatment to improve haemostasis in surgery when standard surgical techniques are inadequate.
- This sealant powder must be used in combination with gelatin sponge bearing the CE marking.
- RAPLIXA used in combination with gelatin sponge alongside standard methods in elective surgery has been found to reduce the median time to intraoperative haemostasis by a maximum of about 2 minutes compared with gelatin sponge alone.
- Its contribution in reducing morbidity and mortality – in particular transfusions, repeat surgical procedures, operating time, duration of hospitalisation, deaths – has not been demonstrated.
- In the absence of any comparison between RAPLIXA and an adjuvant treatment other than gelatin sponge, it is not possible to assess its therapeutic benefit versus alternatives in routine use, particularly a different fibrin sealant or thrombin product.

Therapeutic use

- The quality of haemostasis depends primarily on that of the surgical 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 rescue situations and to specific cases, is recommended.
- We still await specific data on the use of RAPLIXA for the reinforcement of sutures in vascular surgery, as a tissue sealant, during neurosurgical procedures, for the control of bleeding by application through a flexible endoscope or for gastrointestinal anastomoses and in children (indications not validated by the Marketing Authorisation).
- **Role of the medicinal product in the therapeutic strategy**
  In common with other surgical haemostatic agents including fibrin sealants, RAPLIXA in combination with gelatin sponge is an adjuvant treatment of last resort in rescue situations alongside standard methods, to improve haemostasis when standard surgical techniques are inadequate.

Clinical data

- In a study in 719 patients undergoing spinal, liver, vascular or soft-tissue surgery, the intraoperative efficacy of the combination RAPLIXA + gelatin sponge in a region of mild to moderate bleeding with a mean size of between 1.6 cm$^2$ and 43 cm$^2$ was demonstrated in terms of time to haemostasis versus gelatin sponge alone. Depending on the type of surgery, the median time to haemostasis was between 1 and 2 minutes in the RAPLIXA + gelatin sponge group versus 2 to 4 minutes in the gelatin sponge alone group ($p < 0.0001$).
- Adverse events of grade $\geq 3$ were reported in 105 patients in the RAPLIXA + gelatin sponge group (22%) and in 44 patients in the gelatin sponge alone group (18%).
- Adverse effects that were a particular focus of follow-up were hypersensitivity or allergic reactions, gas emboli and the presence of antibodies against constituents of the fibrin sealant.
- Subsequent exposure to a fibrin sealant, in terms of immunogenicity, was not evaluated.
The relevance of the results presented and their transposability to current surgical practice are debatable:
- the available studies were of open design with an interim primary efficacy endpoint, rather than a clinical endpoint or any "subjective" evaluation of the quality of haemostasis, which limits the level of evidence;
- the benefit of RAPLIXA plus gelatin sponge has not been demonstrated in terms of clinically relevant criteria. In particular, there is no demonstration of any reduced need for transfusions in post-operative complications;
- the duration of follow-up was short (< 1 month), particularly for evaluation of the incidence of long-term complications such as abscesses, formation of granulomas and reactions against a foreign body.

Special prescribing conditions

- Reserved for hospital use.
- The use of RAPLIXA is restricted to experienced surgeons.
- Medicinal product derived from human blood

Benefit of the medicinal product

- The actual benefit* of RAPLIXA in combination with gelatin sponge is substantial.
- In the absence of a comparative study versus a product based on fibrin or thrombin, RAPLIXA in combination with gelatin sponge does not provide clinical added value (CAV V) in the current surgical treatment to improve haemostasis when standard surgical techniques are inadequate.
- Recommends inclusion on the list of reimbursable products for hospital use as an adjuvant treatment in combination with gelatin sponge to improve haemostasis when standard surgical techniques are inadequate.

* 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”.

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