HAUTE AUTORITÉ DE SANTÉ

DIAGNOSTIC
New medicinal product
05 December 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

LYMPHOSEEK (tilmanocept), radiopharmaceutical for diagnostic use

High clinical benefit in the detection of sentinel nodes, but no demonstrated clinical advantage over NANOCIS, NANOCOLL or ROTOP-Nano-HSA.

Main points

- LYMPHOSEEK is authorized for imaging and intraoperative detection of sentinel lymph nodes draining a primary tumour in adult patients with breast cancer, melanoma, or localised squamous cell carcinoma of the oral cavity..
- It plays the same role in the therapeutic strategy than NANOCOLL, NANOCIS and ROTOP-Nano-HSA depending on indications, when SN detection is necessary.
- In squamous cell carcinoma of the oral cavity, the rate of false negatives with LYMPHOSEEK was of 2.56%, below the threshold of 14% predetermined from the literature.
- In breast cancer and melanoma, the diagnostic performance established versus patent blue showed a node-level concordance rate of more than 90%, along with an exploratory false negative rate of between 0 and 7.3%, depending on the study.

Diagnostic strategy

- Two types of lymphotropic agents are available for identifying SNs: colorimetric tracers, including in particular patent blue, and radiopharmaceutical tracers (isotope method). These 2 techniques can be used alone, though they are most often combined to increase the detection rate and to reduce the rate of false negatives. SN detection requires a degree of technical know-how and the experience of several healthcare professionals to guarantee the success of the operation.
- In breast cancer, there is consensus at the French, English and European levels concerning the indications for performing the SN technique, thus avoiding a needless surgical procedure in patients whose histopathological analysis did not reveal any positive nodes.
- In melanoma, SN detection is recommended for melanomas more than 1 mm thick (Breslow index), or for ulcerated melanomas. SN biopsy enables a limited lymph node procedure to be performed, in order to obtain this independent prognostic factor involved in determining the tumour stage.
- In squamous cell carcinoma of the oral cavity, the diagnostic strategy is not clearly established. Pathologically negative excised lymph nodes would entail procedure to follow based on monitoring.
- **Role of the medicinal product in the diagnostic strategy**
  LYMPHOSEEK, like NANOCOLL, NANOCIS and ROTOP-Nano-HSA, depending on the indication, has a place in the therapeutic strategy, when SN detection is necessary.

Clinical data

- In the indication for squamous cell carcinoma of the oral cavity, one single-arm phase III study assessed the rate of false negatives associated with SN detection with LYMPHOSEEK compared to histopathological analysis performed after lymphadenectomy. During the intermediate analysis specified by the protocol, the rate of false negatives with LYMPHOSEEK (primary endpoint) in the ITT population was of 1/39 = 2.56% (CI95% = [0.06; 13.49], p=0.0205), which is below the predetermined threshold of 14%.
- In breast cancer and melanoma, two phase III studies compared the diagnostic performance of LYMPHOSEEK to patent blue in terms of concordance at the lymph node level (primary endpoint). In one of the studies, the concordance between LYMPHOSEEK and patent blue at the lymph node level was of 93.36% ($CI_{95\%}$: [89.58;

96.08], p = 0.0401), statistically significantly higher than the predefined threshold of 90%. In the other study the agreement between LYMPHOSEEK and patent blue, at the lymph node level, as of 100%; CI95% = [98.40; 100.00], p<0.0001), statistically significantly higher than the established threshold of 90%. The results of these studies were put into perspective relative to a European repository including mainly colloids and patent blue. This was not a formal indirect comparison. The analytical level of evidence can't be considered as sufficient to draw conclusions.

Special prescription requirements

- Radiopharmaceutical medicinal product
- Medicinal product for hospital use only
- The medicinal product should only be administered by trained healthcare professionals with technical expertise in performing and interpreting sentinel lymph node mapping procedures.

Benefit of the medicinal product

- The actual clinical benefit* of LYMPHOSEEK is high.
- LYMPHOSEEK does not provide an improvement in actual clinical benefit** (IACB V) compared to other radiopharmaceutical medicinal products indicated for sentinel node detection.
- Approval for hospital treatment.

HAS
HAUTE AUTORITÉ DE SANTÉ
This document was drafted on the basis of the Transparency Committee opinion dated 05 December 2018 (CT-16772) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"