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BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

HEXVIX (hexyl aminolevulinate), diagnostic medicinal product

Minor improvement in the treatment compared with white light cystoscopy alone in the detection of malignant bladder tissue in patients with a history or strong suspicion – on the basis of a screening cystoscopy or a positive urinary cytology – of bladder cancer

Main points

- HEXVIX has Marketing Authorisation in addition to standard white light cystoscopy to contribute to the diagnosis and treatment of bladder cancer in patients with known or strongly suspected bladder cancer.
- The increase in sensitivity resulting from fluorescence cystoscopy with HEXVIX compared with white light cystoscopy is about 20%. The specificity is comparable in each of the groups (10 to 39% false positives).
- The increase in terms of the first tumour recurrence after the use of HEXVIX is low (8 to 10%), and no improvement in overall survival has been demonstrated.

Therapeutic use

- When there is a suspicion of bladder cancer, cystoscopy with mapping of the lesions is one of the examinations that is systematically performed. White light cystoscopy is the reference examination normally performed to map the lesions. Because of the inadequate sensitivity of this technique, the use of supplementary techniques can be considered.
- As part of conservative treatment for superficial bladder cancer, complete endoscopic resection is followed, in the absence of contraindications, by immediate postoperative instillation (IPOP), or mitomycin C. A series of instillations of mitomycin or BCG is then recommended for intermediate to high risk bladder tumours.
- **Role of the medicinal product in the therapeutic strategy**

  In certain situations, fluorescence cystoscopy may be suggested by the urologist if he/she has this equipment. This fluorescence is obtained after instillation of HEXVIX, which leads to intracellular accumulation of porphyrins (fluorescent and photosensitive compounds that emit red fluorescence after excitation with blue light) in the tumours in the bladder wall. Fluorescence is recommended if high-risk lesions are suspected, for example, due to isolation of high-grade cytology even though the cystoscopy does not reveal any lesions, history of high-risk T1G3 tumours and/or carcinoma in situ.

Clinical data

- In terms of the diagnostic parameters, the sensitivity of tumour detection in a phase II study was 96% with fluorescence cystoscopy and 73% with white light cystoscopy. The specificity of each of the techniques was the same (43%). In two phase III studies (N=84 and N=58), the percentage of patients in whom another carcinoma in situ (CIS) (in addition to the existing lesion) was observed by fluorescence cystoscopy alone was between 16 and 20%, versus 3 to 12% in patients with detection of CIS by white light cystoscopy alone. The level of detection of non-infiltrating lesions was between 93 and 97% with fluorescence cystoscopy and between 77 and 79% with white light cystoscopy. The percentage of false positives varied between 13 and 39% with fluorescence cystoscopy and between 10 and 31% with white light cystoscopy.
- Results for the long-term recurrence rate in patients with stage Ta or T1 epithelial bladder cancer were provided by the observation phase of a phase III study, which included 551 patients. The percentage of patients with recurrence was 58% in the fluorescence cystoscopy group and 64% in the white light cystoscopy group, with a median survival of 53 and 55 months, or a difference of 8%. The median survival of the patients with recurrence

was higher in the fluorescence cystoscopy group (16.4 months versus 9.4 months, p=0.04). The mortality rate was similar in each group.

- According to a meta-analysis that included 10 studies, corresponding to 1345 patients, between 10 and 15% of stage Ta or T1 lesions and 41% of CIS that had not previously been detected by white light cystoscopy were identified by fluorescence cystoscopy with HEXVIX. The 12-month recurrence rate, evaluated in three of these 10 studies, was 34.5% after the use of fluorescence cystoscopy and 45.4% after white light cystoscopy.

Benefit of the medicinal product

- The actual benefit* of HEXVIX remains substantial.
- In view of the small reduction in the risk of tumour recurrence compared with white light cystoscopy, the absence of a proven increase in survival, and in the face of methodological limits that do not permit the clear identification of the benefits of HEXVIX in the recommended indication (high-risk lesions), HEXVIX provides minor clinical added value (CAV IV) in the diagnostic strategy for the detection of malignant bladder tissue in patients with a history or strong suspicion – on the basis of a screening cystoscopy or a positive urinary cytology – of bladder cancer.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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[i] * 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".