

# LONG-TERM DECREASE IN BLADDER CANCER RECURRENCE WITH HEXAMINOLEVULINATE ENABLED FLUORESCENCE CYSTOSCOPY



## **Authors:**

H B Grossman, A Stenzl, Y Fradet, L A Mynderse, M Kriegmair, J A Witjes, M S Soloway, A Karl, M Burger

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To assess the effect of early detection of papillary non-muscle-invasive bladder cancer with hexaminolevulinate (Hexvix®) blue-light cystoscopy on long-term recurrence rates.

## METHODS

- This analysis was a long-term follow-up of participants from a prospective, randomized, multi-center study<sup>1</sup>.
- The initial study enrolled 779 patients with suspected Ta/T1 bladder tumors that were considered at increased risk for recurrence. They were treated in one of 19 centers in the US and Canada or at one of 9 centers in Europe.
- Patients were randomized to one of two treatment groups:
  - White light group, in which patients underwent cystoscopy and mapping of bladder lesions using white light, followed by transurethral resection of the bladder (TURB) where indicated (n=280).
  - Hexvix® group, in which patients underwent cystoscopy and mapping of bladder lesions with white light. Patients in this group were then further randomized to either:
    - Discontinue study involvement.
    - Undergo a second bladder mapping using Hexvix® blue-light cystoscopy, followed by TURB under white and blue-light, to detect additional lesions and assess completeness of resection (n=271).
- Following institutional review board approval, long-term follow-up data were retrospectively obtained from 516 patients at 25 of the centers.
- 261 (93%) patients from the white-light group and 255 (94%) from the Hexvix® group.
- Median follow-up was 53.0 months in the white-light group and 55.1 months in the Hexvix® group.

*To note: The extension study was not powered to show statistical significance for any clinical parameter.*

## RESULTS

### Summary of primary study results<sup>1</sup>

- Significantly improved detection of Ta/T1 tumors was reported using Hexvix® blue-light cystoscopy as an adjunct to white light cystoscopy compared to detection using white light alone (p=0.001).
  - In 43% of the 47 patients in whom additional tumors were detected with blue-light cystoscopy, the additional tumors were T1G2, T1G3 or TaG3.
  - The difference in recurrence rates between the groups at 9 months was statistically



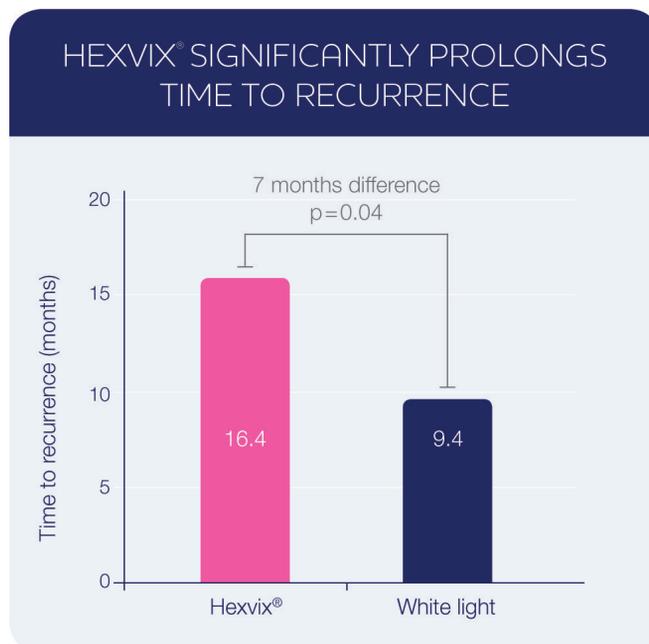
significant ( $p=0.026$ ), in favor of the Hexvix<sup>®</sup> group.

- Fewer patients in the Hexvix<sup>®</sup> group than in the white light group experienced recurrences of worrisome cancers— e.g. carcinoma in situ (CIS), T1 or T2 ( $p=0.17$ ).

### Summary of long-term follow-up study results

- Significantly increased time to recurrence in the Hexvix<sup>®</sup> group (16.4 months) compared with the white light group (9.4 months;  $p=0.04$  [Figure 1]).
- At the end of the follow-up period, 38% of patients in the Hexvix<sup>®</sup> group and 32% in the white light group remained tumor free ( $p=0.14$ ).
- Tumor progression to T2– T4 bladder cancer was reported in 3% of patients in the Hexvix<sup>®</sup> group and in 6% of those in the white light group ( $p=0.066$ ).
- The cystectomy rate was 5% in the Hexvix<sup>®</sup> group and 8% in the white light group ( $p=0.16$ ).

Figure 1



The intravesical therapy rate was similar in both groups.

## CONCLUSION

White light TURB can miss tumors in the bladder, leading to increased recurrence. Hexvix<sup>®</sup> blue-light cystoscopy, used as an adjunct to white light cystoscopy, allows better detection and therefore better resection of bladder cancer lesions. This results in significantly longer time to recurrence than with white light only cystoscopy and TURB, as well as a trend toward improved bladder preservation.

### References:

1. Stenzl A, Burger M, Fradet Y et al. Hexaminolevulinat guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. J Urol 2010; 184: 1907–1914.

# PRESCRIBING INFORMATION HEXVIX® (HEXAMINOLEVULINATE)

Please refer to full national Summary of Product Characteristics (SPC) before prescribing. Indications and approvals may vary in different countries. Further information available on request. Hexvix 85 mg, powder and solvent for solution for intravesical use.

**PRESENTATION** Pack of one 10ml glass vial containing 85mg of hexaminolevulinate as 100mg hexaminolevulinate hydrochloride as a powder and one 50ml polypropylene vial containing solvent. After reconstitution in 50ml of solvent, 1ml of the solution contains 1.7mg hexaminolevulinate which corresponds to a 8mmol/l solution of hexaminolevulinate.

**INDICATIONS** This medicinal product is for diagnostic use only. Hexvix blue light fluorescence cystoscopy is indicated as adjunct to standard white light cystoscopy to contribute to the diagnosis and management of bladder cancer in patients with known or high suspicion of bladder cancer.

**DOSAGE AND METHOD OF ADMINISTRATION** Hexvix cystoscopy should only be performed by health care professionals trained specifically in Hexvix cystoscopy. The bladder should be drained before the instillation. Adults (including the elderly): 50 ml of 8 mmol/l reconstituted solution (see section 6.6) is instilled into the bladder through a catheter. The patient should retain the fluid for approximately 60 minutes. Following evacuation of the bladder, the cystoscopic examination in blue light should start within approximately 60 minutes. The cystoscopic examination should not be performed more than 3 hours after Hexvix is instilled in the bladder. Also if the retention time in the bladder is considerable shorter than one hour, examination should start no earlier than after 60 minutes. No minimum retention time has been identified making examination non-informative. For optimal visualisation it is recommended to examine and map the entire bladder under both white and blue light before any surgical measures are initiated. Biopsies of all mapped lesions should normally be taken under white light and complete resection should be verified by switching to blue light. Only CE marked cystoscopic equipment should be used, equipped with necessary filters to allow both standard white light cystoscopy and blue light (wavelength 380–450 nm) fluorescence cystoscopy. Children and adolescents: There is no experience of treating patients below the age of 18 years.

**CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients of the solvent. Porphyria.

**WARNINGS AND PRECAUTIONS** The possibility of hypersensitivity including serious anaphylactic/ anaphylactoid reactions should always be considered. Advanced life support facilities should be readily available. Repeated use of Hexvix as part of follow-up in patients with bladder cancer has not been studied. Hexaminolevulinate should not be used in patients at high risk of bladder inflammation, e.g. after BCG therapy, or in moderate to severe leucocyturia. Widespread inflammation of the bladder should be excluded by cystoscopy before the product is administered. Inflammation may lead

to increased porphyrin build up and increased risk of local toxicity upon illumination, and false fluorescence. If a widespread inflammation in the bladder becomes evident during white light inspection, the blue light inspection should be avoided. There is an increased risk of false fluorescence in the resection area in patients who recently have undergone surgical procedures of the bladder.

**INTERACTIONS** No specific interaction studies have been performed with hexaminolevulinate.

**FERTILITY, PREGNANCY AND LACTATION** No clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to the reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Hexvix during pregnancy.

**UNDESIRABLE EFFECTS** Most of the reported adverse reactions from clinical studies were transient and mild or moderate in intensity. The most frequently reported adverse reactions from clinical studies were bladder spasm, reported by 2.4 % of the patients, dysuria by 1.8%, bladder pain by 1.7 % and hematuria by 1.7%, of the patients. Other commonly reported adverse reactions are: headache, nausea, vomiting, constipation, diarrhea, urinary retention, haematuria, pyrexia and post procedural pain. Uncommonly reported adverse reactions are cystitis, sepsis, urinary tract infection, insomnia, urethral pain, pollakuria, micturition urgency, urinary tract disorder, back pain, incontinence, white blood cell count increase, bilirubin and hepatic enzyme increase, post operative fever, anaemia, gout, rash and balanitis. The adverse reactions that were observed were expected, based on previous experience with standard cystoscopy and transurethral resection of the bladder (TURB) procedures.

**OVERDOSE** No case of overdose has been reported. No adverse events have been reported with prolonged instillation times exceeding 180 minutes (3 times the recommended instillation time), in one case 343 minutes. No adverse events have been reported in the dose-finding studies using twice the recommended concentration of hexaminolevulinate. There is no experience of higher light intensity than recommended or prolonged light exposure.

**INSTRUCTIONS FOR USE AND HANDLING** Hexaminolevulinate may cause sensitisation by skin contact. The product should be reconstituted under aseptic conditions using sterile equipment.

**MARKETING AUTHORISATION HOLDER**  
Photocure ASA, Hoffsvæien 4, N-0275 Oslo, Norway

**PRICE** Denmark DKK 4 718.50 Finland EUR 464.20 Norway NOK 4 234.50 Sweden SEK 4 222,00

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