



# HEXAMINOLEVULINATE GUIDED FLUORESCENCE CYSTOSCOPY REDUCES RECURRENCE IN PATIENTS WITH NON-MUSCLE INVASIVE BLADDER CANCER



## **Authors:**

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## AIM

- To assess the effect that early detection of non-muscle-invasive bladder cancer (NMIBC) with Hexvix® blue-light cystoscopy may have on early recurrence rates.
- Additional endpoints included the proportion of patients with additional Ta/T1 lesions detected with blue-light, carcinoma in situ (CIS) lesions detected with blue-light, and the rate of false positives.



## METHODS

- This trial was a prospective, randomized, multi-center study.
- Eligible patients had suspected Ta/T1 bladder tumors and were considered at increased risk for recurrence. They were being treated at one of 28 centers in the USA, Canada (19) and Europe (9).
- Randomization was performed centrally and stratified for patients presenting with initial and recurrent bladder cancer.
- Patients were randomized into one of two treatment groups:
  - White light group: Patients in this group underwent cystoscopy and mapping of bladder lesions with white light, followed by TURB.
  - Hexvix® group: Patients in this group underwent cystoscopy and mapping of bladder lesions with white light. A second randomization was then performed, with patients assigned to:
    - Discontinue involvement in study.
    - Continue in the study: These patients underwent bladder mapping again with Hexvix® blue-light cystoscopy, followed by a TURB (where indicated) under white light and blue-light to assess completeness of resection.
- Patients with histologically confirmed Ta or T1 tumors by a central pathology consensus read were followed up using white light cystoscopy at 3,6 and 9 months from initial resection until histologically confirmed recurrence.



## RESULTS

779 patients were randomized.

### **Tumor detection**

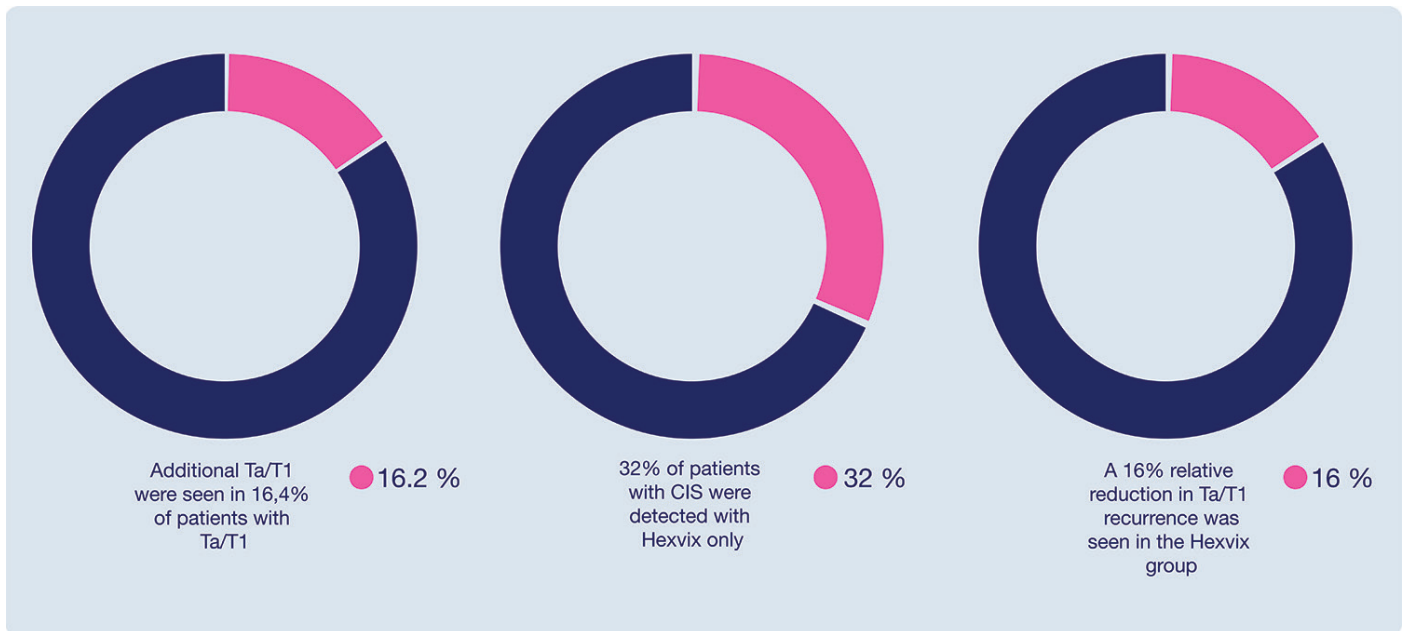
- Detection was assessed as a within-patient comparison in the Hexvix® group only.
- Additional Ta/T1 were seen in 16,4% of patients with Ta/T1 (47 of 286; p=0.001).
  - In these patients, the worst stage and grade of tumors found per patient with Hexvix® blue-light cystoscopy was: TaG2 in 27 (57%), T1G2 in 1 (2%), TaG3 in 12 (26%) and T1G3 in 7 (15%).



- 32% of patients with CIS were detected with Hexvix<sup>®</sup> only (13 of 41;  $p < 0.0001$ ).
- The rates of false positives were similar for white light and blue-light cystoscopy (11% and 10% for white light and 12% for blue-light cystoscopy).

### Recurrence

- Recurrence was assessed by comparing the recurrence rates in patients with Ta or T1 at baseline in both treatment groups.
- A 16% relative reduction in Ta/T1 recurrence was seen in the Hexvix<sup>®</sup> group (47% [128 of 271] in the Hexvix<sup>®</sup> group vs 56% [157 of 280] in the white light group).
- 9% absolute decrease in recurrence rates at 9 months' follow-up.
- Reduced recurrence of aggressive/clinically significant lesions (i.e. T1, CIS and muscle invasive) was seen in the Hexvix<sup>®</sup> group versus the white light group.
  - 16% recurrence in the Hexvix<sup>®</sup> group versus 24% in the white light group ( $p = 0.17$ ).



## CONCLUSION

Compared with white light cystoscopy alone, Hexvix<sup>®</sup> blue-light cystoscopy used as an adjunct to white light cystoscopy significantly improves the detection of bladder cancer, leading to a more complete resection and significantly better disease-free survival.

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

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