A PHASE III, MULTICENTER COMPARISON OF HEXAMINOLEVULINATE FLUORESCENCE CYSTOSCOPY AND WHITE LIGHT CYSTOSCOPY FOR THE DETECTION OF SUPERFICIAL PAPILLARY LESIONS IN PATIENTS WITH BLADDER CANCER

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AIM

To compare Hexvix® blue-light cystoscopy with white light cystoscopy for detecting Ta and T1 papillary lesions in patients with bladder cancer

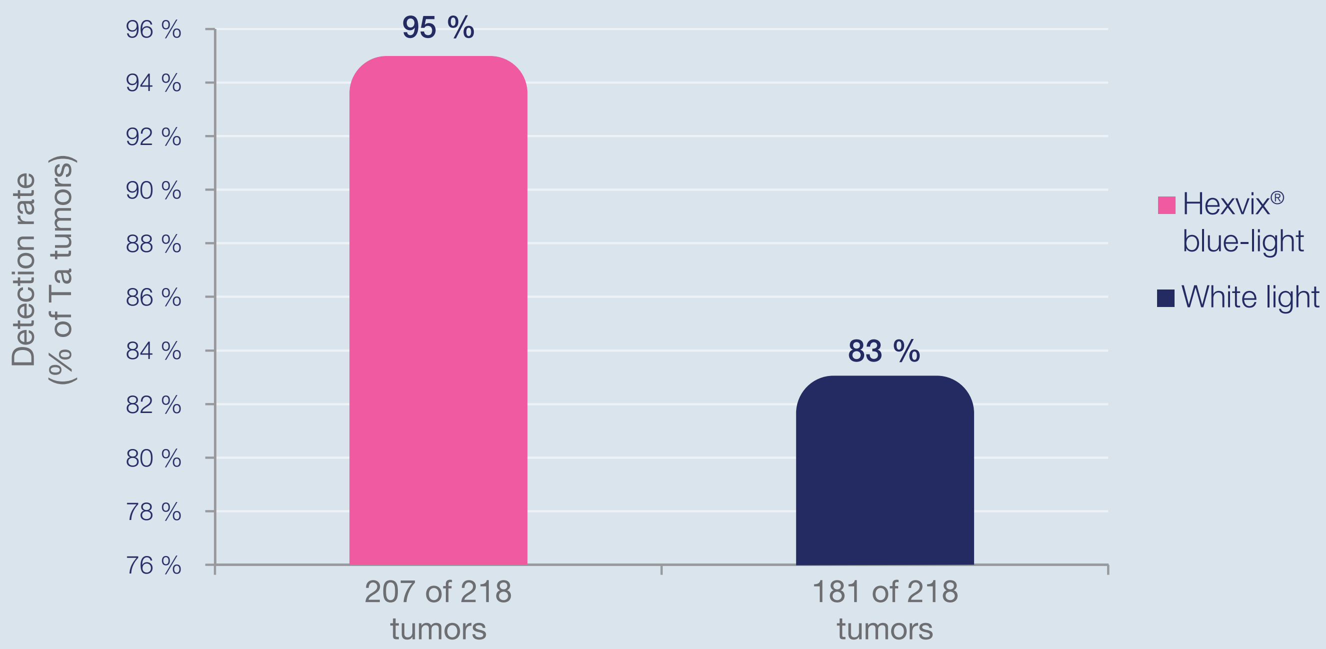
METHODS

- In this open, comparative (within patient) study, 311 patients with known or suspected bladder cancer were investigated at 18 centers in North America
- 50ml Hexvix® (8mM) was instilled into the bladder of 298 patients (safety population) at least 1 hour prior to cystoscopy and transurethral resection of the bladder
- The bladder was first inspected under white light. Lesions and suspicious areas were classified, mapped and recorded by video. The light system was then changed to blue-light mode and the procedure repeated
- At the end of the blue-light inspection, papillary lesions were resected for histological examination, and biopsies taken of all flat lesions and suspicious areas. A control biopsy was taken from urothelium that appeared normal under white- and blue-light
- All histology and biopsy samples were examined by two reference pathologists and one local pathologist, blinded to whether the samples were identified under white- or blue-light
- After exclusion of some subjects for protocol violation and 5 training patients per center without experience of the technique, the evaluable population was 196 patients

RESULTS

- Hexvix® blue-light cystoscopy detected at least one more Ta tumor than standard white light cystoscopy in 29% of patients ($p<0.05$) (31 of 108 patients with tumor)

SIGNIFICANTLY IMPROVED Ta TUMOR DETECTION RATE ($p=0.0001$)



- Of the 31 patients mentioned above, in 12 of them Hexvix® blue-light cystoscopy detected multiple tumors compared to single tumor with standard white light cystoscopy alone, and in a further 6 patients tumor was only detected using Hexvix® blue-light cystoscopy
- Hexvix® blue-light cystoscopy showed an improved detection rate for T1 tumors versus standard white light cystoscopy alone, 95% vs 86% ($p=0.3$)
- Hexvix® instillation was well tolerated with few local or systemic side effects (2.4%) attributed to its instillation

CONCLUSION

Hexvix® blue-light cystoscopy is an effective, well tolerated procedure for diagnosing Ta and T1 papillary lesions in patients with known or suspected bladder cancer. Furthermore, it is able to detect at least 1 more Ta lesion than white light cystoscopy in a statistically significant proportion of patients with existing Ta disease ($p<0.05$).

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 wide-spread 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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