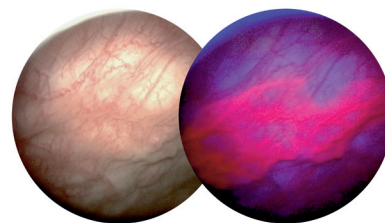


Fact sheet

Clinical aspects of bladder cancer



Clinical situation in general

Urinary bladder cancer has a recurrence rate of between 50 and 75 percent at 20 years¹ after treatment in spite of predominantly superficial tumours at first diagnosis. In particular, carcinoma in situ (CIS; a non-invasive, superficial, flat lesion) is aggressive, unpredictable in behaviour and associated with an increased risk of progression.^{2,3,4}

As a consequence, highly sensitive as well as specific diagnostic techniques capable of comprehensively detecting as many tumours as possible - in particular CIS - must be employed in order to ensure optimal treatment - thus feasibly extending the time until recurrence and limiting progression. It is suspected that among other things the high recurrence rate may be due to poor detection of lesions at investigation⁴ emphasising the need for reliable diagnostic techniques and tools.

Diagnosis: Techniques and Tools

Cystoscopy and urinary cytology are both used in the diagnosis and monitoring of bladder cancer.

Standard white light cystoscopy

Cystoscopy allows for direct visual inspection of the urothelium and mucosa. Cystoscopy-guided biopsy of suspicious lesions and areas remains the standard procedure for detection of bladder cancer - including CIS. However, detection of flat lesions - such as CIS -, which may be diffuse and indistinguishable from normal or nonspecific inflammatory-appearing mucosa, is limited when conventional standard white light cystoscopy is used. Therefore, random biopsies are frequently taken to detect and confirm previously overlooked CIS. This approach, however, is of questionable benefit, as detection is random as well as low and the risk of tumour seeding may be increased.²

Urinary cytology

Urinary cytology has both a high specificity and sensitivity towards the detection of high-grade lesions

thus constituting the non-invasive tool of choice for bladder cancer diagnosis. Urinary markers, which may also be employed, appear to have better sensitivity especially for low-grade non-muscle invasive tumours, but lack the specificity associated with cytology. The most serious drawbacks of both cytology and urinary markers are that results are not immediately available, are highly dependent on the interpreter, and provide no information on the location and extent of the disease.²

The Present Diagnostic Situation

Missed diagnosis leading to delayed or incomplete treatment has significant prognostic implications for patients with potentially aggressive tumours, such as CIS. Furthermore, missed diagnosis contributes to the high rate of recurrence of non-muscle-invasive cancers after transurethral resection (TUR) and it carries considerable economic costs through additional medical interventions necessary after initial treatment.^{2,5}

"The high recurrence rate of bladder cancer - up to 45.8% of multiple tumours at first follow-up - is of some concern and may be due to poor detection at investigation.

Standard diagnosis with white light cystoscopy is inadequate for detecting many bladder lesions", commented Professor Dieter Jocham, department of urology, University of Schleswig Holstein, Campus Luebeck, current president of the German Association of Urology (DGU).

Improved Diagnosis

Two new approaches to improve the diagnostic situation are bladder tumour markers, which are currently being studied extensively, and fluorescence cystoscopy with Hexvix® (hexaminolevulinate), which is already available.



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Bladder tumour markers

Extensive research to develop and evaluate bladder tumour markers is under way. The ideal marker should be non-invasive, easy to use, non-expensive, objective and reproducible with a high sensitivity and specificity for high-grade as well as low-grade lesions. Several reviews and meta-analyses have been performed on these markers looking at up to 10,000 patient cases. However, while a number of promising markers have been identified, studies are pending to validate their utility. Furthermore, based on the current knowledge about urinary markers it is difficult to select the ideal marker.

Nevertheless, some urinary markers have a higher sensitivity than cytology, both overall and after stratification by stage and grade. Specificity, however, is inferior to cytology overall. Yet superior sensitivity makes it possible to discriminate between patients with low-grade and high-grade malignancies. The goal in high-grade lesions is to detect a tumour as early as possible, while the goal in low-grade lesions is to perform a minimum of unnecessary cystoscopies. In summary, the potential benefit of using bladder tumour markers for diagnostic purposes and in determining subsequent treatment seems to be significant.⁶

For further details on Hexvix cystoscopy please see fact sheet: Cystoscopy

Summary of the product characteristics

Name of the Medicinal Product

Hexvix 85 mg, powder and solvent for solution for intravesical use

Qualitative and Quantitative Composition

Each vial of powder contains 85 mg of hexaminolevulinate as 100 mg hexaminolevulinate hydrochloride.

After reconstitution in 50 ml of solvent, 1 ml of the solution contains 1.7 mg hexaminolevulinate which corresponds to a 8 mmol/l solution of hexaminolevulinate.

For excipients, see below list of excipients

Pharmaceutical Form: Powder and solvent for solution for intravesical use.

Powder: white to off-white or pale yellow, Solvent: clear, colourless solution

Clinical Particulars

Therapeutic indications This medicinal product is for diagnostic use only. Detection of bladder cancer, such as carcinoma in situ, in patients with known bladder cancer or high suspicion of bladder cancer, based on e.g. screening cystoscopy or positive urine cytology. Blue light fluorescence cystoscopy should be used as an adjunct to standard white light cystoscopy, as a guide for taking biopsies.

Posology 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. Patients should be examined with both white and blue light to obtain a map of all lesions in the bladder. Biopsies of all mapped lesions should normally be taken under white 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. The light doses given during cystoscopy will vary. Typical total light doses (white light and blue light) range between 180 and 360 J at an intensity of 0.25 mW/cm². 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. Women of child-bearing potential (see section below).

Special warnings and special precautions for use 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.

Interaction with other medicinal products and other forms of interaction No specific interaction studies have been performed with hexaminolevulinate.

Pregnancy and lactation For hexaminolevulinate, no clinical data on exposed pregnancies are available. Reproductive toxicity studies in animals have not been performed. Hexaminolevulinate is contraindicated in women of child-bearing potential (see section above).

Effects on ability to drive and use machines No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects Most of the reported adverse reactions were transient and mild or moderate in intensity. The most frequently reported adverse reactions were bladder spasm, reported by 3.8 % of the patients, bladder pain, reported by 3.3 % of the patients and dysuria, reported by 2.7 % of the patients. The adverse reactions that were observed were expected, based on previous experience with standard cystoscopy and transurethral resection of the bladder (TURB) procedures.

Infections and infestations, Uncommon, Cystitis, sepsis, urinary tract infection

Psychiatric disorders, Uncommon, Insomnia

Nervous system disorders, Common, Headache

Gastrointestinal disorders, Common, Nausea, vomiting, constipation

Renal and urinary bladder disorders, Common, Bladder spasm, bladder pain, dysuria, urinary retention haematuria, pollakuria, Uncommon, Urethral pain, incontinence
General disorders and administration site conditions, Common, Pyrexia
Investigations, Uncommon, White blood cell count increased, increased bilirubin, hepatic enzyme increased

Injury, poisoning and procedural complications, Uncommon, Post procedural pain

Blood and lymphatic system disorders, Uncommon, Anaemia

Metabolism and nutrition disorders, Uncommon, Gout

Skin and subcutaneous tissue disorders, Uncommon, Rash

Common adverse reactions: Adverse reactions occurring in >1/100, <1/10 of patients. Uncommon adverse reactions: Adverse reactions occurring in >1/1000, <1/100 of patients. Only adverse reactions reported by more than one patient in the clinical studies are included.

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.

Pharmacological Properties

Pharmacodynamic properties Pharmacotherapeutic group: Other diagnostic agents, ATC code: V04CX. In vitro studies have shown a considerable build-up of porphyrin fluorescence in malignant urothelium after exposure to hexaminolevulinate. In humans, a higher degree of accumulation of porphyrins in lesions compared to normal bladder urothelium has been demonstrated with Hexvix. After instillation of the reconstituted solution for 1 hour and subsequent illumination with blue light, tumours can be readily visualized by fluorescence. Clinical studies using Hexvix included 605 evaluable patients with known bladder cancer or high suspicion of bladder cancer, who underwent white light, followed by blue light cystoscopy, and biopsies. In the clinical studies, the patients had known or suspected bladder cancer by cystoscopy or positive urine cytology. Significantly more CIS and papillary lesions were detected after blue light cystoscopies, as compared to standard white light cystoscopy. The detection rate for CIS was 49.5% for standard white light cystoscopy and 95.0% for blue light cystoscopy, and the detection rate for papillary lesions ranged between 85.4% and 94.3% for white light and between 90.6% and 100% for blue light cystoscopy. One study was designed to investigate the influence of patient management according to the European Association of Urology Recommendations on treatment of superficial bladder cancer. In 17% of patients, findings after blue light cystoscopy led to more complete therapy, and in 5.5% of patients less complete therapy was identified using only blue light cystoscopy. Reasons for more complete therapy was improved tumour detection compared to standard cystoscopy, and included more pTa lesions (20% of the patients), more CIS lesions (14%), and more pT1 lesions (11%) only detected with Hexvix cystoscopy. The rate of finding false positive lesions was increased after blue light cystoscopy, 21.3% for white light cystoscopy and 27.8% for blue light cystoscopy. Mechanism of Action: After intravesical instillation of hexaminolevulinate, porphyrins will accumulate intracellularly in bladder wall lesions. The intracellular porphyrins (including PpIX) are photoactive, fluorescing compounds which emit red light upon blue light excitation. As a result, premalignant and malignant lesions will glow red on a blue background. False fluorescence may be seen as a result of inflammation.

Pharmacokinetic properties In vivo autoradiography studies in rats after intravesical administration have shown high concentrations of hexaminolevulinate in the bladder wall. After intravesical instillation of radiolabelled hexaminolevulinate in healthy volunteers, the systemic bioavailability of total radioactivity was approximately 5-10%.

Preclinical safety data Studies in rats and dogs have not indicated any risks for systemic toxicity. Seven-day intravesical tolerance studies, without light exposure, were performed in rats and dogs. The study in rats showed cases of leukocytosis, suggesting a proinflammatory activity of hexaminolevulinate. Cases of azotemia, red coloured urine and weight loss were also seen. In dogs treated with hexaminolevulinate there was a marginally increased incidence and severity of transition cell hyperplasia and basophilia in the urinary epithelium. Potential genotoxicity has been investigated in vitro in prokaryotic and eucaryotic cells in the presence and absence of photoactivating illumination and in vivo. An increase in chromosome aberrations in CHO cells after treatment in combination with light was observed. The other studies of genotoxic potential were negative (Ames test, TK assay, in vivo micronucleus cell model, and Comet assay on vesical samples from a dog local tolerance study with blue light activation). A genotoxic potential cannot be ruled out entirely due to the mechanism of action of the product which entails production of singlet oxygen at light activation. A local lymph node assay in mice has demonstrated that hexaminolevulinate has a potential to cause skin sensitisation. Carcinogenicity studies or studies on the reproductive function have not been performed with hexaminolevulinate.

Pharmaceutical Particulars

List of excipients Powder: None Solvent: Disodium phosphate, Potassium dihydrogen phosphate, Sodium chloride, Hydrochloric acid, Sodium hydroxide, Water for injections

Incompatibilities This medicinal product must not be mixed with other medicinal products.

Shelf life 3 years. After dilution with the solvent: Chemical and physical stability of the solution has been demonstrated for 2 hours at 2°C - 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 2 hours at 2°C - 8°C.

Special precautions for storage This medicinal product does not require any special storage conditions. Solution (after reconstitution): See section under shelf life

Nature and content of container Pack of one 10 ml Type I colourless glass vial with butyl rubber stopper containing powder, and one 50 ml polypropylene vial or one 50 ml Type I colourless glass vial with butyl rubber stopper containing solvent.

Instructions for use and handling Hexaminolevulinate may cause sensitisation by skin contact. All steps should be performed with sterile equipment and under aseptic conditions. Transfer 50.0 ml of the solvent for Hexvix into a sterile 50 ml syringe.

Add about 5 ml of this to the vial of Hexvix powder. Ensure complete dissolution by gentle shaking. Transfer all of the solution containing the dissolved powder back into the 50 ml syringe and mix the content gently. Reinject and withdraw about 5 ml of the mixed contents from the syringe into the vial for powder twice more to ensure a complete transfer of the powder from the vial to the syringe. The appearance of the reconstituted solution is clear to slightly opalescent, and colourless to pale yellow. For single use only. Any unused product should be discarded.

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Marketing Authorisation Number 19227

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