SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hexvix 85 mg, powder and solvent for intravesical solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 85 mg hexaminolevulinate (as 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 the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for intravesical solution.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic 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. See 5.1.

4.2 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. 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.

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/cm^2.

Children and adolescents:
There is no experience of treating patients below the age of 18 years.

Method of administration
Precaution to be taken before handling or administrating the medicinal product.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Porphyria.

4.4 Special warnings and precautions for use

The possibility of hypersensitivity including serious anaphylactic/anaphylactoid reactions should always be considered (see section 4.8). Advanced life support facilities should be readily available.

Post-marketing experience with repeated use of Hexvix does not indicate that it represents a risk when used in follow-up in patients with bladder cancer, however no specific studies have been conducted.

Hexaminolevulinate should not be used in patients at high risk of bladder inflammation, e.g. after BCG therapy, or in moderate to severe leucocytouria. 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.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with hexaminolevulinate.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data on the use of hexaminolevulinate in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to the reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Hexvix during pregnancy.

Breast-feeding
It is unknown whether hexaminolevulinate/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during the treatment with Hexvix.

Fertility
Animal studies do not indicate effects on female fertility (see section 5.3). Male fertility has not been investigated in animals.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Most of the reported adverse reactions 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. The adverse reactions that were observed were expected, based on previous experience with standard cystoscopy and transurethral resection of the bladder (TURB) procedures.

The table below includes adverse reactions from clinical trials and spontaneous reporting. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (>1/10), Common (>1/100 to < 1/10), Uncommon (> 1/1,000 to < 1/100), Rare (> 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

System Organ Class (MedDRA)	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Cystitis, sepsis, urinary tract infection
Blood and lymphatic system disorders	Uncommon	White blood cell count increased, anaemia
Immune system disorders	Not known	Anaphylactoid shock
Metabolism and nutrition disorders	Uncommon	Gout
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Nausea, vomiting, constipation, diarrhea
Hepatobiliary disorders	Uncommon	Increased serum bilirubin, hepatic enzyme increased

Skin and subcutaneous tissue disorders	Uncommon	Rash
Musculosceletal and connective tissue disorders	Uncommon	Back pain
Renal and urinary bladder disorders	Common	Bladder spasm, bladder pain, dysuria, urinary retention, haematuria
	Uncommon	Urethral pain, pollakuria, micturition urgency, urinary tract disorder
Reproductive system and breast disorders	Uncommon	Balanitis
General disorders and administration site conditions	Common	Pyrexia
Injury, poisoning and procedural complications	Common	Post procedural pain
	Uncommon	Post-operative fever

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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 1072 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.

In studies in patients with increased risk of CIS, 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 of the above studies 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.

A randomized, white light only comparative study was undertaken in patients with papillary tumors and increased risk of recurrence. A within patient comparison showed that a total of 16.4% (47/286) of patients with pTa/pT1 lesions had additional such lesions detected with Hexvix blue light cystoscopy only. Patients with pTa/pT1 lesions were followed for 9 months after cystoscopy, and the proportion of patients with recurrence was lower in the Hexvix group (47%, 128/271) than in the white light only cystoscopy group (56.1%, 157/280) in the ITT population, where all patients with missing data were assumed to have recurrence. The number of patients with missing data in the study was too high (56/128 and 59/157, in the Hexvix and control groups respectively) for the difference to be considered statistically robust (p=0.03-0.06 pending on ways to handle missing data). Further follow-up information was obtained for 86% of the participants. Median follow-up in the white light only and Hexvix groups were 53 and 55 months, respectively. The patients in the Hexvix group had a median of 7 months longer time to recurrence and recurrence-free survival (16 months in the Hexvix group versus 9 months in the white light group, p=0.04-0.06, pending on handling of missing data and deaths).

The overall rate of finding false positive lesions was increased after blue light cystoscopy, 17.3% for white light cystoscopy and 21.9% 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.

5.2 Pharmacokinetic properties

*In viv*o 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%.

5.3 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.

A local lymph node assay in mice has demonstrated that hexaminolevulinate has a potential to cause skin sensitisation.

Potential genotoxicity has been investigated *in vitro* in procaryotic and eucaryotic cells in the presence and absence of photoactivating illumination and *in vivo*. All the studies of genotoxic potential were negative (Ames test, TK assay, *in vivo* micronucleus cell model, chromosome aberrations in CHO cells, and Comet assay on vesical samples from a dog local tolerance study with blue light activation).

Reproductive toxicity has been investigated in rats and rabbits. The incidences of embryo-fetal mortality, fetal weights, and the fetal abnormalities and variants, including skeletal ossification parameters did not indicate any obvious effect of treatment. There were no effects on female fertility and on early embryonic development when investigated in rats.

Carcinogenicity studies have not been performed with hexaminolevulinate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
None

Solvent:
Disodium phosphate dihydrate
Potassium dihydrogen phosphate
Sodium chloride
Hydrochloric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

4 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.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 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 cyclic olefin copolymer syringe with plunger stopper (bromobutyl rubber) and plunger rod, containing solvent.

Pack sizes:
Pack containing 1 vial with powder and 1 prefilled syringe with solvent, with or without a Mini-Spike transfer device.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Hexaminolevulinate may cause sensitisation by skin contact.

Handling instructions for the pharmacist or other healthcare professionals:
All steps should be performed with sterile equipment and under aseptic conditions. A brief description of the reconstitution procedure is provided below. For detailed description, see package leaflet section *Instruction for handling*.

1. Using the prefilled syringe, inject about 10 ml of the solvent into the vial of Hexvix powder. The vial should be about ¾ full.
2. Without withdrawing the syringe from the vial, hold the powder vial and the syringe in a firm grip and shake gently to ensure complete dissolution.
3. Withdraw all of the dissolved solution from the powder vial into the syringe.
4. Disconnect the empty vial from the syringe and discard the vial.
5. Gently mix the contents of the syringe.
6. Hexvix is now reconstituted and ready for use. 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.

7 MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8 MARKETING AUTHORISATION NUMBER

<To be completed nationally>

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed nationally>
For Sweden:
Date of first authorisation: 17 September 2004
Date of latest renewal: 17 September 2009

10 DATE OF REVISION OF THE TEXT

2 January 2019