IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0735/010/001
Case No: 2045884

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

GE Healthcare AS

Nycoveien 1-2, **4220 Nydalen**, **Oslo N-0401**, **Norway**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Hexvix 85 Milligram Pdr+Solv/Soln/Intravesical Use

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/02/2008** until **15/02/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hexvix 85 mg, powder and solvent for solution for intravesical use
(Solvent glass vial)

2 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 section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for intravesical use.

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.

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.

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.

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/cm^2.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of the solvent.
Porphyria.
Women of child-bearing potential (see section 4.6).

4.4 Special warnings and 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.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with hexaminolevulinate.

4.6 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 4.3).

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 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.

Body system (MedDRA)	**Frequency***	**Adverse reaction**
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.		

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 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.

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.

Potential genotoxicity has been investigated *in vitro* in procaryotic 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
None

Solvent:
Disodium phosphate
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

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Solution (after reconstitution): See section 6.3.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Hexaminolevulinate may cause sensitisation by skin contact.

All steps should be performed with sterile equipment and under aseptic conditions.

1. Transfer 50.0 ml of the solvent for Hexvix into a sterile 50 ml syringe.
2. Add about 5 ml of this to the vial of Hexvix powder. Ensure complete dissolution by gentle shaking.
3. Transfer all of the solution containing the dissolved powder back into the 50 ml syringe and mix the content gently.
4. 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.
5. 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

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P.O Box 4220 Nydalen
NO-0401
Oslo
Norway

8 MARKETING AUTHORISATION NUMBER

PA 735/10/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th February 2007

10 DATE OF REVISION OF THE TEXT

February 2008