NEW ZEALAND DATASHEET

HEXVIX 85mg Powder for intravesical solution and diluent

hexaminolevulinate (as hydrochloride) 85 mg

1. PRODUCT NAME

The name of the medicine is HEXVIX hexaminolevulinate (as hydrochloride) 85 mg Powder for intravesical solution and diluent

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 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.

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 section 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 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 considerably 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 cystoscopic equipment equipped with necessary filters to allow both standard white light cystoscopy and blue light (wavelength 380–450 nm) fluorescence cystoscopy should be used.

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 listed in section 6.1.

Hexvix is contraindicated in porphyria and gross haematuria.

4.4 Special warnings and precautions for use

The possibility of hypersensitivity including serious anaphylactic/anaphylactoid reactions should always be considered (see section Adverse Effects). 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.

Hexvix 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 Interactions with other medicinal products and other forms of interaction

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

No specific interaction studies have been performed with hexaminolevulinate.

4.6 Fertility, pregnancy, lactation

Pregnancy
There are no or limited data on the use of hexaminolevulinate in pregnant women. Reproductive toxicity has been investigated in rats and rabbits. The incidences of embryo-fetal mortality, fetal weights, and fetal abnormalities and variants, including skeletal ossification parameters did not indicate any obvious effect of treatment in rats receiving hexaminolevulinate doses up to 150 mg/kg/day IV (yielding 195 times the exposure in patients at the maximum recommended dose, on a body surface area –BSA– basis, assuming 7% bioavailability in humans) or in rabbits at up to 40 mg/kg/day IV (relative exposure based on BSA, 104 times). As a precautionary measure, (and since the animal studies were not conducted with photo-stimulation), 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. The excretion of hexaminolevulinate, its metabolites or PPIX in milk has not been studied in animals. Breast-feeding should be discontinued during the treatment with Hexvix

Fertility
Hexaminolevulinate hydrochloride had no effects on fertility and reproductive performance indices in female rats at an IV dose of 100 mg/kg/day (yielding 130 times the exposure in patients at the maximum recommended dose, on a body surface area –BSA– basis, assuming 7% bioavailability in humans) from 2 weeks before mating until gestation day 6. 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

Hypersensitivity, including anaphylactoid shock (4 cases in > 350 000 exposures), has been reported post-marketing following exposure to Hexvix.

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 haematuria 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	Very rare	Anaphylactoid shock
Metabolism and nutrition disorders	Uncommon	Gout
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Nausea, vomiting, constipation, diarrhoea
Hepatobiliary disorders	Uncommon	Increased serum bilirubin, hepatic enzyme increased
Skin and subcutaneous tissue disorders	Uncommon	Rash
Musculoskeletal 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 medicine is important. It allows continued monitoring of the benefit / risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdosage

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMALOGICAL PROPERTIES

5.1 Pharmaceodynamic 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 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 randomised, 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).

There were fewer patients with progression to muscle-invasive disease in the Hexvix group compared with the white light group, 8 patients (3.1%) versus 16 patients (6.1%), respectively over the 4.5 years follow up period. The difference between the groups approached statistical significance for tumor stage at worst recurrence (p=0.066) but less so for first recurrence (p=0.102). Fewer patients in the Hexvix group compared to white light group had to undergo cystectomy ,(13 (4.8%)) patients compared to (22 (7.9%)) patients (p=0.162).

Hospitalisation due to bladder cancer was 72 (26.6%) patients in the Hexvix group and 79 (28.2%) patients in the white light group. There were 44 (15.7%) deaths in the white light group and 39 (14.4%) in the Hexvix group with 8 (2.9%) and 6 (2.2%), known bladder cancer related deaths respectively. Patients in both groups were hospitalised for bladder cancer a mean of 1.0 times, although 20 (7.4%) patients in the Hexvix group and 13 (4.6%) patients in the white light group were hospitalised four or more times.

In an open-label, randomised Phase 3 two-centre study patients with non-muscle invasive papillary tumours were compared for recurrence after Hexvix and white light guided TURBT. A secondary endpoint was to detect lesion detection rates. 79 and 86 patients were eligible in the two groups respectively. Recurrence rates at 4 months after TURB were 25.3% in the Hexvix group and 34.9% in the white light group. At 12 months the recurrence rates were similar in the ITT analysis set. Of the 90 patients with at least one tumor, 44 (48.9%) had at least one tumor detected in blue light that was not detected in WL.

Sensitivity and specificity of Hexvix was determined in a Phase 2 study in 52 patients with suspected primary or recurrent bladder cancer. Biopsies were taken from all fluorescent and non- fluorescent lesions as well as additional 5 random biopsies from normal bladder tissue. The lesion sensitivity under blue light cystoscopy was 76% compared to 46% under standard white light. Lesion specificity in blue light cystoscopy was 79% compared to 93% in standard white light. The specificity in blue light is related to a higher false positive, 20% vs 7% in blue and white light respectively. Of the 13 patients with CIS tumours 12 were diagnosed with Hexvix.

Table 1 Lesion detection rates of Hexvix (N=52 pts/422 biopsies)

	Blue Light with Hexvix	Standard White Light
Sensitivity	76%	46%
Specificity	79%	93%

False positive fluorescence may lead to additional biopsy. The benefit of finding more lesions that can be treated outweighs the risk of a possible extra biopsy.

An integrated analysis across the Phase 3 studies indicated an overall rate of finding false positive lesions was increased after blue light cystoscopy, 17.3 % for the white light

cystoscopy and 21.9 % for blue light cystoscopy with Hexvix.

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, malignant lesions will glow red on a blue background. False fluorescence may be seen as a result of inflammation.

5.2 Pharmaceokinetic 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 low, approximately7% (range from 5-10%), C_{max} 343 ng/mL and t_{max} 1 hour.

The elimination of hexaminolevulinate is biphasic with a rapid initial disposition phase with a half-life of 39 minutes, followed by a longer second disposition phase with a half-life of approximately 76 hours.

5.3 Preclincial 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 eukaryotic 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 when stored below 25°.

After dilution with the diluent:
To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2-8 °C for not more than 2 hours. The reconstituted solution, if stored at 2 – 8°C, should be allowed to warm to room temperature before instilling into the bladder.

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

Hexvix powder is packaged in a 10 ml type I, clear glass vial. This vial is closed with grey butyl rubber stopper and sealed with an aluminium seal. The diluent is packaged in a polypropylene Blow-Fill-Seal container.

6.5 Special precautions for disposal and other handling
No special requirements for disposal.

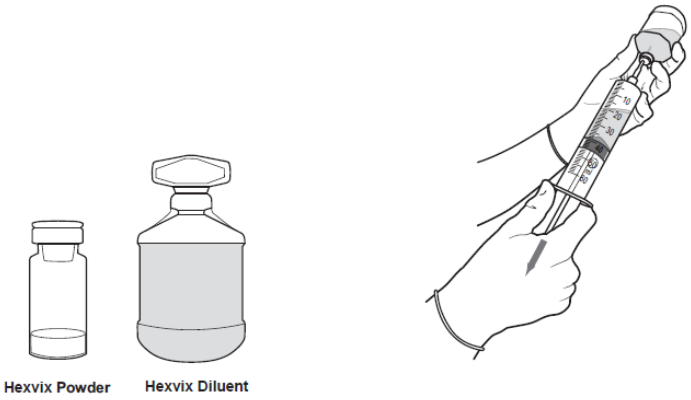
Hexaminolevulinate may cause sensitisation by skin contact.

<u>Handling instructions for the pharmacist or other healthcare professionals:</u>

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

1) Withdraw 50 mL of the diluent for Hexvix into a sterile 50 mL syringe. (Refer to figure 1)

Figure 1

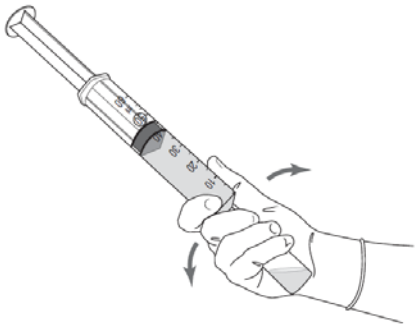


2) Inject about 10 mL of this diluent into the vial of Hexvix powder. (Please refer to figure 2)

Figure 2

3) Without withdrawing the needle from the vial, hold the powder vial and the syringe in a firm grip and shake gently to ensure complete dissolution. (Please refer to figure 3).

Figure 3



4) Withdraw all of the dissolved solution from the powder vial (10 mL) into the 50 mL syringe. Gently mix the contents of the syringe. (Please refer to figures 4 and 5)

Figure 4

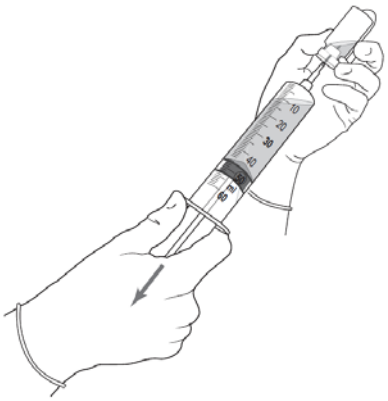
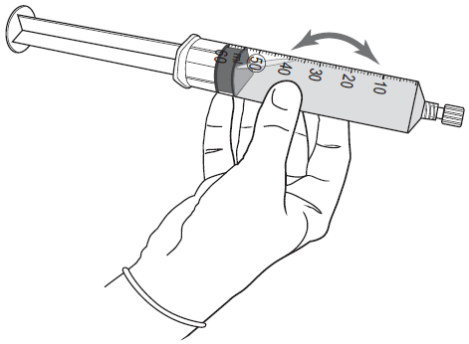
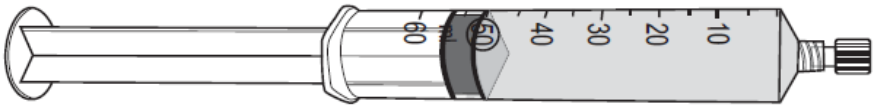


Figure 5



5) Hexvix is now reconstituted and ready for use. The appearance of the reconstituted solution is clear to slightly opalescent, and colourless to pale yellow. (Please refer to Figure 6).

Figure 6



For single use only. Any unused product should be discarded.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Juno Pharmaceuticals NZ Pty Ltd
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For Medical Information please call 0800 816 921

9. DATE OF FIRST APPROVAL

26 October 2017

10. DATE OF REVISION OF THE TEXT

NA