OLYMPUS

Your Vision, Our Future

OLYMPUS BLUE-LIGHT MANUAL

Hexvix® blue-light cystoscopy using Olympus equipment

Olympus PDD equipment, in combination with the optical imaging agent Hexvix® (hexaminolevulinate), is indicated for photodynamic blue-light cystoscopy as an adjunct to white light cystoscopy for the detection of non-muscle invasive bladder cancer (NMIBC) in patients suspected or known to have lesion(s) on the basis of prior cystoscopy.

The aim of this document is to provide a guide for physicians on the use of the Olympus equipment in combination with Hexvix®. It includes important information on the set up and use of the equipment, and a troubleshooting guide for consultation when undertaking Hexvix® blue-light cystoscopy.

For further assistance please call your local Photocure or Olympus representative.

HEXVIX®
Hexaminolevulinate 85mg

PHOTOCURE®

EQUIPMENT OVERVIEW AND BLUE-LIGHT ACTIVATION

Camera and light source

CV-180

- The PDD function is built into the CV-180
- Before switching to PDD, check the white-light balance
- To activate the PDD settings, use the keyboard and press Shift F2, then select “Urology PDD” by activating fetch
- Answer Y to close the settings
- All special settings for PDD are now activated

CLV-180

- The PDD function is activated through the camera head or foot switch
- No settings are made on the light source for PDD operations

Foot switch MAJ-1391 and camera head OTV-S7ProH-FD

- During the PDD procedure, it is necessary to switch between white and blue-light
- Switching between light sources can be done either by using a foot switch or using the function switches on the camera head
- The mode that the camera is in will be shown at the top right of the image—e.g., PDD 1 when it is in blue-light mode and PDD 2 when it is in intensified blue-light mode
- If no text appears in the top right corner of the image, white light mode is activated PDD optics and light guide cable

All optics for PDD are marked as follows:

4 WA20016A: 12° PDD telescope
5 WA20017A: 30° PDD telescope
6 WA20018A: 70° PDD telescope
7 A93200A: Fluid light guide cable

Olympus equipment:

PRIOR TO THE PROCEDURE

Checklist:

- Hexvix® should be stored for a maximum of 2 hours at 2–8°C after mixing
- Recommended Hexvix® instillation time prior to surgery is 1 hour

Make sure that:

✓ Blue-light-specific light guide fluid, telescope and camera head (everything marked with a violet colored ring)is in place.

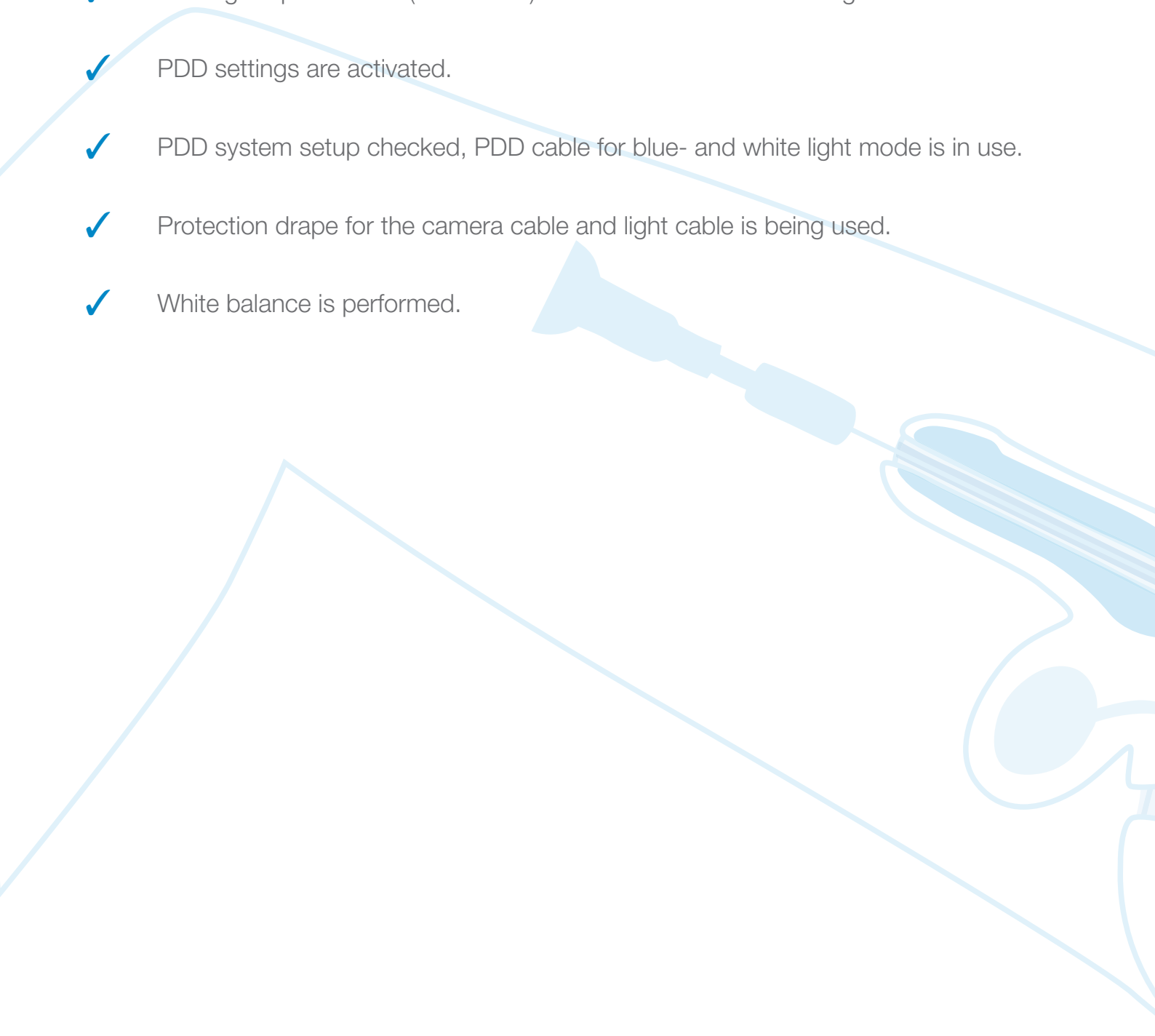
✓ Blue-light-specific filter (MAJ-1429)is attached to the CLV-180 light source.

✓ PDD settings are activated.

✓ PDD system setup checked, PDD cable for blue- and white light mode is in use.

✓ Protection drape for the camera cable and light cable is being used.

✓ White balance is performed.



DURING THE PROCEDURE

A complete cystoscopic examination should be performed under white light before switching to PDD blue-light mode and repeating the examination.

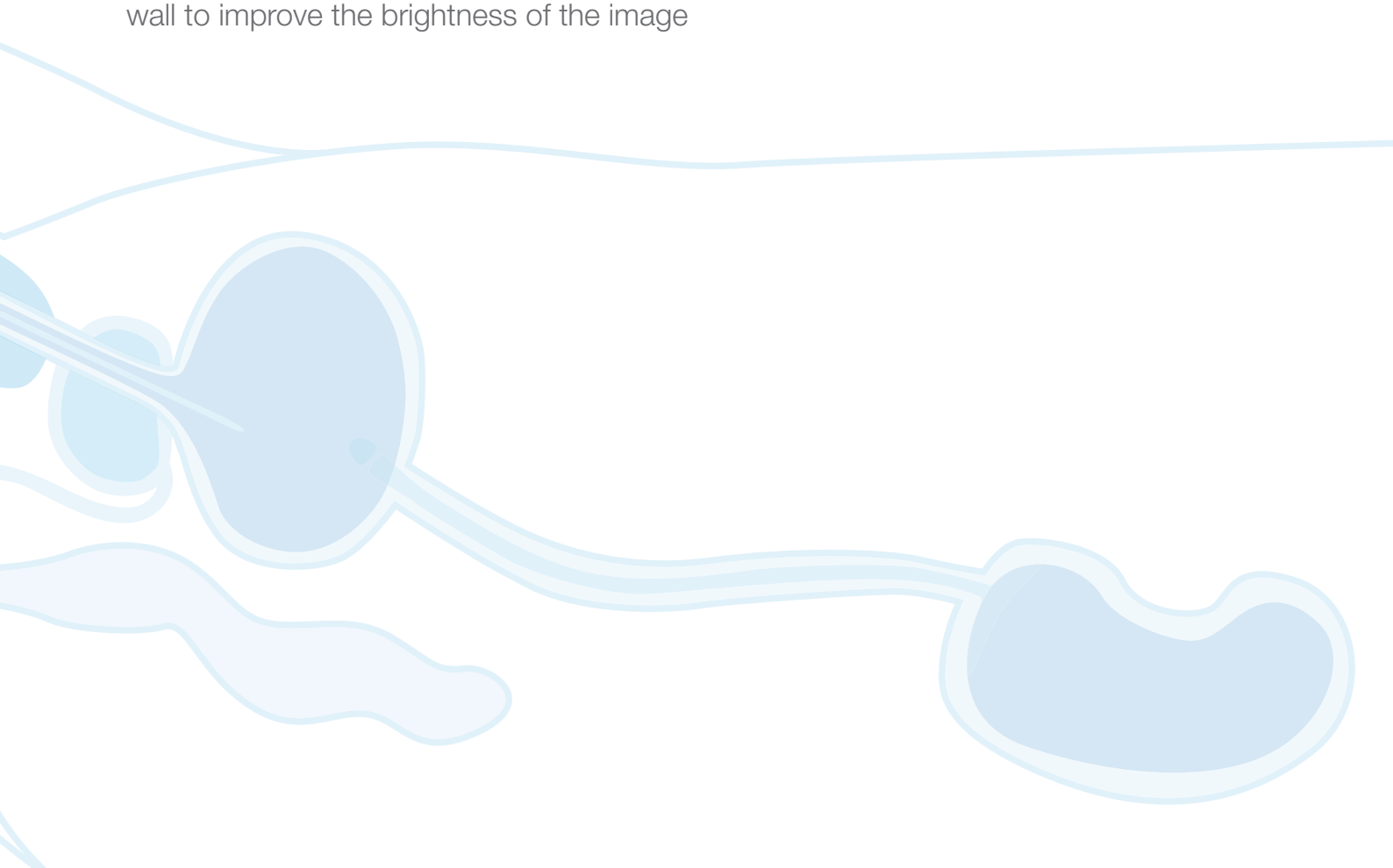
The blue-light mode should only be used in combination with the imaging agent Hexvix®, as there will be no fluorescent images present unless Hexvix® has been instilled into the bladder prior to the operation.

To avoid false-positive diagnoses

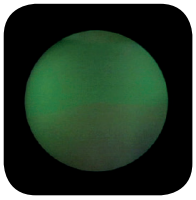
- Be aware that inflammation, scope trauma, scar tissue or the presence of immunotherapy or chemo-preventive agents may result in images appearing positive
- Beware of tangential lighting, for example of the bladder outlet
  - Hold the endoscope perpendicular and close to the bladder wall, with the bladder distended
- Be aware that dysplasia and hyperplasia can occur
  - Not all findings are tumors. Take biopsies if needed

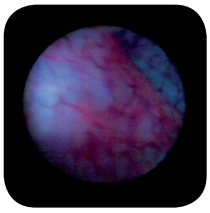
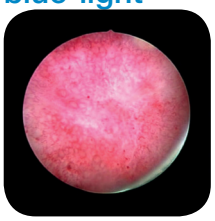
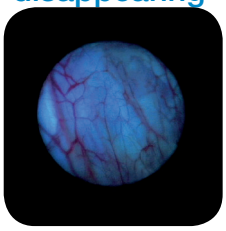
To avoid false-negative diagnoses

- Ensure adequate bladder instillation of Hexvix® solution (1 hour)
  - This will result in even dispersion of the imaging agent
- There should always be red fluorescence on the bladder neck; this is a sign that the drug has been administered properly
- Once a suspicious lesion has been located, move the cystoscope closer to the bladder wall to improve the brightness of the image



TROUBLESHOOTING

Observation	Cause	Solution
No fluorescence	PDD blue-light system is not activated	• Ensure that the settings for PDD are activated • Ensure that PDD optics and light guides are being used • Ensure that the light guide cable at the back of the CV-180 and CLV-180 is connected
	The equipment has not been set up correctly	• Inspect the camera and the settings • Check if the special light guide cable or special optics are in use (violet ring)
Unclear image	Camera not in focus	• Check the camera is in focus
	Optics are damaged	• Remove the camera and check the optics are not damaged
	Camera is dirty	• Ensure the camera is clean and free of dirt
	Floating particles in the bladder	• Empty the bladder and refill with bladder irrigation fluid
The light in blue-light mode is weak	The light guide is not correctly positioned	• Check that the light guide is properly positioned in the light source
	The light guide is damaged	• Inspect the light guide at both inputs; if there are signs of “bubbles”, the light guide is damaged and must be replaced
	Optics are damaged	• Remove the camera and check the optics are not damaged
Photobleaching	Long observation time in blue-light may result in photobeaching	• Make sure blue- and white-light mode is used alternately
Green hue 	Urine in the bladder	• Always drain the bladder at the start of the procedure

Observation	Cause	Solution
Weak fluorescence 	Equipment failure	• Conduct a quality check to include examination of the optic cables and their attachment to the plugs
	Blood in the bladder	• If blood is present, flush the bladder
	Air bubble present	• Remove air bubbles
	Concealed tumor	• Check behind any folds
	Inadequate instillation time	• Ensure that Hexvix is instilled 1 hour prior to cystoscopy
Entire bladder appears red under white light and blue-light 	Recent BCG treatment	• If clinically feasible, avoid blue-light cystoscopy until 9–12 weeks after last BCG treatment and in patients with bladder infections • It may be possible to continue the procedure under white light alone, but tumor detection may be compromised • Either continue the procedure without the benefit of blue-light diagnosis, or reschedule for a subsequent session
	Recent infection	
Lateral walls fluoresce red but the fluorescence is prone to 'disappearing' 	Tangential view	• Consider changing the angle of view • Gently stretch the bladder wall to see if fluorescence disappears

If none of the above proposed solutions helps you, please contact your local Photocure or Olympus representative.

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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