EN – Instructions for use

ProveDye®
Methylene Blue 0,5%

COMPOSITION:
Each vial of PROVEDYE® 0.5% sterile solution contains 10 mg of Methylene Blue (Proveblue®) diluted in 2 ml of water for injection.

INDICATIONS:
Marker for surgical visualisation such as intra operative seal tests, leakage visualisation, delineation of fistula tract and visualisation of Sentinel Lymph Nodes (SLN) in oncologic surgery.

CONTRAINDICATIONS:
Do not administer PROVEDYE®:
- In case of known hypersensitivity to methylene blue or to any other thiazine dyes,
- In case of recent (end of treatment less than one month ago) or ongoing treatment with Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Monoamine Oxidase Inhibitors (MAOI), bupropion, buspirone, clomipramine, mirtazapine and venlafaxine,
- In case of Glucose-6-Phosphate Dehydrogenase deficiency,

In case of pregnancy or breastfeeding, PROVEDYE® should be avoided.

ADMINISTRATION ROUTE:
PROVEDYE® is administered locally.

METHOD OF ADMINISTRATION AND DOSAGE:
PROVEDYE® can be administered through local injection, undiluted or diluted in isotonic saline solution. For visualisation of Sentinel Lymph Nodes (SLN) in oncologic surgery, PROVEDYE® must be diluted in isotonic saline solution, prior being administered through local injection.

PROVEDYE® must be used immediately after opening or dilution.
PROVEDYE® dilution and volume to be administered depend on the destination of the colouration. PROVEDYE® could be diluted until 0.01%. For example: for a 0.01% dilution, dilute 2 parts of PROVEDYE® 0.5% with 100 parts of isotonic saline solution; for a 1.25 mg/ml dilution in isotonic saline solution, dilute 1 part of PROVEDYE® 0.5% with 3 parts of isotonic saline solution.

Details on recommendations on method of administration according to the use are presented in section SPECIAL PRECAUTIONS FOR USE.

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ProveDye®
Methylene Blue 0,5%

SPECIAL PRECAUTIONS FOR USE

(Document to keep in the operative theatre)

PROVEDYE® 0.5% sterile solution
Preparation for local administration. Do not inject PROVEDYE® intravenously, intrathecally, intra-amniotically or intraocularly.
PROVEDYE® may be diluted in isotonic saline solution for local injection.
PROVEDYE® must be used immediately after opening or dilution.
PROVEDYE® can be diluted until 0.01%. For example: for a 0.01% dilution, dilute 2 parts of PROVEDYE® 0.5% with 100 parts of isotonic saline solution; for a 1.25 mg/ml dilution in isotonic saline solution, dilute 1 part of PROVEDYE® 0.5% with 3 parts of isotonic saline solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

TABLE OF USAGE EXAMPLES:

PROVEDYE®	USE	METHOD OF ADMINISTRATION (Proposed route of administration and dilution)	
BREAST SURGERY	**Visualisation of sentinel lymph nodes in breast cancer**	Peritumoral or subareolar injection	2 ml (or less) of 1.25 mg/ml solution of PROVEDYE® diluted in isotonic saline solution
	Visualisation during transaxillar endoscopy in breast surgery	Local injection directly into the infra-mammary fold	1 ml of undiluted PROVEDYE® solution
	Nipple discharge visualisation	Local injection directly into the breast duct	2 ml of undiluted PROVEDYE® solution
URO-GYNECOLO-GICAL SURGERY	**Visualisation of sentinel lymph nodes in endometrial or cervical cancer**	Uterine Cervix injection	1 ml of 2.5 mg/ml solution of PROVEDYE® diluted in isotonic saline solution
	Intra-operative delineation of vagino/utero-vesical or colorecto-vesical fistula tract	Local injection	200 – 300 ml of diluted PROVEDYE® solution in isotonic saline solution
	Ureter leaks and anastomosis visualisation during colorectal or vascular surgery	Local retrograde injection via a urinary catheter	Diluted PROVEDYE® solution in isotonic saline solution
OTHER SURGERY	**Pilonidal sinus visualisation**	Local injection into the pilonidal sinus	2 to 4 ml of solution of PROVEDYE® undiluted or diluted in isotonic saline solution
	Cysts delineation	Local injection directly into the cyst	0.1 to 0.5 ml of undiluted PROVEDYE® solution
	Bladder leaks visualisation	Local injection via a urinary catheter (Foley)	200 – 300 ml of diluted PROVEDYE® solution in isotonic saline solution
	Visualisation of sentinel lymph nodes in melanoma	Peritumoral, intradermal injection	Less than 1 ml of 1.25 mg/ml or 2.5 mg/ml solution of PROVEDYE® in isotonic saline solution

WARNINGS AND PRECAUTIONS:

- PROVEDYE® must be administered by a Healthcare Professional.
- A preoperative assessment is recommended before using PROVEDYE®.
- Protective measures against patient exposure to strong light, including that within instruments such as pulse oximeters should be taken, because there is a risk of cutaneous photosensitivity reaction.
- The wearing of gloves is recommended for PROVEDYE® users.
- Do not use a damaged vial of PROVEDYE®. Do not use PROVEDYE® if the solution is colourless.
- PROVEDYE® must be used immediately after opening or dilution.
- Do not inject PROVEDYE® intravenously, intrathecally, intra-amniotically or intraocularly.
- PROVEDYE® is for single use only: discard any remaining solution after opening.
- In case of re-use of PROVEDYE®, there is a risk to loss sterility due to potential contamination of the sterile solution (it is considered as a decrease of technical performance).
- PROVEDYE® should be disposed of in clinical waste.
- In case of moderate or severe renal disease patients must be closely monitored.

ADVERSE EFFECTS:

- Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain, blue colour of faeces and saliva.
- Hematologic: haemolysis (in glucose-6-phosphate dehydrogenase deficiency or high doses), methemoglobinemia (after high doses), hyperbilirubinemia.
- Cardiovascular: hypertension, hypotension, arrhythmia, chest pain.
- Body as a whole: profuse sweating.
- Dermal: rash (blue macules, severe burning pain), skin discolouration, urticaria, increased sensitivity of the skin to the light (photosensitivity).
- Central Nervous System: headaches, dizziness, mental confusion, anxiety, tremor, fever, aphasia, agitation; serotonin syndrome when certain medicines to treat depression or anxiety have been taken.
- Administration site: thrombophlebitis, necrosis (resulting from high doses, if not adequately diluted).
- Renal: blue colour of urine.
- Respiratory, thoracic and mediastinal: dyspnea, tachypnea, hypoxia.
- Ophtalmic: mydriasis.
- Immune: anaphylactic reaction.

Use of methylene blue for endoscopic tattoo has been associated with vascular necrosis, mucosal ulceration, mural necrosis, extramural fat necrosis and inflammatory changes in the colon.

Note to the user

Any serious incident that has occurred in relation to the device should be reported to the manufacturer at safety@provepharm.com and the competent authority of the Member State in which the user is established.

SHELF-LIFE

48 months

STORAGE:

Do not refrigerate PROVEDYE® under 8°C. Do not freeze.
Keep the vial in the original package to protect it from light.

CONDITIONING:

2 ml vials, in packs of 5 vials.

PUBLICATION DATE :

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GASTRO-DIGESTIVE SURGERY	**Colon & bile leakage visualisation**	Local injection via a catheter	1 to 20 ml of a diluted PROVEDYE® solution in isotonic saline solution
	Intra-operative delineation of anal fistula tract	Local injection directly in the external opening	Undiluted PROVEDYE® solution
ENDOCRINE SURGERY	**Visualisation of sentinel lymph nodes in thyroid cancer**	Peritumoral injection	Up to 0.5 ml diluted PROVEDYE® solution in isotonic saline solution
	Parathyroid glands identification	Local administration	1 ml of undiluted PROVEDYE® solution