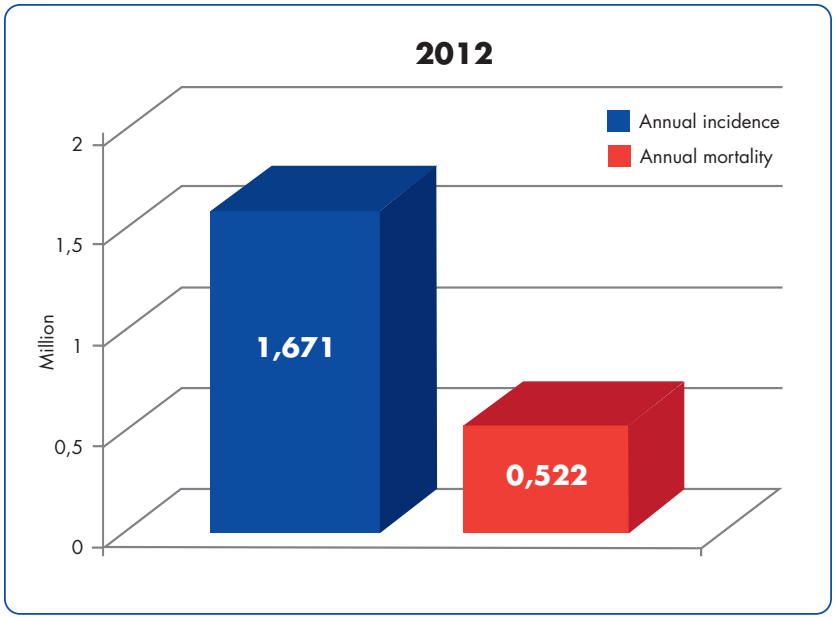
Patent Blue V

Patent Blue V sodium

Contents

Breast cancer epidemiology

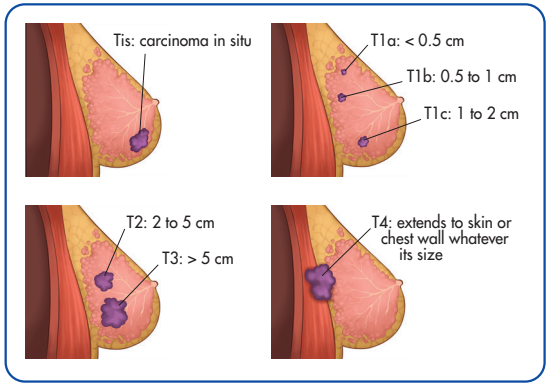
- Second most common cancer in the world[1]
- Most frequent cancer in women: 1.67 million new cases diagnosed in 2012 (25% of all cancers)[1]
- 5th cause of death from cancer overall (522,000 deaths in 2012)[1]



BREAST CANCER STILL AN IMPORTANT CAUSE OF DEATH

Breast cancer staging

Tumor and metastasis localization and size[2]



TNM Classification of breast cancer [3]

Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0

Anatomic stage/prognostic groups			
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

TNM System

The TNM System, developed by the American Joint Committee on Cancer (AJCC) is considered very precise and this system is widely used for classification of breast cancer.

T: Primary Tumor **N:** Regional Lymph Nodes **M:** Distant Metastases

* T1 includes T1mi
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB

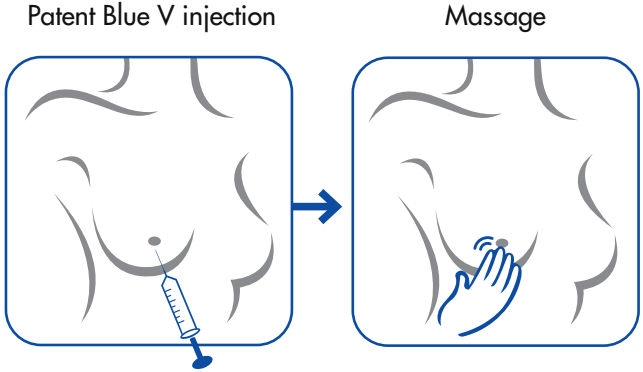
STAGING – CRUCIAL TO DETERMINE APPROPRIATE TREATMENT

Patent Blue V indication in breast cancer

Marking sentinel nodes before biopsy in patients with operable breast cancer.

Sentinel lymph node identification – SLNI:

- Injection into the immediate area surrounding the tumor or into the tumor bed periaeolar
- Subcutaneous but not intradermal injection
- Systematically breast massage



PATENT BLUE V INDICATION TO FIGHT BREAST CANCER

Sentinel Lymph Node Biopsy (SLNB) international management guidelines

SLNB: standard-of-care for axillary staging in early breast* cancer according to the clinical practice guidelines[4]

Europe | ESMO guidelines (European Society for Medical Oncology)[4]

*« The **choice of treatment strategy is based on biology** (pathology including biomarkers, gene expression) and **tumour extent/location** (size and location of primary tumour, number of lesions, **number and extent of lymph node involvement**) as well as on the age, body habitus and general health status of the patient and her/his preferences. »*

*« SLNB rather than full nodal clearance is now accepted as **the standard of care** for axillary staging in early breast cancer… »*

Level of evidence & Grade of recommendation: SLNB as the standard of care for axillary staging — [II, A]; SLNB delivers less morbidity & allows for a reduced hospital stay— [I, A]

Australia | NBOCC guidelines (National Breast and Ovarian Cancer Centre)[5]

*«Patients with unifocal tumours equal to or less than three centimetres in diameter and clinically negative axillary nodes should be offered **sentinel node biopsy as an alternative** to axillary dissection. »*

Level of evidence: SNB for staging and management of the axilla— I

America | ASCO Guidelines (American Society of Clinical Oncology)[6]

*«Women with operable breast cancer and multicentric tumors, […] who received preoperative/neoadjuvant systemic therapy may be **offered SNB**. »*

Evidence quality & Strength of recommendation: SLNB for early-stage breast cancer — High & Strong

**early breast: breast cancer that has not spread beyond the breast or the axillary lymph nodes*

SLNB – STANDARD-OF-CARE FOR AXILLARY STAGING

Patent Blue V for SLNB – endorsement by international clinical practice guidelines

Europe

« … There are two current techniques used ***to identify the sentinel node(s):*** *Radiopharmaceutical, technetium sulfur colloid, and isosulfan blue dye (used in the United States) Technetium-labeled albumin and* ***Patent blue dye*** *(used in Europe)*[7]*… »*

« ***…Dyes cause the blue colouring*** *as they pass slowly through the sentinel node. Isosulfan blue is of greater use in the United States, and* ***Patent blue V*** *in Europe*[8]*… »*

UK

« …Increasingly ***sentinel lymph node biopsy (SLNB) is the preferred method*** *for staging the axilla in early breast cancer (NICE Guidelines 2009). In the UK the SLN is successfully localized in 99% of patients using a combined technique of radioactive (TcM99m) labelled nanocolloid and 2 mls of diluted* ***Patent V blue dye*** *injected into the breast (NEW START Programme). SLNB using the dual localisation protocol is* ***now being used for other tumours, notably melanoma, penile, testicular, cervical and head and neck cancers***[9]*… »*

France

« ***…Le traceur utilisé est un colorant, un radio isotope ou les 2****. L'injection du colorant (****bleu patenté****, bleu isosulfan ou bleu de méthylène) a lieu au bloc opératoire après induction de l'anesthésie, une dizaine de minutes avant l'incision*[10]*… »*

*[The tracer is either a dye, a radiopharmaceutical or both. The dye (****Patent Blue****, isosulfan blue or methylene blue) is injected in an operating room under anaesthesia, approximately ten minutes before incision…]*

PATENT BLUE V ENDORSED BY INTERNATIONAL GUIDELINES

Efficacy & Accuracy Van la Parra R.F.D et al. EJSO (2014)[11]

Multicenter prospective trial: SMMaC trial

30 patients with multicentric breast cancer.

- Periareolar injection of radioisotope and Patent blue dye was administered
- SLN biopsy (SLNB) was validated by back-up completion axillary lymph node dissection

Endpoint: to assess SLNB feasibility and accuracy in multicentric breast cancer

Results:

« The SLN was successfully identified in 30 of 30 patients (identification rate 100%). The incidence of axillary metastases was 66.7% (20/30). The false negative rate was 0% (0/20) and the sensitivity was 100% (20/20). The negative predictive value was 100% (10/10) »

n	Tumor	Injection	Identification rate %	FN rate %	Sens	NPV %
30	MC	SA	100	0	100	100

MC = multicentric; SA = subareolar; FN = false negative rate; Sens = sensitivity; NPV = negative predictive value

Conclusion:

« SLN biopsy in multicentric breast cancer seems feasible and accurate and should therefore be considered in patients with multicentric breast cancer and clinically negative axilla. »

SLNB – ACCURATE FOR MULTICENTRIC BREAST CANCER

Efficacy & Accuracy Elmadahm A. et al. ANZ J Surg 85 (2015)[12]

Monocenter prospective randomized trial: SNAC trial

1 088 patients

- Preoperative lymphoscintigraphy (LSG) and gamma probe (GP) combined with peritumoural injection of Patent Blue V (BPV): 971 patients
- BPV alone: 106 patients

Endpoint: Effect of clinical factors on sentinel node (SLN) identification in the sentinel node biopsy versus axillary clearence (SNAC) trial

Objective:

« …to define the contribution of each detection technique on the identification of SLNs in women involved in the sentinel node biopsy versus axillary clearance (SNAC) trial who were randomized to either SLNB with axillary clearance only if the removed SLNs were positive (SLNBM group) or SLNB followed by immediate axillary clearance (AC) »

Results:

« Blue SLNs were removed in 890 of 1073 patients ***(82.9%)*** *»*

« The identification rate among patients who ***had BPV injection only*** *as the identification technique was* ***85.8%*** *(91 of 106 patients) »*

« BPV detected the SLNs in ***141 of 178 women with negative LSG mapping*** *and in* ***44 of 79 women with no hot SLNs detected intraoperatively*** *»*

Conclusion:

*« **BPV had an important salvage role** in the SNAC trial when SLN identification failed using the GP and LSG »*

*« The use of **BPV is recommended** in patients who have unsuccessful SLN detection utilizing the radioactive tracer in order to improve the detection rate »*

*« There is merit in the use of patent blue in a combined technique, which could **outweigh concerns about allergic reactions** »*

*« **BPV enabled the detection of SLN when use of scintigraphy and GP failed** and retention of its use in a **combined technique is recommended** »*

PATENT BLUE V DETECTS SLN WHEN OTHER TECHNIQUE FAIL

Efficacy & Accuracy Jean-François Rodier et al. J. Clin. Oncol. (2007)[13]

Fransenode trial

449 patients

- A prospective randomized multicentric study was initiated to compare the peritumoral (PT) injection site to the periareolar (PA) site in 449 patients.
- The peritumoral (PT) injection site: 222 patients ; The periareolar (PA) site: 223 patients

Endpoint: To determine the optimal injection path for **blue dye** and radiocolloid for **sentinel lymph node (SLN) biopsy** in early breast cancer.

Objective:

« The primary objective of the study was to determine the axillary sentinel lymph node (SLN) identification rate and the secondary objectives were to determine locoregional recurrence, survival, and morbidity. »

Results:

*« Intraoperative detection rate **by blue dye** and/or gamma probe **was similar (99.11%) in both groups**. »*

*« The rate of SLN detection **was somewhat higher in the PA group** than in the PT group: **95.6%** versus 93.8% **with blue dye** (P =.24) and **98.2%** versus 96.0% by probe (P = .16), respectively. »*

Conclusion:

*« This study strongly **validates the PA injection** technique given **the high detection rate (99.1%) of SLN** and **the high concordance (95.6%)** between **blue dye** and the radiotracer, as well as higher significant ex and in vivo counts, improving SLN probe detection. »*

SLNB PROCEDURE IS EQUALLY EFFECTIVE WITH PA OR PT INJECTION

Patent Blue V safety Van la Parra R.F.D et al. EJSO (2014)[14]

Review of adverse reactions of Patent Blue V in patients who participated to NEW START training programme and the ALMANAC trial

7 917 patients

- All patient underwent sentinel lymph node biopsy for breast carcinoma using Patent Blue V in combination with ^{99m} Tc-albumin colloid

Outcome: allergic potential of Patent Blue V dye

Objective:

« Patent blue V is used in the UK while its isomer isosulfan blue is used in the US. The allergic potential of isosulfan blue is well documented (1.4% adverse reactions) but that of patent blue V is less clearly defined.»

« In this paper we review the adverse reactions of patent blue V… »

Results:

*« In total, 72 of 7 917 (**0.9%**) patients experienced adverse reactions… »*

Adverse reactions to patent blue V dye.

Study	Adverse reactions to patent blue V dye	95% confidence interval
NEW START *(n=6586)*	0.9% (58/6586)	0.7%–1.1%
ALMANAC randomised phase *(n=492)*	1.0% (5/492)	0.4%–2.4%
ALMANAC validation phase *(n=839)*	1.1% (9/839)	0.6%–2.0%
Total *(n=7917)*	0.9% (72/7917)	0.7%–1.1%

Side-effects of patent blue V dye.

Allergic reactions		
Grade I	Urticaria, blue hives, pruritis or generalised rash	23 patients
Grade II	Transient hypotension/bronchospasm/ laryngospasm	16 patients
Grade III	Severe hypotension (requiring vasopressor support) ***and/or*** change/abandoning of planned procedure ***and/or*** HDU/ITU admission	5 patients
Grade IV	Cardio-respiratory arrest ***and/or*** death	-
Unspecified		24 patients
Total allergic reactions		**68**
Non-allergic reactions		
Skin tattooing		1 patient
Bluish hue persisting for few hours		3 patients
Total allergic + non-allergic reactions		**72**

Conclusion:

« The allergic potential of patent blue V dye compares favourably with isosulfan blue. Severe anaphylaxis is rare… »

LESS THAN 1% SIDE EFFECTS WITH PATENT BLUE V

Morbidity & Quality of life Mansel R.E. et al. JNCI (2006)[15]

Multicenter, randomized trial

1 031 patients

- Sentinel lymph node biopsy (SLNB): 515 patients
- Standard axillary surgery: 516 patients

1ary outcome = arm & shoulder morbidity + quality of life

Objective:

« Compare quality-of-life outcomes between patients with clinically node-negative invasive breast cancer who received sentinel lymph node biopsy and patients who received standard axillary treatment »

Results:

Lymphedema: *« Moderate or severe lymphedema was reported more often by patients in the standard axillary treatment group than by patients in the* ***sentinel lymph node biopsy*** *group at 1, 3, 6, and 12 months after surgery* ***(all P<.001)*** *»*

Sensory deficit: *« At all time points, statistically significantly more patients in the standard treatment group than in the* ***sentinel biopsy*** *groups reported sensory deficit* ***P<.001 for all)*** *»*

Intercostobrachial nerve damage: *« Was more extensive in the standard treatment group than in the* ***sentinel lymph node biopsy*** *group at 1, 3, 6, and 12 months after surgery* ***(all P <.001)*** *»*

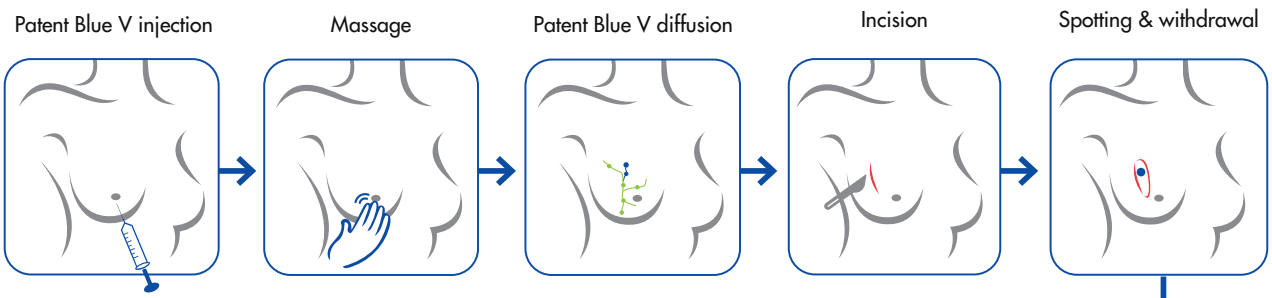
Quality-of-Life Assessments: *« TOI score (Trial Outcome Index): statistically significant differences in TOI scores between treatment groups favoring the* ***sentinel lymph node biopsy*** *group at all time points (****P <.001****, 1 month after surgery;* ***P = .001****, 3, 6, and 12 months after surgery) »*

Conclusion:

« Sentinel lymph node biopsy is associated with reduced arm morbidity and better quality of life than standard axillary treatment and should be the treatment of choice for patients who have early-stage breast cancer with clinically negative nodes »

SLNB WITH PATENT BLUE V REDUCES MORBIDITY & IMPROVES QUALITY OF LIFE

SLN identification with Patent Blue V alone & biopsy procedure



ANATOMO-PATHOLOGY EXAMINATION

NO CANCERS CELLS

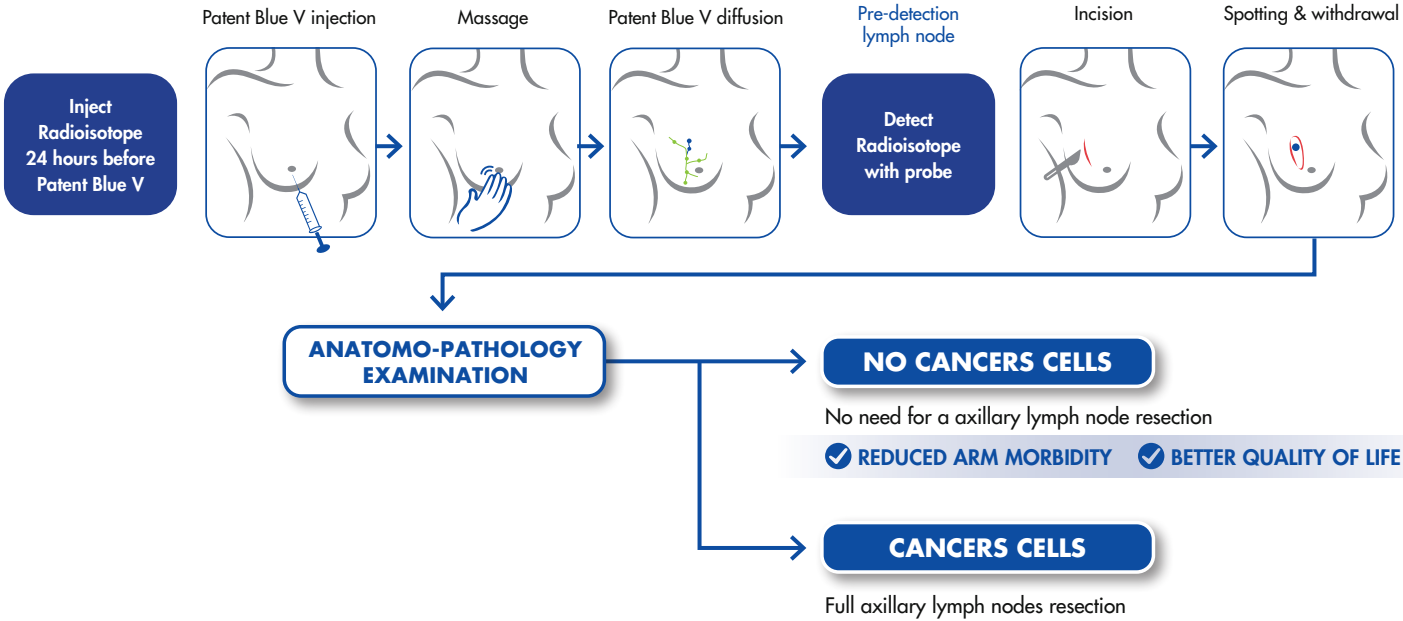
No need for a axillary lymph node resection

- REDUCED ARM MORBIDITY
- BETTER QUALITY OF LIFE

CANCERS CELLS

Full axillary lymph nodes resection

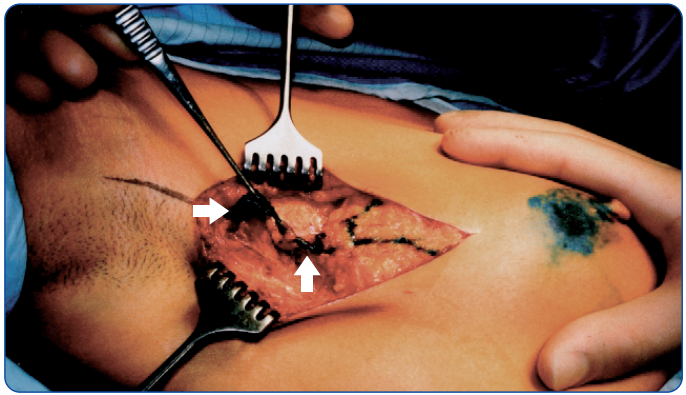
SLN identification with Patent Blue V and radioisotope & biopsy procedure



IDENTIFICATION WITH PATENT BLUE V REDUCES MORBIDITY & IMPROVES QUALITY OF LIFE

Patent Blue V use and mechanism of action

- **Volume preparation:** Identification of SLN consists to inject 2 ml of Patent Blue V [16]
- **Injection site:** Injection into the immediate area surrounding the tumor or into the tumor bed periaeolar [16]
- **Injection path:** Subcutaneous but not intradermal injection [17]
- **After injection:** Systematically breast massage [17]
- *« After approximately 5 minutes' delay, during which time the injection site was gently massaged, a 3- to 5-cm axillary incision was made in the standard location for ALND or the predetermined line for mastectomy »* [18]



« Two blue (axillary) lymphatic trunks clearly visible after periareolar intradermal blue dye injection. The vessels pass over the breast tissue and join to drain into a single blue sentinel node (held in the forceps) in the lower axilla.[18] *»*

SENTINEL NODE CLEARLY VISIBLE 5 MIN. AFTER INJECTION

Features & benefits of Patent Blue V

Features	Benefits
▸ Visualizer	• Clear Identification & localization of Sentinel nodes 5 mins after injection [17] • High identification rate [19]
▸ Improver	• Participate to reduce morbidity • Improve quality of life [15,20]
▸ User-friendly	• Subcutaneous injection • No obligation to dilute [16,17]

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PATENT BLUE V. Composition: PATENT BLUE V SODIUM 2.50 g per 100 ml of solution for injection. List of excipients: Sodium chloride, disodium phosphate dodecahydrate, water for injection. **Indications (**):** diagnostic use only - Marking lymph vessels and arterial regions, Marking sentinel nodes before biopsy in patients with operable breast cancer. **Posology and method of administration (*):** Posology - Marking arterial regions: not more than 10 ml intra-arterially, marking lymph vessels: 0.5 to 2 ml subcutaneously, marking the sentinel node: 1 to 2 ml subcutaneously around the tumor or areola. **Contraindications (*):** Hypersensitivity to Patent Blue V, tryphenylmethane dyes or any of the excipients. **Special warnings and special precautions for use (*):** There is a risk of allergic reactions whatever the administration route or dose. Patent Blue V may cause minor or major immediate allergic reactions that may be life-threatening or even fatal (anaphylactic shock). They are often unpredictable but they occur more frequently in patients with a history of hypersensitivity reactions to Patent Blue V or related triphenylmethane dyes contained in drugs, food and cosmetics. The indication should be very carefully assessed in these predisposed patients. Corticosteroids and H1-type antihistamines have been suggested as premedication in patients at risk for intolerance reactions (history of intolerance to Patent Blue V or related triphenylmethane dyes). However, they do not prevent the occurrence of serious or fatal anaphylactic shock. The risk of a major reaction implies that emergency measures must be immediately available especially in patients on beta blockers in whom adrenaline and vascular perfusion would be insufficiently effective. Therefore, Patent Blue V must only be administered in an establishment capable of adequate treatment. Before the administration of Patent Blue V: Identify subjects at risk by a precise interview on their history. Insert an indwelling venous catheter. Throughout the examination, maintain: Medical monitoring. An indwelling intravenous catheter. Drugs and equipment for resuscitation readily available. After the administration of Patent Blue V, the patient must be monitored for at least 30 minutes. Warnings and precautions specific to the sentinel node marking: In the event of an allergic reaction, an investigation must be carried out to determine whether, among all the medicinal products used during the operation and general anaesthesia, Patent Blue V is actually responsible. This result is important in the event of subsequent surgery (for contralateral cancer, for example). When marking the sentinel node, all staff caring for the patient must be trained in the technique. Data in the literature show that the rate of identification is improved by carrying out double detection with a radiopharmaceutical and a dye. **Interaction with other medicinal products and other forms of interactions (*):** Medicinal products - Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists. These medicinal products reduce the efficacy of cardiovascular compensation mechanisms for haemodynamic disorders. The physician must be aware of this before injecting Patent Blue V and emergency measures must be available. Other forms of interaction - The value of partial oxygen pressure measured by spectrophotometry may show a transient false decrease of 5 to 10% below baseline values during examinations with Patent Blue. When in doubt, it is advisable to check by arterial blood gas analysis. The value of serum methaemoglobin measured by the same spectrophotometric method may be falsely increased. **Fertility, pregnancy and lactation (*):** Pregnancy The use of this medicinal product is not recommended during pregnancy. Lactation - It is not known whether Patent Blue V is excreted in breast milk. **Effects on ability to drive and use machines (*) – Undesirable effects (*)** immediate hypersensitivity reactions are possible. These reactions may involve one or more effects, occurring concomitantly or successively, and usually including cutaneous, respiratory and/or cardiovascular manifestations, each of which can be a warning sign of incipient shock and, in very rare instances, can even prove fatal. A bluish coloring of the integuments is observed after the injection, which disappears within 24 to 48 hours. In patients with lymph stasis or circulatory disorders, the coloring may last longer. **Overdose (*) – Pharmacodynamic properties (*)** Pharmacotherapeutic group: Dye for vascular marking, ATC code: V04CX. **Pharmacokinetic properties (*)** the dye is eliminated in 24 to 48 hours, mainly in urine (which is highly colored) but also in bile. **Nature and content of container :** colorless type I glass ampoule containing 2 ml. Date of revision: September 2015.

(*) For complete information please refer to the local Summary of Product Characteristics
(**) Indications may differ from country to country.
Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

Indications and dosage may vary from country to country.
Countries where indication, Sentinel Nodes Identification, before biopsy in patients with operable breast cancer is registered are: Belgium/Luxembourg, Canada, France, Germany, Hong Kong, Hungary, Israel, Mexico, The Netherlands, Peru, Philippines, Slovakia, Switzerland, Cambodia, Taiwan, Thailand.
For complete information please refer to country's local SmPC.
For a copy of the SmPC, please contact a Guerbet representative.

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