

Verdye (Indocyanine Green)

Reconstructive Surgery Market Focus



Diagnostic Green is the leading provider of trusted high quality fluorescence products for physicians worldwide.

Reconstructive surgery is performed to treat structures of the body affected aesthetically or functionally by congenital defects, trauma, infection, developmental abnormalities, tumours or disease. In the US alone, over 6 million reconstructive surgery procedures are performed annually with 5.2M plastic/reconstructive procedures following tumour removal.¹ The global reconstructive surgery market is expected to grow by 8.8% CAGR 2020-2024, with the breast reconstruction sector dominating the plastic surgery market with over 107,000 undertaken annually in the US alone.²

PERFUSION ASSESSMENT IS KEY

Plastic surgeons are faced daily with the risks of skin, pedicled or free flap harvesting. They are motivated more than any other surgeon to use rapid, reliable, safe and easy to use approaches to assess tissue viability and perfusion before, during and after surgical procedures.

VERDYE USE IN PREFUSION ASSESSMENT IN PLASTIC MICRO-RECONSTRUCTIVE SURGERY

Breast Reconstruction (Flaps)	Oral & Maxillofacial Surgery	Trauma & Burns
-------------------------------	------------------------------	----------------

BREAST RECONSTRUCTION (FLAPS)

Breast reconstruction has greatly changed in the last decade as skin-sparing and nipple sparing mastectomies, post tumour removal, have been shown to be oncologically safe allowing better aesthetic and functional results.³ Skin perfusion in skin sparing mastectomies and the areolar-papillary complex (APC) perfusion as undertaken in nipple sparing mastectomies, are fundamental to the success of a patient's breast reconstruction procedure. Failure to detect perfusion problems that could compromise tissue vascularisation may result in postoperative complications including necrosis, infection, implant loss and reoperation.⁴

Laser-assisted Indocyanine Green Angiography (ICGA) allows surgeons to determine inter-operative flap perfusion and achieve the best outcomes in breast reconstruction. In a review and meta-analysis of over nine studies and over 2,000 patients, the authors concluded that ICGA reduces the risk of skin necrosis and the need for surgical re-intervention by allowing intraoperative diagnosis of perfusion complications. The analysis also showed a further benefit of ICGA in that it reduced the risk of wound infections.¹³



Fig 1: Breast Flap reconstruction - greyscale image of DIEP Flap using Verdye, checking vascular perfusion of the perforator blood vessel feeding the tissue flap.

Breast reconstruction methods

Implants	Autologous (own tissue) flaps
Prosthesis	Pedicled (Latissimus Dorsi – Breast)
	Free Flaps (blood supply harvested with the flap) <ul style="list-style-type: none">• DIEP (Deep Inferior Epigastric Perforator)• TRAM (Transverse Rectus Abdominis Myocutaneous)

Because autologous reconstructions more closely resemble the pre-operative form, they are now considered gold standard. TRAM uses rectus abdominal muscle which can lead to loss of abdominal strength, whereas the DIEP procedures spares the rectus abdominal muscle and halves the likelihood of hernias, resulting in shorter recovery time. DIEP is considered the gold standard in free flap breast reconstruction.

Pooled outcomes from meta-analysis of ICG use in breast reconstruction⁵

Use of ICGA compared to clinical assessment alone resulted in:

- Significantly lower risk of necrosis (reduced by more than half across number of quoted studies)¹³
- Lower reoperation rates (reduced by more than two thirds in number of studies)
- Lower infection risk (secondary benefit)

ORAL & MAXILLOFACIAL SURGERY

Microvascular reconstruction of the head and neck represents one of the most advanced surgical options available for the rehabilitation of surgical defects related to the removal of head and neck tumours. Pedicled flaps and free-tissue transfers have become invaluable tools for reconstruction of the head and neck region. These methods are used routinely to reconstruct hard and soft tissue defects, but compromised blood supply and subsequent flap failure remains a constant concern for the surgeon, particularly in free-tissue transfer. Early detection of vascular compromise and its prompt correction is thus critical to the success of these procedures.^{5,15}

TRAUMA & BURNS

Indocyanine Green (ICG) angiography has been reported to be highly efficacious in assessing burn depth (with an accuracy of almost 100%) and predicting long-term wound outcomes. In studies it is considered superior to Laser Doppler Imaging for evaluating burn wounds.⁶ In the 30 burn sites that were assessed, in one study, the accuracy of ICG angiography was 100.0%, compared with 50.0% for clinical assessment ($p < 0.001$). Clinical assessment yielded a sensitivity of 33.3% and specificity of 66.7%, while ICG angiography yielded both a sensitivity and specificity of 100.0%.⁶

Figures 2 & 3 Free myocutaneous latissimus dorsi flap procedure during a joint prosthesis replacement surgery due to relapsing implant infections.

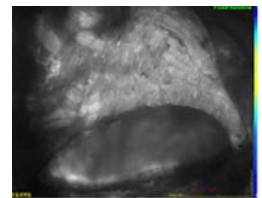


Fig 2: ICG angiography revealing mal-perfused latissimus flap areas at the periphery.

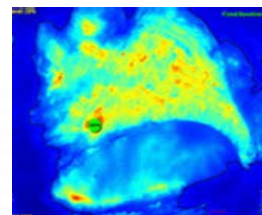


Fig 3: Colour mode and contour level at 20% in relation to a reference point of maximum fluorescence within the flap.

Why use ICG in plastic and reconstructive surgeries?

While many surgeons still assess flap perfusion and viability based solely on clinical experience, there is an increasing wealth of evidence now available to recommend using ICG for dynamic perfusion imaging during flap reconstruction, be that breast reconstruction, oral & maxillofacial surgery or burn and trauma reconstructive procedures. Studies have shown that employing ICG as a method to evaluate perfusion reduces complication rates, lowers morbidity, shortens hospital stays and produces for the patient a better overall result.^{7,8,13,16}

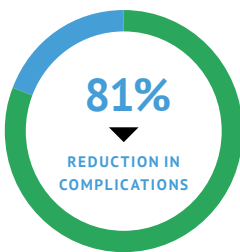
THE ADVANTAGE OF PERFUSION ASSESSMENT USING ICG

- ⊙ Easy to implement⁸
- ⊙ Allows for perforator mapping¹⁵
- ⊙ Provides real time perfusion assessment (flap & skin at attachment site)¹⁵
- ⊙ Optimises flap design¹⁶
- ⊙ Supports intraoperative flap monitoring¹⁶
- ⊙ Gives surgeon a tool to facilitate flap planning, dissection and insertion⁷

COST BENEFITS ON USE OF ICG DURING RECONSTRUCTIVE SURGERY

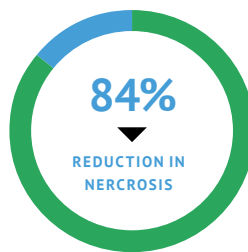
A comprehensive literature review of complications after breast reconstruction surgery revealed laser-assisted ICG angiography used to assess perfusion consistently improved clinical outcomes and reduced costs.^{9,13}

Breast Reconstruction Surgery⁹



Clinical assessment vs laser-assisted ICG angiography

Mastectomy Skin Flap Necrosis¹⁰



Clinical assessment [n=254] vs laser-assisted ICG angiography [n=213]; p=0.02

Increased costs associated with surgical complications

Necrosis following breast reconstruction - \$11,076 inpatient costs per patient¹¹

Potential savings with the use of ICG in surgical procedures

Up to \$610 per patient due to reduced necrosis and reoperation^{12,14}

REFERENCES:

1. *Plastic Surgery Statistics Report 2020*, <https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf>
2. *Breast Reconstruction Market, 2020-2024* <https://www.technavio.com/report/breast-reconstruction-market-industry-analysis>
3. Oda G, Nakagawa T, Uemura N, Mori H, Mori M, Fujioka T, Onishi I, Uetake H. Immediate breast reconstruction is oncologically safe for node-positive patients: Comparison using propensity score matching. *Medicine (Baltimore)*. 2021 Sep 10;100(36):e27184. doi: 10.1097/MD.00000000000027184. PMID: 34516518; PMCID: PMC8428751
4. Jones GE, King VA, Yoo A, Abu-Ghname A, Rammos CK. Use of New Technologies in Implant-Based Breast Reconstruction. *Semin Plast Surg*. 2019 Nov;33(4):258-263. doi: 10.1055/s-0039-1696987. Epub 2019 Oct 17. PMID: 31632209; PMCID: PMC6797494.
5. Yeoh MS, Kim D, Ghali E. Fluorescence Angiography in the Assessment of Flap Perfusion and Vitality, Oral and Maxillofacial Surgery Clinics of North America, 2013, <https://www.sciencedirect.com/science/article/abs/pii/S104236991200177X?via%3Dihub>
6. Wongkietkachorn A, Surakunprapha P, Winaikosol K, et al. Indocyanine green dye angiography as an adjunct to assess indeterminate burn wounds: A prospective, multicentered, triple-blinded study, *May 2019, Journal of Trauma and Acute Care Surgery*, doi: 10.1097/TA.00000000000002179
7. Bigdeli AK, Thomas B, Falkner F, Gazyakan E, Hirche C, Kneser U. The Impact of Indocyanine-Green Fluorescence Angiography on Intraoperative Decision-Making and Postoperative Outcome in Free Flap Surgery. *J Reconstr Microsurg*. 2020 Oct;36(8):556-566. doi: 10.1055/s-0040-1710552. Epub 2020 May 14. PMID: 32408364.
8. Hembd AS, Yan J, Zhu H, Haddock NT, Teotia SS. Intraoperative Assessment of DIEP Flap Breast Reconstruction Using ICG Angiography: Reduction of Fat Necrosis, Resection Volumes and Post-operative Surveillance. *Plast Reconstr Surg*. 2020 Apr 13. doi: 10.1097/PRS.00000000000006888. Epub ahead of print. PMID: 32301911
9. Chatterjee A. A comparison of free autologous breast reconstruction with and without the use of laser-assisted indocyanine green angiography: A cost-effectiveness analysis. *Plast Reconstr Surg*. 2013;131(5):693e-701e.
10. Johnson, Ariel C. BS; Colakoglu, Salih MD; Chong, Tae W. MD; Mathes, David W. MD. Indocyanine Green Angiography in Breast Reconstruction: Utility, Limitations, and Search for Standardization. *Plastic and Reconstructive Surgery - Global Open* 8(3):p e2694, March 2020. | DOI: 10.1097/GOX.00000000000002694
11. Yalanis GC, Nag S, Georgek JR, Cooney CM, Manahan MA, Rosson GD, et al. Mastectomy weight and tissue expander volume predict necrosis and increased costs associated with breast reconstruction. *Plast Reconstr Surg Glob Open*. 2015 Aug;3(7):e450.
12. Losken A, Schaefer TG, Newell M, Styblo TM. The impact of partial breast reconstruction using reduction techniques on postoperative cancer surveillance. *Plast Reconstr Surg* 2009 Jul;124(1):9-17. doi: 10.1097/PRS.0b013e3181ab10e5.
13. Wang Z, Jiao L, Chen S, Li Z, Xiao Y, Du F, Huang J, Long X. Flap perfusion assessment with indocyanine green angiography in deep inferior epigastric perforator flap breast reconstruction: A systematic review and meta-analysis. *Microsurgery*. 2023 May 11. doi: 10.1002/micr.31056. Epub ahead of print. PMID: 37165852.
14. Vettoretto N, Foglia E, Ferrario L et al., Could fluorescence-guided surgery be an efficient and sustainable option? A SICE (Italian Society of Endoscopic Surgery) health technology assessment summary, *Surg Endosc*. 2020 Jul;34(7):3270-3284, <https://pubmed.ncbi.nlm.nih.gov/32274626/>
15. Eguchi T, Kawaguchi K, Sato K, Hamada Y. Using indocyanine green angiography to achieve complete engraftment of pectoralis major myocutaneous flaps. *Int J Oral Maxillofac Surg*. 2023 May;52(5):539-542. doi: 10.1016/j.ijom.2022.09.036. Epub 2022 Oct 13. PMID: 36243644.
16. Tange FP, Verduijn PS, Sibinga Mulder BG, van Capelle L, Koning S, Driessen C, Mureau MAM, Vahrmeijer AL, van der Vorst JR. Near-infrared fluorescence angiography with indocyanine green for perfusion assessment of DIEP and msTRAM flaps: A Dutch multicenter randomized controlled trial. *Contemp Clin Trials Commun*. 2023 Apr 2;33:101128. doi: 10.1016/j.conctc.2023.101128. PMID: 37091505; PMCID: PMC10119502.

VERDYE PRESCRIBING INFORMATION

Name of the Medicinal Product

Verdyne 5 mg/ml Injection
25 mg / 50 mg, Powder for Solution
for Injection

Pharmaceutical Form

Powder for Solution for Injection
Dark-green powder

Clinical Particulars

Therapeutic indications

This medicinal product is for diagnostic
use only.

Diagnostic Indications

Cardiac, circulatory and micro-circulatory diagnostics:

- measurement of cardiac output
and stroke volume
- measurement of circulating
blood volumes
- measurement of cerebral perfusion

Liver function diagnostics:

- measurement of liver blood flow
- measurement of excretory function
of the liver

Ophthalmic angiography diagnostics:

- measurement of perfusion of
the choroid

Posology and method of administration

Method of administration

Before administration the powder must
be reconstituted with water for injection.

Shelf Life

5 years. After reconstitution, the solution
should be used immediately, protected
from light.

Instructions for use and handling

This medicinal product should be
reconstituted immediately prior to use.
This medicinal product is reconstituted by
addition of 5 ml water for injections to the
vial containing 25 mg of active substance
or 10 ml water for injections to the vial
con-taining 50 mg of active substance,
respectively, giving in both cases a
dark-green solution for injection with a
concentration of 5 mg/ml (0.5 % w/v). If
an incompatibility is noted in the form of
unclear solution then the reconstituted
solution should be discarded. Visually
inspect the reconstituted solution. Only
use clear solutions free from visible
particles.
This medicinal product is for single use
only.

The reconstituted solution is clear and free
from visible particles.

Diagnostic procedures with Verdyne should
be performed under the supervision
of a physician. Verdyne is intended for
intravenous injection via an injection
needle, a central or peripheral catheter or
cardiac catheter.

The administration and site of Verdyne are
of critical importance for the quality of the
measurements. In principle, for obtaining
optimal quality first pass indicator dilution
curves, the injection should be as close
as possible to the vascular bed, organ or
tissue of interest.

On peripheral injection the injection should
be made immediately after application of
tourniquet and the arm should be raised
after release of tourniquet. This ensures
rapid transport of the dye from the site of
injection and peripheral injection is then
practically equivalent to central venous
injection.

Dosage

Single dose per measurement in adults,
elderly, children:

**Cardiac, circulatory, micro-circulatory and
tissue perfusion diagnostics** as well as
cerebral blood flow: 0.1 to 0.3 mg/kg body
weight as bolus injection

Liver function diagnostics: 0.25 – 0.5 mg/
kg body weight as bolus injection

Ophthalmic angiography: 0.1 to 0.3 mg/kg
body weight as bolus injection

Total daily dose:

Adults, elderly, adolescents 11-18 years:

The total daily dose of Verdyne should be
kept below 5 mg/kg body weight.

Children 2 – 11 years:

The total daily dose should be kept below
2.5 mg/kg body weight.

Children 0 - 2 years:

The total daily dose should be kept below
1.25 mg/kg body weight.

Contraindications

Verdyne is contraindicated for safety
reasons in:

- patients with hypersensitivity to
indocyanine green or to sodium iodide
unless special precautions are taken,
- patients with hypersensitivity to iodine,
- patients with hyper-thyroidism,
patients with autonomic thyroid
adenomas
- as in-vitro experiments have shown
that indocyanine green displaces
bilirubin from its protein binding,
Verdyne should not be used in
premature infants or neonates in
whom an exchange transfusion is
indicated due to of hyperbilirubinemia,
- if injection of Verdyne was poorly
tolerated in the past it must not be
used again, since severe anaphylactic
reactions might occur.

For full prescribing information go to www.diagnosticgreen.com

Diagnostic
Green

© 2023 Diagnostic Green
info@diagnosticgreen.com
www.diagnosticgreen.com

Diagnostic Green Ltd
IDA Business Park Garrycastle
Athlone, Co. Westmeath
N37 F786, Ireland

Diagnostic Green LLC
38955 Hills Tech Drive
Farmington Hills
MI 48331, United States