Inside of pocket

Gleolan (aminolevulinic acid HCl) is an optical imaging agent indicated in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery[1]

- Proven for use in suspected WHO Grade III and IV glioma[1]
- Surgeons using Gleolan fluorescence-guided surgery demonstrated significant improvement in extent of resection vs white light[1]
- Facilitates real-time visualization[12]
- Not limited by brain shift[4]
- >95% PPV for identification of malignant tissue[1]
- Improved visualization, beyond that identified by preoperative MRI[6,13]
- Compatible with other technologies used during resection[14]
- Rates of long-term neurologic complications in procedures that used Gleolan fluorescence-guided surgery vs white light are similar.[3,15] Short-term (within 1 week of surgery) neurologic events occurred in 29% of patients receiving Gleolan.[1] Please see section 6.1 of the accompanying Prescribing Information

REQUIRED NEUROSURGEON TRAINING

Gleolan should only be used by neurosurgeons who have completed the **Gleolan Neurosurgeon Training Program** on the use of fluorescence in surgery and passed the exam. The **Gleolan Neurosurgeon Training Program** is provided by NX Development Corp (this is not surgical training).

Access the online training **at Gleolan.com**

ADVERSE REACTIONS (CONTINUED)

Absolute levels ranged from 2 times to greater than 10 times the upper limit of normal for each parameter. At 6 weeks, these measurements remained elevated in 2.9% and 7.5% of patients, respectively. There were no cases of liver failure.

DRUG-DRUG INTERACTIONS

See information under Warnings and Precautions regarding phototoxic reactions.

References

1. GLEOLAN [aminolevulinic acid hydrochloride (ALA HCl)] for oral solution Prescribing Information. www.gleolan.com/wp-content/uploads/2018/10/Prescribing_Information.pdf **2.** Briefing Package, Medical Imaging Drugs Advisory Committee, May 10, 2017. www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/medicalimagingdrugsadvisorycommittee/ucm557138.pdf **3.** Stummer W, et al. Lancet Oncol. 2006;7:392-401. **4.** Widhalm G. *Clin Neuropathol.* 2014;33:260-278. **5.** Data on file, NX Development Corp. **6.** Stummer W, et al. *Neurosurgery.* 2014;74:310-320. **7.** McGirt MJ, et al. *J Neurosurg.* 2009;110:156-162. **8.** National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. 2018. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. **9.** Ryken TC, et al. *J Neurooncol.* 2008;89:271-286. **10.** Oppenlander ME, et al. *J Neurosurg.* 2014;120:846-863. **11.** Suchorska B, et al. Neuro Oncol. 2018;18: 549-556. **12.** Díez Valle R, et al. *J Neurooncol.* 2011;102: 105-113. **13.** Schucht P, et al. *PLoS ONE.* 2013;8:e79846. **14.** Schucht P, et al. Neurosurgery. 2012;71:927-936. **15.** von Campe G, et al. *Acta Neurochir (Wien).* 2012;154:585-588.

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MTF-0008

Please see the enclosed full Prescribing Information

Gleolan™ (aminolevulinic acid HCl)

Gleolan is an optical imaging agent indicated in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery

Gleolan use during neurosurgery has been shown to improve the extent of resection, an essential component of a multimodal strategy, in newly diagnosed and recurrent, suspected high-grade glioma, and is generally well-tolerated

Gleolan has a high degree of accuracy (>95% PPV) to enhance the visualization of suspected high-grade malignant glioma tissue in real time

IMPORTANT SAFETY INFORMATION

Gleolan™ is an optical imaging agent indicated in patients with glioma (suspected WHO Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery. Gleolan can only be used by neurosurgeons who have completed a training program on use of fluorescence in surgery provided by NXDC, the distributor.

CONTRAINDICATIONS

Do not use Gleolan in patients with:

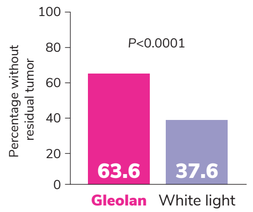
- Hypersensitivity to the active substance
- Acute or chronic types of porphyria

Please see the enclosed full Prescribing Information

Gleolan (aminolevulinic acid HCl) use during neurosurgery has been shown to improve the extent of resection, an essential component of a multimodal strategy, including chemotherapy and radiotherapy, in patients with suspected high-grade glioma, and is generally well-tolerated

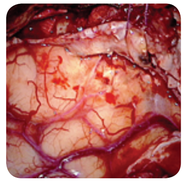
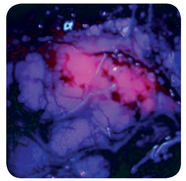
THE IMPACT OF VISUALIZATION

Use of Gleolan fluorescence-guided surgery improved extent of resection vs white light[1,2]



- In a clinical study, patients with suspected malignant glioma amenable to complete resection of contrast-enhancing tumor were randomly assigned to 20 mg/kg Gleolan for fluorescence-guided resection (n=176) or to conventional microsurgery with white light (n=173)[2]
- A primary endpoint was the number of patients without contrast-enhancing tumor on early MRI (within 72 hours after surgery for resection)[3]
- Use of Gleolan is not restricted by age (the safety and effectiveness of Gleolan in pediatric patients have not been established)[1]
- Surgical guidance with Gleolan is not limited by brainshift[4]

Gleolan (aminolevulinic acid HCl) has a high degree of accuracy, and enhances the visualization of suspected high-grade malignant glioma tissue in real-time, as reproduced in multiple studies

SURGICAL FIELD UNDER WHITE LIGHT	SURGICAL FIELD WITH BLUE FILTER AND FLUORESCING TISSUE
	

Photos courtesy of Prof. Dr. Walter Stummer, University of Münster, Germany.

- Fluorescence may also be seen in areas of inflammation or metastases from other tumor types[1]
- Non-fluorescing tissue in the surgical field does not rule out the presence of tumor in patients with glioma. There is a risk of misinterpretation and errors may occur with use of Gleolan including false negatives and false positives[1]
- Gleolan must be used with a standard surgical operating microscope adapted with a blue light emitting light source and ancillary excitation and emission filters to visualize fluorescence excitation in the wavelength of 375 to 440 nm and for observation from 620 to 710 nm[1]

In 1146 biopsies conducted across the 3 pivotal studies, Gleolan demonstrated a high degree of accuracy (PPV >95%) and a low NPV, ranging from 18.8% to 24.1%[5]

MEASURE	STUDY 1 PRIMARY N=297*	STUDY 2 RECURRENT N=370*	STUDY 3 PRIMARY N=479*
Fluorescent biopsies	185	354	319
True positive	178	342	312
False positive	7	12	7
PPV	**96.2**	**96.6**	**97.8**
NPV	**24.1**	**18.8**	**18.8**
Sensitivity	67.7	96.3	70.6
Specificity	79.4	20.0	81.1
Nonfluorescent biopsies	112	16	160
True negative	27	3	30
False negative	85	13	130

*N=number of total (fluorescent and non-fluorescent) biopsies

UNDERSTANDING NPV IN GLIOMA SURGERY

NPV values depend greatly on the sampling algorithm of non-fluorescing tissue as well as the greater ability of immunocytochemistry and microscopy to detect single malignant cells beyond the boundaries of fluorescing tissue. A single malignant cell detected outside the area of fluorescence would be counted as a false negative result[6]

THE IMPORTANCE OF EXTENT OF RESECTION (EOR) IN GLIOMA SURGERY

- Rates for maximal safe resection of malignant gliomas with the help of a microscope with white-light illumination and neuronavigation are estimated to be between 35%[7] and 38%[1]
- 2018 Guidelines from the NCCN, and recommendations from AANS highlight the importance of maximal safe resection in patients with glioma[8,9]
- EOR is associated with improved outcomes in patients with primary and recurrent glioma[3,7,10,11]

> *...the consensus among neurosurgeons and neuro-oncologists is that optimal treatment of glioma includes maximal safe surgical resection of tumor and that increasing the extent of resection is associated with improved patient outcomes.*[5]

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

Due to the risk of phototoxic reactions, do not administer phototoxic drugs for 24 hours during the perioperative period. Reduce exposure to sunlight or room lights for 48 hours after administration of Gleolan.

Errors may occur with the use of Gleolan for intraoperative visualization of malignant glioma, including false negatives and false positives. Non-fluorescing tissue in the surgical field does not rule out the presence of tumor in patients with glioma. Fluorescence may be seen in areas of inflammation or metastases from other tumor types.

WARNINGS AND PRECAUTIONS (CONTINUED)

Hypersensitivity reactions, including serious hypersensitivity reactions have occurred; these reactions include anaphylactic shock, swelling, and urticaria. Always have cardiopulmonary resuscitation personnel and equipment readily available and monitor all patients for hypersensitivity reactions.

ADVERSE REACTIONS

Adverse reactions occurring in >1% of patients in the week following surgery were pyrexia, hypotension, nausea, and vomiting.

Nervous system disorders occurred in 29% of patients within the first week after surgery and events occurring in >1% of patients included: aphasia (8%), hemiparesis (7.8%),

ADVERSE REACTIONS (CONTINUED)

hemianopsia (3.2%), headache (2.7%), seizure (1.9%), hemiplegia (1.9%), monoparesis (1.3%) and hypoesthesia (1.1%). Brain edema occurred in <1% of patients in the first 6 weeks after surgery. In a randomized clinical trial, the numbers of serious neurologic adverse events in the post operative period were higher in patients randomized to ALA fluorescence arm compared to the control arm. An imbalance was notable for the adverse events aphasia, ataxia, convulsion and hemianopsia and is likely related to the higher amount of brain resection performed in the ALA arm. At longer follow up periods, the numbers between the two arms appeared similar.

Worsening of ≥2 Common Toxicity Criteria grades in alanine aminotransferase and gamma-glutamyl transferase occurred in 15.8% and 11.6% of patients, respectively, within the first week after surgery.

Please see the enclosed full Prescribing Information