NX Development Corp
870 Corporate Drive, Suite 403,
Lexington, KY 40503
1-833-GLEOLAN
sdesena@nxdevcorp.com
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Re: NCCN Central Nervous System Cancers Panel

On behalf of **NX Development Corp**, I respectfully request the **NCCN Central Nervous System Cancers Panel** to review the enclosed data for inclusion of Gleolan™ (Aminolevulinic acid hydrochloride (ALA) into the NCCN Guidelines for Anaplastic Oligodendroglioma, Anaplastic Oligoastrocytoma, Anaplastic Astrocytoma, Anaplastic Gliomas and Glioblastoma.

Specific Changes:

1. For the Anaplastic Oligodendroglioma, Anaplastic Oligoastrocytoma, Anaplastic Astrocytoma, Anaplastic Gliomas and Glioblastoma (GLIO-1) workflow, under surgery, we recommend inclusion of Aminolevulinic acid hydrochloride (ALA, Brand Name Gleolan™) as an adjunct for the visualization of malignant tissue and to improve the completeness of resection during fluorescence guided glioma surgery.
2. For the Anaplastic Oligodendroglioma, Anaplastic Oligoastrocytoma, Anaplastic Astrocytoma, Anaplastic Gliomas and Glioblastoma (GLIO-5) workflow, under recurrence resection, we recommend inclusion of Aminolevulinic acid hydrochloride (ALA, Brand Name Gleolan™) as an adjunct for the visualization of malignant tissue and to improve the completeness of resection during fluorescence guided glioma surgery.

FDA Approval: In 2017**,** Gleolan™ was approved as an optical imaging agent indicated in patients with glioma (suspected World Health Organization Grades III or IV) as an adjunct for the visualization of malignant tissue during surgery.

Rationale: The primary goal in the management of patients with a suspected high grade glioma, a universally lethal disease, is to maximize the safe surgical resection of these brain tumors without affecting areas of the brain considered “eloquent” (those regions that control motor and sensory function or neurocognitive functions such as speech). Achieving maximal safe resection in glioma surgery is a challenge given the visual similarity of tumor-infiltrated and non-infiltrated brain. In addition, it can be difficult to estimate the true extent of tumor infiltration on the preoperative MRI images that are used to plan a resection. Moreover, preoperative MRI images become less and less useful over the course of an operation as tissues and key neurovascular structures shift in position.

Consequently, methods for direct and accurate visualization of these tumors during surgery are of considerable value in achieving maximal-safe resection. Gleolan, utilized for several years across the globe, and more recently in the US, provides the surgeon with an unparalleled opportunity to visualize otherwise invisible tumor-infiltrated brain. Accordingly, high-quality evidence from a randomized, prospective trial (Stummer et al, 2006) demonstrates that high-grade gliomas are resected more completely when Gleolan is utilized.

Studies explaining the improvement in surgical outcomes with Gleolan provide evidence that ALA fluorescence enables surgeons to identify residual locations of tumor seen in real time under blue light which were not identified under white light alone. This is also supported with data from numerous peer-reviewed literature articles which have also shown that more tumor-containing areas were identifiable under blue light as compared to white light. In addition, the efficacy of ALA as an optical imaging agent for the real time detection and visualization of malignant tissue during glioma surgery is supported by its high positive predictive value [PPV] of greater than 95% for detecting malignant tissue.

Importantly, Gleolan is well tolerated by patients, is appropriate for use in patients with primary or recurrent brain tumors, and it can be used with most existing operating neurosurgical microscopes.

It must however be emphasized that fluorescing tissue cannot always be removed completely if eloquent areas are involved. Gleolan may be used with the following existing, proven modalities such as brain mapping techniques, intraoperative ultrasound, imaging techniques such as intraoperative MRI, and stimulated Raman histology to ensure maximal safe resection.

ALA is a naturally occurring metabolite in the heme biosynthesis pathway. It functions as a non-fluorescent prodrug, which is metabolized intracellularly in tumor cells to form the fluorescent molecule protoporphyrin IX (PpIX). Following oral ingestion, ALA is absorbed, crosses the blood-brain barrier, and is converted into PpIX in tumor cells. PpIX which selectively accumulates in malignant brain tissue has a unique fluorescent profile unlike any other molecule. It is stimulated by excitation with blue light (wavelength range of 375 nm to 410 nm) and observed by emission of red light (wavelength range of 620 to 710 nm). This allows for identification of malignant glioma tissue, facilitates improved tumor visualization, and enhances tumor removal by neurosurgeons. This FDA approved imaging agent has been used over the last decade in more than 80,000 patients throughout 42 countries.

In summary, ALA induced fluorescence provides neurosurgeons with a class of vital information on the location and extent of high-grade glioma that can be integrated with anatomic and functional considerations to achieve the best possible surgical outcomes. The following articles are submitted in support of this proposed change.

1. Gleolan™ Package Insert: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=cdeded66-0017-42cf-9471-13f231014323&type=display
2. Stummer, et al, Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence, 1998; 42(3):518-25
3. Stummer, et al, Fluorescence-guided surgery with 5-aminolevulinic, acid for resection of malignant glioma: A randomized controlled multicenter phase III trial, Lancet Oncology, 2006; 7:392-401
4. Stummer, et al, Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias, Neurosurgery, 2008; 62:564-576
5. Stummer, et al, Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study, Journal of Neurosurgery, 2011; 114(3):613-623
6. Stummer, et al, Favorable outcome in the elderly cohort treated by concomitant temozolomide radio-chemotherapy in a multicentric phase II safety study of 5-ALA, Journal of Neuro-Oncology, 2011; 103(2):361-70
7. Stummer, et al, 5-Aminolevulinic acid-derived tumor fluorescence: the diagnostic accuracy of visible fluorescence qualities as corroborated by spectrometry and histology and postoperative imaging, Neurosurgery, 2014; 74:310-320
8. Hefti, et al, 5-aminolevulinic acid induced protoporphyrin IX fluorescence in high-grade glioma surgery: a one-year experience at a single institution, 2008; 138(11-12):180-5
9. Panciani et al, 5-aminolevulinic acid and neuro-navigation in high-grade glioma surgery: results of a combined approach, 2012; 23(1):23-8
10. Coburger, et al, Tumor detection with 5-aminolevulinic acid fluorescence and Gd-DTPA-enhanced intraoperative MRI at the border of contrast-enhancing lesions: a prospective study based on histopathological assessment, 2014; 36(2):1-9

Regards,

Salvatore DeSena

Salvatore DeSena MD MBA
EVP, Clinical and Medical Affairs
NX Development Corp