CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

DATE	MAY 25, 2017
From	Nushin Todd, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA # **Submission Type / Supplement #** **Designation(s)**	208630 Priority review; 505(b)(2) / SDN 2 Orphan drug
Applicant	NX Development Corp
Date of Submission	December 6, 2016
PDUFA Goal Date	June 6, 2017
Proprietary Name **Non-Proprietary Name**	Gleolan 5-aminolevulinic acid hydrochloride (5-ALA HCl)
Dosage form(s) / Strength(s)	Powder for oral solution, 1.5 g / vial
Applicant Proposed Indication(s) / Population(s)	Gliolan is a porphyrin precursor indicated as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery
Recommendation on Regulatory Action	***Approval***
Recommended Indication(s) / Population(s) (if applicable)	Gleolan is an optical imaging agent indicated in patients with gliomas (suspected grades III or IV) on preoperative imaging as an adjunct for the visualization of malignant tissue during surgery

1. Introduction

The applicant, NX Development Corp, submitted a new drug application (NDA) for Gleolan, an optical imaging agent, to facilitate the real time detection and visualization of malignant tissue during glioma surgery. This NDA is a 505(b)(2) submission relying upon clinical data from studies conducted in Europe that were used for approval by the European Medicines Agency (EMA) in 2007 as well as published literature. Gleolan received Orphan Drug Designation by the FDA on January 15, 2013, and a Fast Track designation on December 21, 2015.

Gleolan is a lyophilized powder for oral solution after reconstitution and is composed of 5-aminolevulinic acid hydrochloride (5-ALA HCl), a short chain amino acid. 5-ALA is an endogenous compound (approximately 600 mg/day is synthesized by the body) that serves as a precursor in the heme synthetic pathway where 5-ALA is enzymatically converted to protoporphyrin IX (PpIX). PpIX is photoactive and is fluorescent when exposed to long ultraviolet waves.

Malignant glial cells are capable of producing PpIX from 5-ALA and the exogenous administration of 5-ALA leads to selective accumulation of PpIX in tumor cells. During neurosurgery, Gleolan is used with an operating microscope adapted with a blue emitting light source and filters for excitation allowing for tumor tissue to be visualized as red fluorescence. Tissues lacking sufficient PpIX concentrations appear blue.

The findings and conclusions reached in this cross discipline team leader review are based on the review of relevant portions of the application, findings from an advisory committee meeting, and on examination of the primary and secondary review documents from the respective disciplines within the FDA. The disciplines and reviewers involved with evaluating this NDA are provided in Table 1.

Table 1 FDA Disciplines and Reviewers Involved in the Evaluation of NDA 208036

Discipline	Reviewer	Team Leader
Chemistry, Manufacturing and Controls Drug Product Drug Substance Process Facility Microbiology	 Dr. John Amartey Dr. Martin Haber Dr. Yongming Lu Dr. Carl Lee Dr. Erika Pfeiler	Dr. Danae Christodoulou Dr. Danae Christodoulou Dr. Donna Christner Dr. Pei-I Chu Dr. Vidya Pai Dr. John Arigo
Nonclinical Pharmacology/Toxicology	Dr. Ronald Honchel	Dr. Adebayo Laniyonu
Clinical Pharmacology/Biopharmaceutics	Dr. John Christy	Dr. Gene Williams
Clinical	Dr. Betsy Ballard	Dr. Nushin Todd
Biostatistics	Dr. Anthony Mucci	Dr. Jyoti Zalkikar
Pediatric and Maternal Health	Dr. Carrie Ceresa	Drs. M.Khurana / J.Liedtka
Office of Prescription Drug Promotion	Dr. Zarna Patel	Dr. Zarna Patel
Division of Medication Error Prevention and Analysis Labeling: Prescribing Information	Dr. Idalia Rychlik Dr. Michele Fedowitz	Dr. Hina Meta Dr. Michele Fedowitz
Division of Oncology Products 2	Drs. Joohee Sul / Diana Bradford	Dr. Suzanne Demko
Center for Devices and Radiological Health	Dr. Collin Kejing	Mr. Neil Ogden

2. Background

Surgical resection of malignant gliomas

Malignant gliomas are the most aggressive of the primary brain tumors and exhibit steadfast resistance to treatment. The World Health Organization (WHO) grading system is a widely accepted scale used to categorize these tumors, with the 2 chief histopathologies being anaplastic astrocytoma (AA, WHO grade III) and glioblastoma multiforme (GBM, WHO grade IV). With optimal upfront therapy including maximal safe surgical resection, radiation therapy and chemotherapy, median overall survival (OS) is 3 to 5 years for AA, and < 15 months for GBM.

As with most other solid tumor malignancies that present with localized disease, maximal safe resection for malignant gliomas is the accepted standard of care, despite lack of definitive evidence demonstrating an association between extent of resection (EOR) and survival. A

prospective trial conducted by Vuorinen et al randomized 30 elderly patients (age > 65 years) with suspected malignant glioma to stereotactic biopsy or open craniotomy and resection[1]. The median OS in the craniotomy versus biopsy was 171and 85 days, respectively. Available retrospective data consistently indicate progression free survival (PFS) and OS are correlated with EOR[2-6]; however, these studies have been problematic as most assessments are based on the surgeons' determination of degree of resection[7]. Despite the inadequacies of the available data, the current consensus among neurosurgeons and neuro-oncologists is that optimal treatment of malignant glioma should include maximal safe resection, and that increasing the EOR correlates with improved patient outcomes.

The primary barriers to achieving complete resection (CR) are the diffuse nature of gliomas and the risks of neurologic deficits from resection of eloquent cortex. Infiltrating tumor cells invade adjacent areas of normal brain impeding the ability to identify tumor from brain parenchyma at the time of resection. Numerous techniques aimed at improving extent of safe resection have been developed such as intraoperative MRI, intraoperative cortical mapping, and neuro-navigation tools; however, these procedures are not readily available to most patients. Also, there are currently no FDA approved drugs for visualization of malignant glioma during surgery.

Gleolan (Gliolan)
The proprietary name of the drug under review for this application is Gleolan. This drug has been approved abroad as Gliolan. The drug is the same, despite the spelling.

Gleolan contains the active substance 5-ALA, a prodrug that is metabolized intracellularly to form a fluorescent molecule PPIX. Administration of 5-ALA leads to preferential accumulation of PPIX in tumor cells and following exposure to blue light (λ= 375 - 410 nm) PPIX emits a red-violet fluorescence, distinguishing tumor cells to guide surgical resection. According to information in the EMA EPAR, this phenomenon appears to be restricted to high grade tumors; conversely, in low-grade tumors (WHO grade I/II, medulloblastoma, oligodendroglioma) fluorescence is not observed after administration of 5-ALA. Explanations for higher 5-ALA uptake in malignant cells include a disrupted blood-brain barrier, increased neo-vascularization, and overexpression of membrane transporters.

Gliolan was approved in 2007 by the EMA and in 2013 by the Australian Therapeutic Goods Administration (TGA). In Europe, the indication is for visualization of malignant tissue during surgery for malignant glioma (WHO grades III and IV), while in Australia the indication is limited to patients with GBM. Approval by regulatory agencies in Europe and Australia was based primarily on data from a multicenter trial (study ALS-3) that randomized 415 patients with radiographic evidence of a single focus of suspected malignant glioma amenable to gross tumor resection (GTR) of contrast enhancing tumor, to either fluorescence-guided resection after administration of 20 mg/kg orally of 5-ALA HCl (n=205) or conventional white light surgery (n=208). The primary endpoints were rate of GTR of contrast-enhancing tumor on post-operative MRI (within 72 hours after surgery), and 6 month progression-free survival (PFS6) after surgery. Secondary endpoints included PFS 9, 12, 15, and 18 months after surgery, volume of residual tumor, OS, toxicity[8].

Sixty-four percent (64%) of all patients in the fluorescence-guided (FL) group and 38% of all patients in the control group (white light, WL) did not show residual tumor on early postoperative MRI. Additionally, the PFS at 6 months was 20.5% in the group undergoing resection with Gliolan, and 11.0% in the standard resection group. Median OS was comparable in both treatment arms (14.3 months in the Gliolan arm vs 13.7 months in the control arm); however, the trial was not powered to detect a difference in OS. Adverse events (AEs) related to Gliolan included hypotension, nausea, photosensitivity reactions, and there were more neurological deficits (hemianopia, aphasia and epilepsy) observed in the experimental arm, thought to be related to more aggressive resection.

The European Committee for Medicinal Products for Human Use (CHMP) debated the benefit of Gliolan use given increased neurological deficits in patients with more extensive resection, and received input from the Scientific Advisory Group (SAG) for Oncology. Ultimately, the CHMP considered the overall benefits of Gliolan to have been adequately demonstrated.

Brief regulatory history

In 2011, a meeting was held between the applicant and the FDA to discuss the clinical development plans for Gliolan and a proposed phase III study. FDA expressed concerns with the use of a radiological surrogate endpoint as a primary efficacy endpoint, and emphasized that clinical benefits need to be demonstrated. On September 22, 2014, another meeting was held to discuss plans for the submission of an NDA for Gliolan. The proposed indication was an "imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery."

In addition to the existing data from study ALS-3, the sponsor proposed to provide data from two studies: study ALS-28 and study ALS-30, both designed to determine the positive predictive value (PPV) of Gliolan induced tissue fluorescence for tumor cell detection in patients with newly diagnosed or recurrent malignant glioma. FDA agreed with the plan to provide data on the performance of Gliolan for distinguishing between normal and malignant tissue by using the histopathology from brain biopsies as a truth standard; however, FDA again cautioned that the assessment of extent of tumor resection based on postoperative imaging is not an adequate efficacy endpoint. FDA recommended the sponsor provide data that demonstrate the use of Gliolan for enhancing delineation of tumor resection margins in an adequately controlled study and proposed that patients with WHO grade III and IV gliomas undergo maximal tumor resection under white light only, followed by additional Gliolan-aided resection. Documentation of fluorescence in the resection margin would be performed and biopsies would be obtained for verification of tumor status.

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3. CMC

The product quality assessment for Gleolan encompassed chemistry, manufacturing, and controls (CMC), sterility, biopharmaceutics, environmental assessment, and facility reviews. There were no unresolved product quality issues. Dr. Danae Christodoulou, supervisory reviewer, provided summary review of the product quality subdisciplines that culminated in an overall CMC approval recommendation.

The drug substance for Gleolan is 5-aminolevulinic acid hydrochloride (5-ALA HCl), a short chain amino acid that is highly soluble in water. It is referenced to Drug Master File (b) (4) by (b) (4). The drug product is 1.5 g lyophilized drug substance without excipients presented in a glass vial capped with a rubber stopper. The lyophilized powder is reconstituted in 50 ml water (equivalent to 1.17 g 5-ALA) or 30 mg/ml 5-ALA HCl (equivalent to (b) (4) mg/ml 5-ALA). The formulation is (b) (4) (b) (4)

Gleolan is (b) (4). Stability data for the lyophilized powder are available up to 60 months and microbial limits up to 36 months. A 36-month expiry is granted for the drug product. The reconstituted oral solution is stable up to 24 hours at 25 °C (77 °F). The reconstituted oral solution is for single dose and the remaining solution is to be discarded.

Two manufacturing facilities inspections have been completed and determined to be acceptable. One labeling and secondary packaging site was also evaluated by review of inspections conducted in 2015 and 2013 and found acceptable.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review discipline recommends approval of the NDA.

The nonclinical safety studies identified two target organs of toxicity: liver and skin. The toxicity occurred from exposure to direct light following 5-ALA administration and has been attributed to PpIX formation. PpIX is photoactive and fluorescent when exposed to long ultraviolet waves (375 to 440 nm). Pivotal nonclinical safety studies were therefore conducted either in the dark or under subdued light in order to avoid adverse effects due to phototoxicity. Measures to protect patients from light exposure following Gleolan administration are discussed in the labeling.

There was only one reproductive and developmental toxicity study report submitted in the application: rabbit embryo-fetal developmental toxicity study. 5-ALA HCl was administered to rabbits at oral doses of 15, 50 and 150 mg/kg/day (approximately 0.1, 0.6, and 3 times the maximum human recommended dose respectively based on area under the curve (AUC) comparisons) from gestation days 6 to18. The no observed adverse effect level (NOAEL) for maternal toxicity was 50 mg/kg/day, and the NOAEL for maternal reproduction function and embryo-fetal development was 150 mg/kg/day. The lack of further reproductive toxicology studies was not imperative for this application considering the intended patient population and that 5-ALA is an endogenous compound.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology information provided in the application and recommends approval. Summary OCP findings are presented here.

Dose

The recommended dose of Gleolan is 20 mg/kg. Dose-efficacy relationship was studied among three dose levels: 0.2, 2 and 20 mg/kg. There was a direct correlation between the dose level and the extent and quality of fluorescence in the tumor core, with the highest dose studied (20 mg/kg) being the most effective. However, there was considerable variability in fluorescence intensity in the 20 mg/kg selected dose.

Review of literature reveals that higher than recommended oral administration of Gleolan, approximately 40 mg/kg, led to increased incidence of nausea, vomiting, hypotension, transient increases in liver enzymes and phototoxicity. Doses of 30 to 60 mg/kg were associated with increased frequency of adverse effects.

Pharmacokinetics

Under violet-blue excitation light, and to a lesser extent under white light, the intensity of PpIX fluorescence emitted by the tissue surface decreases continuously due to photochemical decomposition of PpIX called photobleaching. After excitation with light (400 to 410nm) the half-life of PpIX is approximately 15 to 20 minutes. It is dependent on the intensity of the irradiating light, distance from the operating microscope and the associated light source. In *ex vivo* studies on glioma biopsies, a decrease in PpIX fluorescence to 36% of the baseline value was observed under violet-blue excitation light after 25 minutes and under white light after 87 minutes.

Overall, the mean half-life of 5-ALA is about 1 hour (range of 0.8 to 1.3 hours). Maximum concentration of PpIX, the 5-ALA metabolite, occurs in 4 hours (range of 1 to 8 hours). The elimination half-life of PpIX is 3.6 hours (range of 1 to 8 hours).

The mean protein binding of 5-ALA was 12% in *in vitro* experiments using 5-ALA concentrations up to approximately 25% of the maximal concentration that occurs in plasma following the recommended dose of Gleolan solution. Exogenous 5-ALA is metabolized to PpIX, but the fraction of administered 5-ALA that is metabolized to PpIX is unknown. Approximately 30% of 5-ALA, orally administered at a dose of 20 mg/kg, is excreted unchanged in urine within 12 hours.

Pharmacodynamics
The effect of the timing of Gleolan dosing on fluorescence intensity in brain tissue is unknown. The relationship between systemic 5-ALA plasma concentrations at the time of visualization and fluorescence intensity in brain is also unknown.

Intrinsic factors
The effect of hepatic or renal impairment on the pharmacokinetics of 5-ALA following Gleolan administration is unknown. Literature data shows that renally impaired patients have endogenous 5-ALA plasma concentrations that increase linearly with creatinine clearance. It is therefore presumed that 5-ALA clearance may be reduced in patients with renal impairment. It is not known if dose adjustment is needed in patients with impaired renal function.

Likewise, Gleolan has not been studied in patients with hepatic impairment. The role of the liver in eliminating endogenous as well as exogenous 5-ALA is unclear. Dose adjustment in patients with hepatic impairment is not discussed in the labeling.

Drug-drug interactions
In vitro studies suggest that phenytoin and other anti-convulsants may decrease cellular PpIX accumulation following Gleolan dosing. There are no clinical studies that examined the effect of concomitant drug administration on fluorescence intensity or image quality. There are also no clinical studies that examined the effect of concomitant drug administration on phototoxicity. Due to the risk of possible phototoxic interactions, phototoxic drugs are not to be used 24 hours during the perioperative period.

QT assessment
QT results were reported in only one of the submitted studies (study ALS-8). This study enrolled 12 patients and no QTc abnormalities were detected in any patient. The applicant also reviewed the worldwide postmarketing database for adverse drug reactions. There were no reported cases of QT prolongation.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical - Efficacy

The efficacy of Gleolan was based on the applicant's submission of reanalyzed data from 3 studies conducted in Europe between 1999 and 2005 as well as 12 publications. There were considerable discussions regarding the appropriateness of a single primary endpoint, positive predictive value (PPV), determined on a post-hoc basis by the applicant, in assessing the efficacy of the product. An advisory committee meeting was also held to review the evidence and merits of Gleolan. Based on the totality of the evidence, the statistical and clinical review teams have recommended approval of Gleolan as an **adjunct** for intraoperative visualization of malignant tissue during glioma surgery in patients with grades III or IV gliomas.

The 3 studies submitted to support efficacy included two Phase 2 studies and one Phase 3 study:

- Study ALS-3: Phase 3, randomized, controlled, multicenter study (conducted 10/1999 to 7/2004). In this study, 349 patients with newly diagnosed glioma were randomized in 1:1 ratio to Gleolan fluorescence arm or to white light control arm. Biopsies were obtained before the initial debulking from tumor-core, tumor-margin and regions just distant to the tumor margins. In patients randomized to the Gleolan fluorescence arm, presence of fluorescence at a biopsy level was compared to tumor status using histopathology as the reference standard.

- Study ALS-28: Phase 2, prospective, uncontrolled, single arm, multicenter study in patients with first occurrence of glioma (conducted 10/20002 to 6/2004; 36 patients).

- Study ALS-30: Phase 2, prospective, uncontrolled, single arm, multicenter study in patients with recurrent glioma (conducted 6/2003 to 9/2005; 33 patients). In both Phase 2 studies, after initial debulking was carried out under white light, biopsies were obtained under fluorescent light from fluorescent and non-fluorescent sites. Presence of fluorescence (positive/negative) was compared to tumor status (true/false) using histopathology as the reference standard; true positives and false positives among fluorescent biopsies and true negatives and false negatives among non-fluorescent biopsies.

In all three studies, histology had to be consistent with a high grade glioma: grades III or IV.

When the above studies were conducted in Europe, the endpoints were different than what was submitted in the current application. The original primary endpoint for the Phase 2 studies was visualization. The pivotal Phase 3 study originally focused on two primary endpoints: completeness of tumor resection and progression free survival (PFS) status at 6 months post-surgery. A discussion of the pivotal Phase 3 study that was conducted in Europe and its results are provided in the Background section of this review.

Positive Predictive Value

The NDA submission replaced all primary endpoints with a previous secondary endpoint, positive predictive value (PPV), on a post-hoc basis**,** to serve as the single primary endpoint.

PPV = percentage of histology positive biopsies among all fluorescent biopsies

The applicant did not discuss trial designs, biopsy plans and analyses plans of the clinical trials with the FDA prior to the NDA submission. All studies were conducted outside of the investigational new drug (IND) paradigm. As a result, the submitted Phase 2 studies lacked hypothesis testing and appropriate randomization schemes.

To reiterate: the applicant selected biopsy level PPV, originally a secondary endpoint, **on a post-hoc basis**, to demonstrate efficacy in all three studies.

Negative Predictive Value
Due to the post-hoc nature of the calculations, the statistical review team was concerned there could be **ascertainment bias** in reporting the results of biopsy-level PPV as a "stand-alone" endpoint. In all three studies, the PPV was noted to be greater than 96%. Effectively, fluorescent tissue was virtually always histology positive. Because PPV level is affected by high tissue prevalence, it is not completely reliable as a sole endpoint in characterizing performance. Therefore, along with PPV, there needs to be assessment of at least one additional visualization endpoint, such as negative predictive value (NPV).

The FDA statistical review team, therefore, also analyzed the NPV at the biopsy level (Table 1). This was the percentage of histology negative biopsies among all non-fluorescent biopsies.

NPV = percentage of histology negative biopsies among all non-fluorescent biopsies

Table 1 PPV and NPV for Each Study (biopsy level)

	Study ALS-3	Study ALS-28	Study ALS-30
PPV	312/319 (98%)	176/183 (96%)	342/354 (97%)
NPV	30/160 (19%)	27/112 (24%)	3/16 (19%)

Although the PPV of Gleolan are acceptable, the low NPV are concerning. If there is fluorescence, there will be tumor but the converse is not necessarily true.

False Negative Rate
The statistical reviewers also supplemented the PPV data with evaluations of False Negative rates of non-fluorescent biopsies.

False Negative = percentage of histology positive biopsies among all non-fluorescent biopsies

In the Phase 3 study (ALS-3), the presence of fluorescence (positive/negative) at the biopsy level was compared to tumor status (true/false) using histopathology as the reference standard, in patients randomized to the Gleolan fluorescence arm. Similar evaluations were conducted in the two Phase 2 studies (ALS-28 and -30). Results of true positives and false positives

among fluorescent biopsies and true negatives and false negatives among non-fluorescent biopsies for the three studies are provided in Table 2.

Table 2 Presence of Fluorescence Compared to Histopathology (Biopsy Level)

	Study ALS-3 N=479*	**Study ALS-28** N=295*	**Study ALS-30** N=370*
Fluorescent Biopsies	319	183	354
True Positive (**PPV**)	312 (98%)	176 (96%)	342 (97%)
False Positive	7 (2%)	7 (4%)	12 (3%)
Non-fluorescent Biopsies	160	112	16
True Negative (**NPV**)	30 (19%)	27 (24%)	3 (19%)
False Negative	130 (81%)	85 (76%)	13 (81%)

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

The False Negative rate in the three studies was also high. About 4 in 5 non-fluorescent biopsies were histology positive. The studies therefore did NOT demonstrate that: fluorescence implies disease presence, non-fluorescence implies disease absence.

However, exploratory secondary analyses of the results achieved in the Phase 3 study (ALS-3) provide some evidence that Gleolan fluorescence correlates with more "complete" tumor resection. The extent of resection among patients in the Gleolan fluorescence arm was compared to that among patient in the control arm, with the "completeness" of resection being determined by a central blinded read of early post-surgical MRI. Percentage of patients who had MRI-based "completeness" of resection was 64% in the Gleolan arm and 38% in the control arm, with the difference of 26% [95% CI: (16%, 36%)]. These results, however, are subject to operator bias because the blinding of surgeons could not be implemented at study design stage.

Literature Review

The applicant provided 12 published studies to support their efficacy findings. The literature was reviewed by Dr. Ballard, and is detailed in her clinical review. Similar to the applicant's studies, results of PPV in the literature were 92% or higher for high grade gliomas. The NPV

was highly variable from 12% to 90%, demonstrating that tumor cells were present despite absence of fluorescent activity. This is consistent with the infiltrative nature of this disease.

8. Safety

The Gleolan clinical trial safety database is comprised of 527 patients from 5 clinical studies who received 1 dose of 20 mg/kg Gleolan. The median age of patients was 61 years; two-thirds of patients were male and the median body weight was 78 kg.

There were a total of 284 deaths in the clinical studies. Treatment emergent adverse events (TEAEs) leading to death occurred in 25 patients. Five of the deaths occurred during the early postoperative period (within 1 week) and were attributed to the underlying disease. No deaths were considered related to Gleolan.

The rate of TEAEs was greater than 60% in the pooled studies. None of the TEAEs led to study discontinuation. Eleven patients (2% of patients in the clinical studies) experienced TEAEs that were deemed possibly related to Gleolan. The most commonly reported TEAEs were nervous system disorders (i.e., aphasia (8% of patients); hemiparesis (8%); hemianopia (3%); and headache (3%)). The overall rate of nervous system disorders following resection was 30%. These TEAEs, however, are not unexpected for this patient population after neurosurgery.

Safety data from the 5 clinical studies revealed no effect of Gleolan on: vital signs, clinical laboratory values, electrocardiogram findings, or QT interval corrected (QTc) prolongation potential. However, increases in liver enzymes, specifically, alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) within the first week after surgery was detected. Across studies, 16% of patients experienced ≥2 toxicity grades in ALT and 12% in GGT within one week post-surgery. By 6 weeks post-surgery, ALT remained elevated in 3% of patients and GGT stayed elevated in 8% of patients. There were no cases of liver failure and the increases liver function parameters were not considered clinically relevant.

Patients with renal or hepatic impairment were not included in the clinical studies. Likewise, no formal studies have been conducted assessing the effects of Gleolan in patients with impaired renal or hepatic function. For these patients, the treating physician and currents practice of medicine determine the individualized risk-benefit profile for the use of Gleolan in this lethal disease.

In support of the clinical safety database, the applicant conducted a literature review of 29 peer-reviewed publications that assessed the use of 5-ALA to visualize glioma during resection surgery in approximately 2,000 patients. The AE data from these studies were consistent with the AE data from the clinical trial safety database.

Photosensitivity is an immediate reaction reported in several publications. Following administration of Gleolan, it is recommended that exposure of eyes and skin to strong light source (e.g., operating illumination, direct sunlight or brightly focused indoor light) be avoided

for 24 hours during the perioperative period. Co-administration of phototoxic substances (e.g., tetracyclines, sulfonamides, fluoroquinolones, hypercin extracts) should also be avoided.

Further supportive data for the safety of Gleolan comes from postmarketing surveillance data from Europe where Gleolan has been approved since 2007. The applicant discussed the EU Periodic Safety Update Report (PSUR) of approximately 58,000 patients receiving Gleolan from 2012 to 2015. The PSUR did not reveal any new or unexpected AEs for Gleolan.

In summary, review of the safety data for Gleolan reveals it to be safe when used in the prescribed manner for patients undergoing resection for high grade gliomas. There is a potential for transient elevations in liver function parameters and patients should be monitored accordingly. Likewise, phototoxicity reactions can occur but this can be mitigated by limiting patient exposure to bright light and avoidance of phototoxic substances during the perioperative period. There is also the potential for worsening neurological effects possibly from increased resection of eloquent brain tissue. Mitigation of this risk is dependent on surgical judgement and expertise.

9. Advisory Committee Meeting

An advisory committee (AC) meeting was held on May 10, 2017, to discuss Gleolan.

The committee members were asked to discuss the efficacy outcomes presented in the NDA and their acceptability for substantiating the proposed claim, and any safety concerns of this drug, such as increased risk of neurological deficits from potential increased resection. The following discussion points were posed to the committee:

1. **DISCUSSION:** Discuss the efficacy outcomes used in this drug development program and their acceptability for substantiating the proposed claim. In your discussion, please consider each of the following points:

    a. The applicant presented data demonstrating the intraoperative visualization of malignant tissue with the calculation of the percentage of visualized tissue fluorescence verified by histopathology (positive predictive value, or PPV). Please discuss the clinical significance of the provided PPV measurement of malignant tissue visualization with the use of 5-ALA and whether the provided data on malignant tissue visualization are sufficient for establishing efficacy of 5-ALA.

    b. Please discuss the potential clinical importance of the finding of non-fluorescent tissue samples being also positive for malignancy on histopathology.

    c. One of the efficacy outcomes used by the applicant is an improved completeness of resection defined on post-operative MRI enhancement. Please discuss the clinical importance of a “complete resection” in the setting of glioma surgery and comment on the clinical meaningfulness of using post-operative MRI to measure the completeness of resection.

d. In assessing the totality of evidence of the potential benefit of 5-ALA, please comment on the clinical significance, if any, of the observed improvement in progression free survival and of the lack of improvement in overall survival. In your discussion please comment on the following:
    i. Whether either should be mentioned in the prescribing information if 5-ALA is approved for marketing in the U.S.
    ii. How the outcome of progression free survival could relate to potential assessment of patient reported outcomes (PROs) and what type of PROs would be relevant to this setting.

2. **DISCUSSION:** Please discuss possible risks associated with increased resection, e.g. the potential for increased neurological deficits

    a. Please discuss any other safety concerns you might have about this drug.

3. **VOTE:** Do you recommend the approval of Gleolan for the proposed indication as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery?

There was unanimous consensus among committee members for approval of Gleolan. All 11 members voted "yes" for approval.

Committee members agreed that PPV was appropriate for assessing efficacy. While they noted the high FN rate, they found it to be acceptable because of the infiltrative nature of gliomas. To paraphrase one member: we know that tumor will be left behind, but this agent will allow removal of more tumor than what is currently available.

The committee also noted the improvement in the amount of tumor volume resection ("completeness" of resection) of Gleolan compared to control (white light), 64% vs 38%. They discussed the concern for the lack of a direct association between PPV and CR. The committee agreed on the difficulty for determining, with the tools currently available, whether CR improves survival. In the oncology community, it's appreciated that PFS is usually associated with OS. Determining PFS is difficult in this setting because of the paucity of adequate comprehensive measures used for assessment. Certain patient reported outcomes (PROs) can be very informative and some quality of life (QOL) markers have been shown to be least sensitive to change.

The committee, therefore, agreed with not including PFS and OS in the prescribing information for Gleolan and recommended that the applicant collect PROs as part of their postmarketing evaluations.

The advisory committee also discussed the potential use of Gleolan in pediatric patients. There was agreement among committee members and the FDA for the benefits of conducting studies in pediatric patients with malignant brain tumors. (b) (4)

Regarding the safety of Gleolan, the advisory committee appreciated the inherent risks associated between increased resection and the potential for neurological deficits. They also noted the extensive safety database of the drug abroad since its approval in Europe over a decade ago. Overall, the committee determined that Gleolan can serve as an additional tool in the limited armamentarium available for the management of this highly lethal disease.

10. Pediatrics

The Pediatric Research Equity Act of 2003 (PREA), and 21 CFR 3 14.55 (a) require that applicants submitting a new application or supplement under section 505 of the Federal Food Drug and Cosmetic Act that involves a new ingredient, new indication, new dosage form, new dosing regimen or new route of administration, submit an assessment of the safety and efficacy of the drug or biological product for the claimed indication in all relevant pediatric subpopulations.

Gleolan received an Orphan Designation by the FDA on January 15, 2013. As such, PREA does not apply to this application. A pediatric assessment is therefore not required and has not been provided in this application. This application was not presented at the Pediatric Review Committee (PeRC).

Safety and effectiveness of Gleolan in pediatric patients has not been established. The pediatric team reviewed the application and provided recommendations pertaining only to section 8.4 (Pediatric Use) in labeling.

It is important to note that during the AC meeting, the potential use of Gleolan in pediatric patients was discussed. There was agreement among committee members and the FDA for the benefits of conducting studies in pediatric patients with malignant brain tumors. (b) (4)

11. Other Relevant Regulatory Issues

"Risk Management Strategy"

The applicant included a risk management strategy in the NDA that would control the release of Gleolan only to neurosurgeons that have acquired certification after undergoing a training program on the appropriate use of Gleolan. Additionally, the applicant proposed language in the prescribing information under (b) (4).
The applicant also submitted a (b) (4) for review by the FDA.

The FDA found the applicant's proposal unacceptable. The Office of Prescription Drug Promotion in the FDA reviewed the (b) (4) and considered it to be promotional and stated it should not be approved as part of product labeling. The FDA was also concerned that the proposed risk management strategy could be easily confused with FDAs Risk Evaluation and Management Strategies (REMS) program. The FDA determined the applicant's training requirement clearly did not qualify for REMS. While the sponsor has

the right to provide a training course, [redacted] (b) (4) in labeling is unwarranted. The [redacted] (b) (4) was therefore removed from the prescribing information.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
Postmarketing assessment of Gleolan in pediatric patients with brain tumors was discussed during the advisory committee meeting. [redacted] (b) (4)

12. Labeling

Proposed product labeling was reviewed by all disciplines involved in the review of this application as well as by the Associate Director of Labeling (ADL), Dr. Michele Fedowitz. Both the Highlights and the Full Prescribing Information have undergone significant revisions. The review team's labeling edits and comments were conveyed to the applicant. Final agreement on product labeling was pending at the time of this CDTL review.

Two major points of discussion focused on the proprietary name and indication for use in labeling. The use of appropriate microscope and filters were also evaluated.

Proprietary name
The initial proprietary name, *Gliolan*, which is used in Europe, was deemed unacceptable by the Division of Medication Error Prevention Analysis (DMEPA). Reasons for denying the proposed proprietary name were based on the stems *Gli-* and *–io* used in Gliolan which were inconsistent with the intended US Adopted Name (USAN) meanings. The 'gli' stem, as prefix, is used by the USAN Council to indicate anti-hyperglycemic drug products. The 'io' stem, either as prefix or infix, is used by the USAN Council to indicate an iodine containing contrast media (e.g., *io*damide, adip*io*done). Since Gliolan is not an iodine containing contrast media agent, nor an anti-hyperglycemic drug, the incorporation of these stems in the proposed proprietary name is inconsistent with the intended USAN meanings.

The use of a USAN stem within the proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary names that are similar to established names, thus increasing the chance of confusion among those drugs, which may compromise patient safety. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names.

The applicant subsequently submitted an alternate proprietary name: *Gleolan*. Review by the FDA found this proprietary name to be acceptable.

Indication statement
The applicant proposed the following indication for Gleolan:

> "…a porphyrin precursor indicated as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery"

After review of the application and after the advisory committee meeting, the FDA determined the proposed indication for Gleolan unacceptable. Gliolan has received approval in Europe for "visualization of malignant tissue during surgery for malignant glioma (WHO grade III and IV)". Information in the EPAR indicates that fluorescence is not observed after administration of 5-ALA in low-grade tumors (WHO grade I/II, medulloblastoma, oligodendroglioma). Additionally, the clinical database submitted by the applicant and reviewed by the FDA only included patients with high grade gliomas (WHO grade III and IV). Therefore, the FDA acknowledges the following indication as appropriate for Gleolan in the prescribing information:

> "*Gleolan is an optical imaging agent indicated in patients with gliomas (suspected grades III or IV) on preoperative imaging as an adjunct for the visualization of malignant tissue during surgery*."

Microscope and filters for use with Gleolan

The Division of General Surgery Devices Branch 1 (GSDB1) in the Center for Devices and Radiological Health (CDRH) was consulted to evaluate the surgical microscope and filters to be used with Gleolan during neurosurgery. They determined that Gleolan may be labeled for use with marketed microscopes as long as the appropriate filter wavelength and excitation power density requirements are met. GSDB1 also recommended that the wavelength and power density information be clearly stated in the prescribing information for Gleolan.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Approval

Risk Benefit Assessment

I recommend the approval of Gleolan, an optical imaging agent, for patients with gliomas (suspected grades III or IV) on preoperative imaging as an adjunct for the visualization of malignant tissue during surgery.

The evidence for the efficacy of Gleolan for the above indication is based on the applicant's submission of reanalyzed data from 3 studies conducted in Europe between 1999 and 2005 as well as 12 publications. Efficacy of Gleolan is demonstrated by greater than 90% PPV of tissue fluorescence to identify glioma confirmed via tumor histopathology.

It should be noted that the false negative rate in the submitted studies was also high (about 4 in 5 non-fluorescent biopsies were found to be histology positive for tumor). The studies therefore did not demonstrate that fluorescence implies disease presence, non-fluorescence implies disease absence.

Overall, the current consensus among neurosurgeons and neuro-oncologists is that optimal treatment of malignant glioma should include maximal safe resection and increasing the extent of resection correlates with improved patient outcomes. It is with this perspective that the clinical usefulness of Gleolan is demonstrated: as an adjunct for the neurosurgeon in the real time identification of malignant tumor under fluorescent light that may otherwise be overlooked during conventional microsurgical resection.

The clinical safety profile of Gleolan is well established. It's been approved Europe since 2007. There are approximately 40 countries so far that have approved this product for intra-operative use for glioma surgery. The European Union PSUR of approximately 58,000 patients receiving Gleolan from 2012 to 2015 was reviewed in this NDA and did not reveal any new or unexpected AEs for Gleolan. There is, however, the potential for worsening neurological effects possibly from increased resection of eloquent brain tissue. This risk can be mitigated by surgical judgement and expertise.

Given the lethal nature of high grade gliomas, the well-established safety profile of Gleolan and the limited tools available to adequately and safely resect this tumor, the overall benefit to risk profile of Gleolan is favorable. Approval is recommended.

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/s/

NUSHIN F TODD
05/30/2017