CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208630Orig1s000

OTHER REVIEW(S)

DMIP Associate Director for Labeling Review of the Prescribing Information

Product Title	**Gleolan** **Aminolevulinic acid hydrochloride [ALA HCl] for oral solution**
Applicant	NX Development Corp.
Application/Supplement Number	208630
Type of Application/Submission[1]	NDA
Is Proposed Labeling in Old Format? (Y/N)	No
Proposed Indication(s) (if applicable)	Gliolan® is a porphyrin precursor indicated as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery
Approved Indication(s) (if applicable)	Gleolan is an optical imaging agent indicated in patients with gliomas (suspected grades 3 or 4) on preoperative imaging as an adjunct for the visualization of malignant tissue during surgery
Date FDA Received Application	December 6, 2016 May 5, 2017 (IR response) May 12, 2017 (IR2 response) May 19, 2017 (complete IR2 response)
Review Classification (Priority/Standard)	Priority
Action Goal Date	June 6, 2017
Review Date	
Reviewer	Michele B. Fedowitz

Background:
The applicant is seeking approval of aminolevulinic acid hydrochloride (ALA HCl) oral solution for use in intraoperative glioma surgery for fluorescent visualization of tumor. This review is being completed during the review cycle.

This review includes a high-level summary of the rationale for major changes to the PI as compared with the applicant's draft PI and currently approved PI.

Product Title

Sponsor's Proposed: **Gliolan® (5-ALA HCl) for oral solution**
FDA Proposed: **GLEOLAN [aminolevulinic acid hydrochloride (ALA HCl)] for oral solution**

Reviewer's Comments:

1. Trademark Removed: There is no need to use trademark or registered symbols in labeling as they do not appear in SPL format due to style sheet restrictions.
2. The "5" removed from product title. The published USAN is aminolevulinic acid hydrochloride.
3. Guidance for Industry *Naming of Drug Products Containing Salt Drug Substances:* "The USP Salt Policy is a naming and labeling policy applicable to drug products that contain an active ingredient that is a salt.

The policy stipulates that USP will use the name of the active moiety, instead of the name of the salt, for such a drug product when creating a drug product monograph title. The USP Salt Policy also states that USP will base the strength of the product on the active moiety. The policy allows for exceptions under specified circumstances... The USP Salt Policy provides for exceptions to the "active moiety" naming approach, when the name of the salt conveys vital information from a clinical perspective. In these cases, the drug product monograph title will include the name of the salt, and the strength of the drug product also is expressed in terms of the salt form (active ingredient)."

The review team felt that this drug fell under the exception to maintain consistency with similar products in its class. A similar product for optical imaging, Cysview, is named and dosed using the active ingredient (hexaminolevulinate hydrochloride). Therefore Gleolan was named and dosed using the active ingredient, aminolevulinic acid hydrochloride with reference to the active moiety: aminolevulinic acid.

Indications and Usage

Sponsor's Proposed: Gliolan® is a porphyrin precursor indicated as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery. (b) (4)

(b) (4)

FDA proposed: 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.

Reviewer's Comments:

4. See comment (1) above regarding the removal of the trademark.
5. The correct EPC was added (optical imaging agent); ALA used for other indications topically are porphyrin precursors.
6. The (b) (4) and was better captured in Dosage and Administration (Imaging Instructions, 2.3)
7. The indicated population was restricted to WHO Grades 3 and 4 as these were the populations included in the 3 studies (28, 30, and 3). Furthermore, the fluorescence in low grade tumors is not demonstrated. In fact, in Study 3, 7 patients had post-operative diagnoses of low grade glioma. Of the 7 patients, 4 patients received the study drug. 9/10 biopsies did not fluoresce (false negative) and only 1/10 did fluoresce. See table below for a summary of the patients with low grade glioma (sponsor's 5/19/2017 Response to FDA 5/4/2017 and 5/12/2017 information requests)

Table 1. Patients Excluded from the Full Analysis Set with Low-Grade Glioma (Study 3, Study 28, and Study 30)

Unique Subject ID Age / Sex Treatment Group	Reason for Discontinuation from Study	Study Discontinuation Specific Reason/Detail	Histology - Surgical Findings	Biopsy	Tissue Type	Fluor-escence	Percent Tumor Cells	Diag-nostic Accuracy
ALS03-(b) (6) 19 / M 5-ALA	Histopathological diagnosis not met	anaplastic oligodendroglioma WHO III, Reference-pathology: WHO Grade II oligodendroglioma, no glioma	Oligodendroglioma (WHO grade ii)	1	Tumor	None	>50%	FN
				2	Margin	None	<10%	FN
				3	Normal			
ALS03-(b) (6) 36 / F 5-ALA	Histopathological diagnosis not met	Protocol Violation	Astrocytoma fibrillar	1	Tumor	None	>50%	FN
				2	Margin	None	>50%	FN
				3	Normal	None	>50%	FN
ALS03-(b) (6) 31 / M 5-ALA	Histopathological diagnosis not met	Protocol Violation	Pilocytic astrocytoma	1	Tumor	None	>50%	FN
				2	Margin	None	>50%	FN
				3	Normal			
ALS03-(b) (6) 42 / F 5-ALA	Histopathological diagnosis not met	Protocol Violation	Astrocytoma fibrillar	1	Tumor	Weak	>50%	TP
				2	Margin	None	>50%	FN
				3	Normal	None	>50%	FN
ALS03-(b) (6) 38 / F Control	Histopathological diagnosis not met	histology: oligo-astrocytoma WHO grade II	Oligoastrozytoma who grade ii	1	Tumor		>50%	
				2	Margin		>50%	
				3	Normal		<10%	
ALS03-(b) (6) 26 / M Control	Histopathological diagnosis not met	grade II astrocytoma	Astrocytoma fibrillar	1	Tumor		>50%	
				2	Margin		10-50%	
				3	Normal			
ALS03-(b) (6) 22 / M Control	Histopathological diagnosis not met	Pilocystic astrozytoma I	Pilocytic astrocytoma	1	Tumor		>50%	
				2	Margin		<10%	
				3	Normal			

WHO=World Health Organization; FN=false negative; TP=true positive; M=male; F=female

Dosage and Administration

Reviewer's Comments: The sponsor's proposed reconstitution and dosing instructions were revised to make this section more clear. Promotional language was removed.

8. The proposed instructions were unclear as to how the healthcare provider would reconstitute the product and administer orally. There was a concern because the container-closure system for the product is an IV vial with rubber stopper and the product is for oral use only.

   The only IV administration exists in a single human PK study (Study MC-ALS.20/BV 12 healthy volunteers) who received 1/10 of the recommended dose IV. This was not an efficacy or safety study.

   The single dose and repeat dose animal toxicity studies were designed primarily to determine lethality and not designed to adequately evaluate toxicity. From the animal toxicity studies, one would expect a slightly higher spike but still transient increase in liver enzymes with intravenous compared to oral single-dose administration of the same dose of ALA due to slightly decreased AUCs with oral administration. One can also predict based on the available nonclinical and clinical data that the intravenous administration of 20 mg/kg ALA is not likely to be life-threating. However, intravenous administration does result in increased risk of non-life threating adverse effects compared to oral administration that is probably due to the much higher Cmax with intravenous administration and one cannot predict if the intravenous administration of 20 mg/kg ALA will produce additional adverse effects compared to oral administration of the same dose based on the available data.

   The sponsor reviewed their foreign PM safety database for events of misadministration and revealed 2 non serious events of I.V. misadministration. No adverse events occurred as a result of the misadministration. (See Sponsor's 5/30/2017 labeling IR response.)
   The risk for misadministration (IV instead of po) was mitigated by the following:
   a. Adding "for oral use only" to the carton and container labels as well as section 2 of the package insert.
   b. Revising the package insert instructions to describe reconstitution and administration with the proposed container-closure system (sponsor's 5/30/2017 labeling IR response).

9. Gleolan was dosed using the active ingredient, aminolevulinic acid hydrochloride: Dual presentations (salt and active moiety) in the dosing section may cause confusion. The corresponding dosage form for ALA (active moiety) is presented in sections 3 and 11 (product information]
10. The dosing is presented in mg per kg. [0.666 ml is a small and uneven number. Remove the dosing information based on milliliters as dual units of measure for dosing may cause confusion]
11. Information regarding Class one standard surgical operating microscope adapted with excitation and observation filters was described in this section (see comment 6).
    a. The excitation wavelength of the excitation filter was corrected (b) (4) to 375-440 nm based on the parameters used in the clinical trials (module 5 of the submission).
12. The neurosurgeon training program was referenced in this section. The sponsor will submit the training program materials for review (to OPDP) after approval.

Dosage Forms and Strengths

Sponsor's Proposed: (b) (4) n® is available in 1 strength (1.5 g of 5-ALA HCl per vial) and 1 dosage form (5-ALA HCl for oral solution).

FDA proposed: For oral solution: 1,500 mg ALA HCl lyophilized powder, equivalent to 1,170 mg ALA, in a 50 mL single-dose clear, colorless, glass vial with rubber stopper. After reconstitution with 50 mL drinking water, the solution contains 30 mg per mL of ALA HCl (equivalent to 23.4 mg per mL of ALA) and is clear and colorless to slightly yellowish in color.

Reviewer's Comments:

13. Dosing deviated from the salt naming policy, however, the review team deemed this to be important based on the naming of established products in the class (see comment 3, above).
14. Dose was expressed in mg to be consistent with dosing instructions (2.1).
15. Information on the characteristics of the reconstituted form was included.

Contraindications:

Sponsor's Proposed:

Hypersensitivity to the active substance or porphyrins

Acute or chronic types of porphyria

(b) (4)

FDA Proposed:

Hypersensitivity to the active substance or porphyrins

Acute or chronic types of porphyria, due to potential ineffectiveness of the drug in these patients.

Reviewer's Comments:

16. According to, 21 CFR 201.57 (c)(5), drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible benefit. Therefore, we recommend deleting the (b) (4) as we believe there is a risk-benefit profile in that population.
17. We explained the contraindication in patients with porphyria based on the Sponsor's 5/3/2017 response to FDA 4/28/2017 IR (question 7). Namely, that these patients will not metabolize ALA and therefore will not have the desired increase in PpIX and desired fluorescence. The drug would be ineffective in this population.

Warnings and Precautions:

Sponsor's Proposed:

5.1 Risk of Phototoxic Reactions

5.2 (b) (4)

5.3

5.4 Standard Special Measures

FDA proposed:
5.1 Risk of Phototoxic Reactions
5.2 Risk of Misinterpretation
5.3 Hypersensitivity Reactions

Reviewer's Comments: The entire section was revised according to 21 CFR 201.57(C)(6).
18. Removed the following warnings:

(b) (4)
Recommend deleting because we are not convinced that the risk is clinically significant and that the mitigation strategy (b) (4) is helpful to mitigate the risk. This information is appropriately reflected in section 6 Adverse Reactions.
(b) (4)
Recommend deleting because this is a non-actionable mitigation strategy. The patient is already under general anesthesia / being monitored. This information is appropriately reflected in section 6 Adverse Reactions.
(b) (4)
Deleted because this is practice of neurosurgery.

19. Added the following Warnings:

5.2 Risk of Misinterpretation : Added this warning based on 5/10/2017 Advisory Committee meeting discussion regarding false negatives in the indicated populations (WHO Grade 3 and 4 glioma). There are also a small number of false positives (inflammation) in the indicated population and false negatives in low grade (WHO 1 and 2) gliomas.
5.3 Hypersensitivity Reactions: Added this warning based on the Sponsor's 5/3/2017 response to FDA 4/28/2017 IR (question 8). The sponsor describes hypersensitivity reactions such as: anaphylactic shock, angioedema, drug eruption, urticaria, and erythema. Other optical imaging agents (cysview) and other ALA products (Ameluz, (b) (4) have contraindications in known hypersensitivity and/or warnings.

Adverse Reactions:
Reviewer's Comments: According to 21 CFR 201.57 (c)(7) an adverse reaction is an undesirable effect, reasonable associated with the use of a drug.
20. The section was re-ordered and organized to include adverse reactions attributable to the drug; with the more frequent reactions (> 1%) emphasized before the less frequent reactions (<1%). Brain edema, hemianopsia, and hypoesthesia were not felt to be drug related. Although neurologic events are likely procedure related, the events are of significant severity and frequency that it is acceptable to include them in labeling.
21. The information regarding elevated transaminases was revised based on the Sponsor's May 19, 2017 response to FDA's May 4, 2017 IR. It was expanded to include the absolute increase in transaminase levels (i.e. 2-10 times the upper limit of normal).

Drug Interactions: The Drug is (b) (4), therefore, this information was deleted.

Special Populations: Revised to comply with PLLR. Please see consult from DPMH.

Drug abuse and Dependence: Section was removed as it was not pertinent.

Overdosage: Section was revised to include only actionable information.

Description (11), Clinical Pharmacology, (12) and Nonclinical Toxicology (13): Please see the respective discipline reviews.

Clinical Studies:

Reviewer's comments:

22. The entire section was reorganized to compare fluorescence to tumor status using histology as the reference standard. The results were presented at the biopsy level as: true positive, false positive, true negative, false negative. The important clinical studies included: ALS.28/GLI = Study 1, ALS.30/GLI = Study 2, and ALS.3 /GLI = Study 3
23. The false positive rate in the non-indicated population (WHO Grade 1 and 2) was described. See Comment (7) above.

References:

(b) (4)

Reviewer's Comments:

24. The literature data is supportive. In general references are not included in labeling unless, according to 21 CFR 201.57 (c)(16), "When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, *because the information is important to prescribing decisions, the labeling may include a reference to the source of the information*." These references do not provide additional information critical to prescribing decisions that is not contained elsewhere in the label.

How Supplied/ Storage and Handling:

This section was revised to remove information regarding:

1. Storage of the reconstituted solution – Moved to (2) Dosage and Administration
2. Administration instructions - Moved to (2) Dosage and Administration
3. (b) (4) - Deleted

Patient Counseling Information:

Sponsor Proposed:

(b) (4)

FDA Proposed:

Advise patients that they may experience an increase serum transaminases (ALT and GGT) within the first week after surgery. This elevation may persist after 6 weeks.

Reviewer Comments:

25. Per 21 CFR (c)(18) This section typically focuses on major risks of the drug and risks in which *a patient* may need to do something actionable. (b) (4)

(b) (4)

Labeling negotiations occurred with the Sponsor and the final approved label was acceptable.

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/s/

MICHELE B FEDOWITZ
06/02/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 31, 2017
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 208630
Product Name and Strength:	Gleolan* (5-aminolevulinic acid hydrochloride) for oral solution 1,500 gm/ vial
Applicant/Sponsor Name:	NX Development Corp
Submission Date:	December 6, 2016 and March 3, 2017
OSE RCM #:	2016-2923-01
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.
Associate Director (Acting):	Mishale Mistry, PharmD, MPH

Reference ID: 4105653

1 PURPOSE OF MEMO

In review of the proposed Prescribing Information, DMEPA identified that the container closure system for the proposed powder for oral solution was described as a 'vial'. In discussions with the team there was no consensus on the description of the vial. In addition, DMEPA had questions regarding the reconstitution procedure for the product. DMEPA requested that the Division send an Information Request to get clarification from the Applicant on the container closure system. Therefore, on April 28, 2017, the Division of Medical Imaging Products issued an Information Request (IR) to NX Development, which included DMEPA's request for a sample product container-closure system to determine if it is acceptable from a patient safety and medication error perspective. On May 24, 2017 we received the requested product container for Gleolan (5-aminolevulinic acid hydrochloride) for oral solution (Appendix A). This memo extrapolates on recommendations from a previous label and labeling review[a] and addresses our assessment of the Sponsor provided container sample.

2 DISCUSSION

The submitted product container closure system is a glass vial that has a rubber stopper and (b) (4) closure system. This container closure design is typically reserved for packaging of injectable products. Drug products should not be packaged in a container/closure system that implies or affords a route of administration other than the route intended[b]. In this instance, oral drug products should not be packaged in vial containers as this may lead to intravenous and/or intrathecal route of administration errors. Additionally, we note that the currently proposed Prescribing Information does not provide clear instructions on how to reconstitute this product in the vial and administer orally. It is unclear how health care practitioners are to remove the rubber stopper in order to add water for reconstitution and withdraw the contents of the vial to an oral dosing cup.

We note that training will be provided to neurosurgeons on the use of 5-aminolevulinic acid hydrochloride as a fluorescent imaging tool to identify malignant tissues.[c] However, this training will not be associated with a Risk Evaluation and Mitigation Strategies (REMS) program and therefore, we acknowledge that the Applicant may stop the training program at any time. We provided recommendations in our previous review to ensure that the route of administration is prominently displayed on the container label and carton labeling of the product. However, despite labeling interventions, we are concerned that the current container closure system for this product will result in wrong route of administration errors.

DMEPA emailed the DMIP clinical team on May 25, 2017 outlining concerns of potential wrong route errors associated with the currently proposed packaging. On May 26, 2017, DMIP stated

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[a] Rychlik,I. Label and Labeling Review for Gleolan (NDA 208630). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. RCM No.: 2017-2923.

[b] Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors. Food and Drug Administration. 2012. (lines 419-421) Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf.

[c] NDA 208630. Submission dated May 5, 2017: Cover Letter.

Reference ID: 4105653

that from a pharmacology/toxicology perspective, there are no concerns. Specifically, "based on the available nonclinical and clinical data…the intravenous administration of 20 mg/kg 5-ALA [dose] is not likely to be life-threating. However, intravenous administration does result in increased risk of non life-threating adverse effects compared to oral administration that is probably due to the much higher C_{max} with intravenous administration…one cannot predict if the intravenous administration of 20 mg/kg 5-ALA [dose] will produce additional adverse effects compared to oral administration of the same dose based on the available data." From a clinical perspective, there are no concerns as Gleolan is administered as a one-time dose.

DMEPA issued an Information Request (IR) on May 26, 2017 requesting an Excel file of all case reports and analysis of postmarket serious and nonserious medication errors, including wrong route of administration errors, associated with Gleolan from the time of approval on the European market. In addition, we requested that the applicant propose n language for Section 2 Dosage and Administration of the Prescribing Information which clearly describes, in a step by step approach, how healthcare providers are to prepare/mix the product (including removal of (b) (4) rubber stopper) and withdraw the reconstituted solution for oral administration.

To ensure that the route of administration information is not overlooked by healthcare providers, DMEPA provided additional recommendations for the container label and carton labeling, in addition to those sent on May 25, 2017. We requested the applicant increase the prominence of the route of administration information on the container label and carton labeling by:

1. Increasing font size of the statement "For Oral Use Only"
2. Use bold-face type and box the statement "For Oral Use Only"
3. Change the font color of the statement "For Oral Use Only" to red font to draw attention to this important information.

The applicant responded to the IR on May 30, 2017. With regard to the postmarket cases of wrong route of administration, the applicant reported two cases of wrong route of administration where the solution was administered intravenously; however, these patients did not experience any adverse events. DMEPA also reviewed the revised container label, carton labeling and Prescribing Information submitted on May 30, 2017. We note that the clinical team does not have concerns with one-time administration of Gleolan via intravenous route of administration. We have attempted to optimize the labels/labeling to highlight the oral route of administration of this product, despite its' packaging in a vial configuration.

In addition, in our previous review, we deferred to Office of Pharmaceutical Quality (OPQ) on the use of the term (b) (4) throughout labels and labeling.[d] In an email communication on May 31, 2017, OPQ recommended all references to (b) (4) should be changed to "single-dose" to align with the draft *Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use*.[e]

[d] Rychlik,I. Label and Labeling Review for Gleolan (NDA 208630). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. RCM No.: 2017-2923

[e] https://www.fda.gov/downloads/Drugs/Guidances/UCM468228.pdf

Reference ID: 4105653

3 CONCLUSION

The revised carton and container labels are unacceptable from a medication error perspective. The strength statement as expressed, (b) (4) is incongruent with the dosage and administration of the product. Furthermore, the use of numerous equations throughout Section 2 of the PI and preparation instructions should be limited in the number of product transfers and steps to increase clarity and to decrease the possibility of medication errors. Revised language for the PI was communicated to the Division of Medical Imaging Products on May 31, 2017.

4 RECOMMENDATIONS FOR NX DEVELOPMENT CORP

We recommend the following be implemented prior to approval of this NDA 208630:

A. Carton and Container Label
   a. Revise the (b) (4) strength statement to only state the strength to avoid confusion, i.e."1,500 mg".
   b. Per Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, revise the term (b) (4) to "Single-Dose Vial" on all labels and labeling .

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

IDALIA E RYCHLIK
05/31/2017

HINA S MEHTA
05/31/2017

MISHALE P MISTRY
05/31/2017

To: Ms. Lisa Skarupa
Regulatory Project Manager, DMIP/CDER

CC: Dr. Binita Ashar
Director, DSD/CDRH

Binita S. Ashar -A
Digitally signed by Binita S. Ashar -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001613 32, cn=Binita S. Ashar -A
Date: 2017.05.31 13:58:31 -04'00'

Ms. Jennifer Stevenson
Deputy Director, DSD/CDRH

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Ms. Courtni Brown
Program Analyst, DSD/CDRH

From: Colin Kejing Chen, Ph.D.
Lead Reviewer
General Surgery Devices Branch 1 (GSDB1)
DSD, ODE

Colin Kejing Chen

Subject: NDA 208630
5-ALA or Glioan (coupled with surgical microscopes)

Sponsor(s):
NX Development Corp

Reference ID: 4112301

Date: **May 12, 2017**

1. Background

The Center for Drug Evaluation and Research received an NDA submission (208630) regarding a new oral drug Gliolan, which is fluorescently labeled chemical compound. The proposed indications are: Gliolan is an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery. During surgery, the excitation light of the appropriate wavelength is coupled with the operating microscope. Normal brain tissue lacking significantly enhanced PPIX level reflects the violet-blue light. Gliolan is used with operating microscopes, equipped with a blue light emitting light source and the appropriate filters.

The sponsor had a preIND submission 110655 back to 2014. There was a question to CDRH in preIND 110655 (Question 8) about the regulation of surgical microscopes. Because surgical microscopes are regulated in Division of Surgical Devices (generally exempt Class I devices unless more than the limitations), the preIND consult was reviewed by DSD, with CDRH Product Jurisdiction and Office of Combination Products involved. In this NDA consult, the question remains the same --- can the company reference a class of microscopes that meet the specifications rather than a specific microscope? Thus, we continue the review from the preIND.

2. Surgical Microscopes Review

The study is entitled "An imaging agent to facilitate the real-time detection and visualization of malignant tissue during glioma surgery". The sponsor included a number of literature articles regarding the use of this investigative drug in animal studies and in clinical trials. The sponsor summarized information about the drug safety, interactions with other drugs and potential phototoxicity.

Microscopes will be used in the study. Intraoperatively, glioma is resected using a standard surgical operating microscope adapted to visualize fluorescence excitation in the wavelength range from 400 nm to 410 nm and for observation from 620 to 710 nm. The adaptation includes a combination of excitation and emission filters with slightly overlapping transmission integrated into its optical configuration. Filters were designed to transmit red porphyrin fluorescence, as well as a fraction of backscattered blue excitation light necessary for distinguishing nonfluorescing tissue. Due to the overlapping transmission, a small fraction of the excitation light is remitted from tissue and to give normal brain a blue tone in contrast to bright red porphyrin fluorescence. Video cameras are needed to visualize fluorescence on a video documentation purpose. Illumination densities, depending on the microscope distance from the resection cavity, are in the range of 40 – 80 mW/cm2. Positioning the microscope so that the illumination light is as perpendicular to the resection surface as possible will also increase fluorescence yields. The microscope should also integrate a three chip camera system optimized for red porphyrin fluorescence visualization by enhanced sensitivity in the wavelength range beyond 600 nm.

Reference ID: 4112301

The efficacy of the drug with surgical microscope is evaluated by the CDER review team. One of the questions regarding the device is that: Can the drug label cite a class of microscopes that meet the specifications used in the clinical study? This question was discussed in preIND 110655 as well. Surgical microscopes in general are exempt Class I devices under 21 CFR 878.4700, intended for use during surgery to provide a magnified view of the surgical field. The intended use for 5-ALA is more specific. If the efficacy of the drug together with the microscopes is established (still subject to the final review although we recognize that the Advisory Panel recommended May 10, 2017, that the clinical trial shows benefits outweighing risks), variations of microscopes with or without the fluorescent filters are minimum and can be covered by general control that has been specified in 21 CFR 878.4700. Microscopes meeting the specifications have the same mechanism of action interacting with the 5-ALA drug and the target tissue. Scientifically, we find that a class of surgical microscopes with the specifications, rather than a specific microscope, can function the same with the proposed drug.

We also recognize that whether a drug label can reference a class of imaging devices or not is also a regulatory question. During the review of preIND 110655, we worked with CDER and OCP on that issue. OCP determined on November 3, 2014, that "it appeared feasible that Gliolan may be labeled for use with marketed microscopes that have appropriate filters that help meet the appropriate specifications for its use. However, a final determination regarding labeling will be made upon review of supportive efficacy and safety data provided n the NDA for the proposed indication". Upon reviewing the device information and data from the NDA, we do not find safety concerns regarding the use of the surgical microscopes. We also understand that the efficacy of the entire product is being established for the indications by CDER review team and the May-10-2017 panel. Assuming the drug and the drug/microscope combination found safe and effective, we still think that it is feasible that Gliolan may be labeled for use with marketed microscopes that have appropriate filters meeting the specifications. Mr. Neil Ogden, Chief of GSDB1/DSD, checked with Mr. James Bertram, CDRH Product Jurisdiction Officer. Mr. Bertram confirmed on April 17, 2017, that it is consistent with the prior policy and with the current review on other similar combination products.

The two key parameters for surgical microscope related to fluorescent imaging are the filter wavelength and excitation power density information. The wavelengths and power density information should be added to the draft label.

Reference ID: 4112301

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatric and Maternal Health Review

Date: May 22, 2017 **Date consulted:** January 24, 2017

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Jane Liedtka, M.D., Acting Team Leader, Maternal Health
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Lynne P. Yao, MD., OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Medical Imaging Products (DMIP)

Drug: Gleolan (5-aminolevulinic acid hydrochloride [5-ALA HCL] for oral solution)

NDA: 208630

Applicant: NX Development Corp (NXDC)

Subject: Pregnancy and Lactation Labeling

Indication: for use as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery

Materials Reviewed:

- 1/24/2017, DMIP consult for NDA 208630, DARRTS reference ID 4045984
- 12/6/2017, NDA 208630 submission for Gleolan

Consult Question: Review of package insert and PLLR format recommendations

INTRODUCTION

The Division of Medical Imaging Products (DMIP) consulted both the Maternal Health and Pediatric Teams in the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of Gleolan (5-aminolevulinic acid hydrochloride [5-ALA HCL HCl] for oral solution) labeling as well as to provide recommendations for pediatric use information in labeling. The applicant is seeking approval in adults only and was not required to provide a pediatric assessment under the Pediatric Research Equity Act as a result of being granted orphan designation for the proposed indication. Therefore, the Pediatric Team's recommendations were limited to the inclusion of the following statement in subsection 8.4 (Pediatric Use) in labeling: "Safety and efficacy in pediatric patients have not been established." The remainder of this review focuses on labeling recommendations from the Maternal Health Team.

REGULATORY HISTORY

On December 6, 2016, NX Development Corp (NXDC) submitted an original New Drug Application (NDA) 208630 for Gleolan (5-aminolevulinic acid hydrochloride [5-ALA HCL HCl] for oral solution) for use as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery. Gleolan is used with operating microscopes equipped with a blue light emitting light source along with appropriate filters. NDA 208630 is a 505(b)(2) application that received Fast Track designation on December 18, 2015, and Orphan designation on January 15, 2013. Gleolan is currently approved for marketing in 40 countries outside of the United States including the EU, Japan, Israel, Australia, Hong Kong, South Korea, Taiwan, Ukraine and Kuwait for use as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery.

On March 31, 2017, DMIP sent NXDC the following Information Request:

> We refer to your submission dated December 6, 2016, for Gliolan[1] (5-aminolevulinic acid hydrochloride [5-ALA HCL HCl] for oral solution). We note that Gliola (b) (4) currently approved for marketing in 40 countries outside of the United States. Please submit a cumulative review and summary of relevant cases reported in your pharmacovigilance database regarding Gliolan[1] use in pregnant and/or lactating women (from the time of product development to present) by April 6, 2017.

[1] The applicant has withdrawn the tradename request for Gliolan and is currently awaiting a new tradename. However, the tradename Gliolan is currently approved in other countries outside of the United States and was used to refer to the drug product in the Information Request.

NXDC responded on April 5, 2017, with the following:

> The postmarketing pharmacovigilance safety database was reviewed for Gliolan[1] use in pregnancy and lactation. There have been no cases reported where pregnancy or lactation was recorded. This is in accordance with the most recent European Union (EU) Periodic Safety Update Report (PSUR), where there has been no report of any case with pregnancy. Pregnancy is a labeled contraindication in major markets outside of the United States where Gliolan[1] is currently approved for marketing, such as EU, Japan, and Australia. Additionally, for the medac GmbH (medac) clinical studies in the NDA, no study report disclosed a pregnancy case. Furthermore, pregnancy was an exclusion criterion in all clinical studies submitted to the NDA.

BACKGROUND

Drug Characteristics[2,3]

Gleolan (5-aminolevulinic acid hydrochloride [5-ALA HCL HCl]) is a porphyrin precursor with a proposed indication as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery. Gleolan, or 5-ALA HCL is an endogenous metabolite formed in the mitochondria from succinyl-CoA and glycine and is synthesized by an intracellular pool of free heme via a negative feedback mechanism. Administration of 5-ALA HCL leads to selective accumulation of its metabolite, PpIX, in malignant tumor cells. Absorption of 5-ALA HCL occurs rapidly with maximum plasma concentrations reached approximately 1 hour after oral administration of 20 mg per kg body weight (bw) 5-ALA HCL. 5-ALA HCL is administered orally 3 ± 1 hours before anesthesia to ensure PpIX is as its maximum during time of tumor resection and remains high for 6 to 8 hours. The half-life of 5-ALA HCL is 0.92 to 3.05 hours and approximately 30% of orally administered 20 mg per kg bw 5-ALA HCL is excreted unchanged within the urine within 12 hours.

The most common treatment-related adverse events reported from six clinical trials submitted to support NDA 208630, occurring the first six weeks after surgery, include brain edema, hemianopia, hypoaesthesia, pyrexia, chills, photosensitivity reaction, solar dermatitis, hypotension, abnormal liver function tests, diarrhea and venous thrombosis. These adverse events occurred in < 1% of patients.

Detection and Visualization of Malignant Tissue during Glioma Surgery and Pregnancy[3,4,5]

There is no published literature on the detection and visualization of malignant tissue during glioma surgery and pregnancy. Limited published literatures are available on glioma treatment during pregnancy. Gliomas are tumors that occur in the brain and spinal cord. Gliomas are one of the most common types of brain tumors. The three types of gliomas include astrocytomas, ependymomas and oligodendropliomas. Typically pregnant patients do not have surgery right away however they receive radiotherapy and/or chemotherapy during pregnancy. A retrospective

[2] NDA 208630. Applicant's proposed labeling.
[3] NDA 208630. Clinical Summary. Summary of Clinical Efficacy.
[4] Glioma. http://www.mayoclinic.org/diseases-conditions/glioma/home/ovc-20129412. Accessed 10 March 2017.
[5] Ronning P, *et al*. (2016). The effect of pregnancy on survival in a low-grade glioma cohort. *J Neurosurg*, 125, 393-400.

cohort study conducted by the Medical Birth Registry of Norway (MBRN) and the Cancer Registry of Norway (CRN) identified all female patients with a World Health Organization (WHO) grade II glioma between the ages of 16-40 years from January 1, 1970 through December 31, 2008. Sixty-five patients who gave birth to 95 children after a diagnosis of low-grad glioma (LGG) were included in the study. The study also identified 281 patients who did not give birth after LGG diagnosis. Additionally, most patient present with seizures and are starting on antiepileptic drug therapy, many of which are associated with birth defects. The authors concluded that pregnancy did not appear to have an impact on the survival of female patients with LGG.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,*"[6] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[7] format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Nonclinical Experience[8]

In a rabbit embryo-fetal development study with 5-ALA HCl, the no-observed-adverse-effect level (NOAEL) was 50 mg/kg/day (mean maternal area under the concentration-time curve (AUC)0-24h = 21.6 ± 1.1 μg·h/mL) for maternal toxicity, corresponding to a less than 1-fold exposure margin compared to human exposure at the maximum recommended dose, based on AUC comparisons compared to human (geometric mean AUC0-inf = 33.13 μg·h/mL). The NOAEL for embryo-fetal developmental toxicity was 150 mg/kg/day (mean maternal AUC0-24h = 99.1 ± 14.1 μg·h/mL), corresponding to an approximate 3-fold exposure margin compared to human exposure at the maximum recommended dose, based on AUC comparisons compared to human (geometric mean AUC0-inf = 33.13 μg·h/mL). Limited published literature show that 5-ALA plus direct light exposure to reproductive organs exerts embryotoxic activity in mouse, rat, and chick embryos; however, these studies are not clinically relevant as the reproductive organs were exposed to the blue light and in clinical practice the blue light exposure will occur in the brain or spinal cord.

[6] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[7] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[8] NDA 208630. Nonclinical Overview. Section 2.4.

Review of Literature
The applicant did not submit a review of published literature. DPMH conducted a search using PubMed and EMBASE revealing no published literature with regard to pregnancy and Gleolan or 5-ALA HCL or 5-aminolevulinic acid hydrochloride exposure.

Summary
There is no available human data with regard to pregnancy and Gleolan or 5-ALA HCL or 5-aminolevulinic acid hydrochloride exposure. DPMH recommends the following statement in subsection 8.1 Pregnancy: *There are no available data on GLEOLAN use in pregnant women to inform a drug associated risk of adverse developmental outcomes.* (b) (4)

LACTATION

Nonclinical Experience
There is no available nonclinical data with regard to lactation and Gleolan or 5-ALA HCL or 5-aminolevulinic acid hydrochloride exposure.

Review of Literature
The applicant did not submit a review of published literature. DPMH conducted a search using PubMed, EMBASE and LactMed[9] revealing no published literature with regard to lactation and GLEOLAN or 5-ALA HCL or 5-aminolevulinic acid hydrochloride exposure.

Summary
There is no available human or animal data with regard to lactation and Gleolan or 5-ALA HCL or 5-aminolevulinic acid hydrochloride exposure; therefore, DPMH recommends the following language in subsection 8.2 Lactation: *There are no data on the presence of 5-aminolevulinic acid hydrochloride (5-ALA HCl) in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Gleolan and any potential adverse effects on the breastfed infant from Gleolan or from the underlying maternal condition.*

Additionally, DPMH recommends the breastfeeding female pump and discard breastmilk for 5 to 6 half-lives which is approximately 24 hours after administration of Gleolan. DPMH notes that the same recommendations can be found in the EU, Australian and Japanese package inserts for 5-ALA HCl.

[9] LactMed is an online database with information on drugs and lactation and is property of the National Library of Medicine's TOXNET system. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. Accessed 10 March 2017.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience
There is no available nonclinical data regarding females and males of reproductive potential and Gleolan or 5-ALA HCL or 5-aminolevulinic acid hydrochloride exposure.

Review of Literature
The applicant did not submit a review of published literature. DPMH conducted a search using PubMed and EMBASE revealing no published literature with regard to females and males of reproductive potential and Gleolan or 5-ALA HCL or 5-aminolevulinic acid hydrochloride exposure.

Summary
There is no available human or animal data with regard to females and males of reproductive potential and Gleolan or 5-ALA HCL or 5-aminolevulinic acid hydrochloride exposure; therefore, DPMH recommends that Section 8.3 be omitted from labeling.

CONCLUSIONS
The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of Gleolan labeling was structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," and "Clinical Considerations" subsections.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on Medical Imaging Products (DMIP) on April 25, 2017. DPMH recommendations are below and reflect the discussions with DMIP. DPMH refer to the final NDA action for final labeling. (See Appendix A for the applicant's proposed pregnancy and lactation labeling)

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Gleolan use in pregnant women to inform a drug associated risk of adverse developmental outcomes. In animal reproduction studies, no adverse developmental effects were observed with oral 5-ALA HCl administration to pregnant rabbits during organogenesis at doses 3 times the maximum recommended human oral dose (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

(b) (4) the no-observed-adverse-effect level (NOAEL) was 50 mg/kg/day (b) (4) for maternal toxicity. (b) (4) . The NOAEL for embryo-fetal developmental toxicity was 150 mg/kg/da (b) (4)

8.2 Lactation

Risk Summary

There are no data on the presence of 5-aminolevulinic acid hydrochloride (5-ALA HCl) in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Gleolan and any potential adverse effects on the breastfed infant from Gleolan or from the underlying maternal condition.

Clinical Considerations

To decrease exposure to Gleolan to the breastfed infant, advise a lactating women to pump and discard breastmilk after the administration of Gleolan for 24 hours (i.e., 5 to 6 half-lives).

APPENDIX A – Applicant's Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no (b) (4) data (b) (4) in pregnant women. Animal studies (b) (4)

(b) (4) (see (b) (4) Data) (b) (4).

Animal data

(b) (4), the no-observed-adverse-effect level (NOAEL) was 50 mg/kg/day (b) (4) (b) (4) for maternal toxicity. (b) (4) The NOAEL for embryo-fetal developmental toxicity was 150 mg/kg/day (b) (4) (b) (4)

8.2 Lactation

Risk summary

(b) (4)

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/s/

CARRIE M CERESA
05/22/2017

JANE E LIEDTKA
05/22/2017

MONA K KHURANA
05/22/2017

LYNNE P YAO
05/22/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 17, 2017

To: Lisa M. Skarupa
Senior Regulatory Health Project Manager
Division of Medical Imaging Products (DMIP)

From: Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 208630**
Gleolan® (5-aminolevulinic acid hydrochloride [5-ALA HCl]) for oral solution

---

On January 4, 2017, DMIP consulted OPDP to review the proposed package insert (PI) and the carton and container labeling for Gleolan. Our review of the PI is based on the proposed PI emailed to us on May 15, 2017 via sharepoint (**Proposed.Gliolan.draft.labeling**). Please note that we referred to Division of Medication Error Prevention and Analysis' review, dated May 12, 2017, for reference to the carton and container labeling for our review.

OPDP has reviewed the carton and container labeling and the attached proposed PI and we have no additional comments at this time.

Thank you for the opportunity to comment on the proposed material. If you have any questions or concerns regarding this review, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
05/17/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 12, 2017
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 208630
Product Name and Strength:	Gliolan* (5-aminolevulinic acid hydrochloride) for oral solution 1,500 gm/ vial
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	NX Development Corp
Submission Date:	December 6, 2016 and March 3, 2017
OSE RCM #:	2016-2923
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

* Proprietary Name “Gliolan” was found unacceptable under OSE# 2016-11908377. New proposed Proprietary Name “Gleolan” is currently under review.

Reference ID: 4097606

1 REASON FOR REVIEW

NX Development Corp. submitted NDA 208630 for Gliolan (5-aminolevulinic acid hydrochloride) on December 6, 2016. Gliolan is a medical imaging oral drug used to assist in the detection and visualization of malignant tissue during glioma surgery. The Division of Medical Imaging Products (DMIP) requested DMEPA review the container label, carton labeling, and prescribing information for Gliolan, to determine if it is acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

NX Development Corp. submitted NDA 208630 for Gliolan (5-aminolevulinic acid hydrochloride) on December 6, 2016. DMEPA evaluated the proposed PI, container label and carton labeling for areas of vulnerability in regards to medication error. We identified areas in the labels and labeling that can be improved to increase readability and prominence of important information. Specifically, we note that (b) (4) dual expression of dosing may lead to medication errors such as overdose and/or under-dose for patients. The PI also contains undefined symbols throughout and does not clearly state the accurate dosage form. Furthermore, the product packaging (glass vial) implies a route of administration other than the intended (oral) route which may lead to severe patient safety implications.

We also note the use of the terminology (b) (4) and the omission of specific instruction for reconstitution (i.e. (b) (4)) in Section 2: Dose and Administration, we defer to Pharmaceutical Quality/CMC for the appropriateness of this terminology and inclusion of

Reference ID: 4097606

mixing instructions in the labels and labeling. We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

The container/closure system is described as a 'vial' on the carton labeling and container label. Per Section 3.P.7, the container closure system is "50 mL clear, colorless, (b) (4) glass vial". However, given that this product is a powder for oral solution, we have requested samples of the container/closure system. Drug products should not be packaged in a container/closure system that implies or allows for an unintended route of administration, because this practice has led to wrong routes of administration. Therefore, we may have further comments on the use of this terminology once the samples have been submitted.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendation in Section 4.1 for the PI and 4.2 for the carton and container label to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. HIGHLIGHTS OF PRESCRIBING INFORMATION

1. **Dosage and Administration**
    i. Remove reconstitution information from the Highlights and point to the Full Prescribing Information (PI) for this information.
    ii. Remove dangerous abbreviations throughout the Highlights as they may lead to confusion when in close proximity with the dose, i.e. 5-ALA HCl.
    iii. Remove the dosing information based on milliliters as dual units of measure for dosing may cause confusion.
    iv. Please revise this section as follows:
        - Recommended reconstituted oral dose of Gliolan is 20 mg/kg.
        - Administer to patient orally 3 hours (range 2 to 4 hours) before anesthesia.
        - Must reconstitute supplied powder with water prior to use. See Full Prescribing Information for reconstitution instructions.
2. **Dosage Forms and Strength**
    i. Revise the dosage form and strength to read as follows:

    "For oral solution: 1,500 mg of 5-ALA HCl lyophilized powder equivalent to ..."

B. PRESCRIBING INFORMATION

1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear on the carton labeling. As part of a national campaign to avoid the use of dangerous abbreviations and dose

Reference ID: 4097606

designations, FDA agreed not to approve such error prone symbols in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:

   i. Replace all "µg" symbols appearing throughout the PI with "mcg"
   ii. Delete the abbreviation of body weight "bw" throughout the PI, dosing of mg/ kg is assumed per body weight, this specification may lead to unnecessary confusion.

2. Section 2: Dosage and Administration
   i. Revise the reconstitution instructions for increased clarity as follows:
      Gliolan powder must be reconstituted prior to administration by a healthcare provider according to the following instructions:
      - Measure 50 mL of water and add to one vial containing Gliolan (1,500 mg)
      - Administer the reconstituted Gliolan for oral solution 3 hours (range 2 to 4 hours) before anesthesia
      - Discard any unused solution
   ii. Revise the recommended dose instructions for increased clarity as follows:
      - The recommended dose of reconstituted Gliolan for adults is 20 mg/kg
3. Section 3: Dosage Forms and Strengths
   i. Revise the dosage form and strength to read as follows:
   "For oral solution: 1,500 mg g of 5-aminolevulinic acid hydrochloride lyophilized powder equivalent to..."
4. Section 16: How Supplied/Storage and Handling
   i. Please include the NDC number under the how supplied section as currently it is missing.

4.2 RECOMMENDATIONS FOR NX DEVELOPMENT CORP

We recommend the following be implemented prior to approval of this NDA 208630:

A. CARTON LABEL

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Revise the (b) (4) strength statement as expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and has led to dosing errors.[a] Thus, revise the strength to be displayed as "1,500 mg".

[a] Draft Guidance: Container and Carton, April 2013 (lines 365-367).

Reference ID: 4097606

3. Remove [redacted] (b) (4) from the box of the strength. Having two statements of strength may cause confusion.
4. Add statement "Discard Unused Portion" below the single use statement to ensure this important information is not overlooked.
5. Currently presented the NDC number is denoted by a placeholder. Please submit the NDC number for review.
6. Add the net quantity statement (i.e. One vial) per the Agency's Draft Guidance: Container and Carton, April 2013 (line 462), net quantity statement should appear on the Principal Display Panel (PDP). Ensure the net quantity statement is away from the product strength, such as to the bottom of the PDP. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength.

B. CONTAINER LABEL

1. See Section A.2 through A.6.
2. Move manufacturer information to side panel.
3. Increase the prominence of the statement, "Reconstitute Prior to Use" and relocate to the Primary Display Panel (PDP) to minimize the risk of the product being administered without reconstitution.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gliolan that NX Development Corp. submitted on December 6, 2016.

Table 2. Relevant Product Information for Gliolan	
Initial Approval Date	N/A
Active Ingredient	5-aminolevulinic acid hydrochloride
Indication	medical imaging oral drug used to assist in the detection and visualization of malignant tissue during glioma surgery
Route of Administration	Oral
Dosage Form	Powder
Strength	1,500 (b) (4) (30 mg/ mL once reconstituted)
Dose and Frequency	20 mg/ kg 2 to 4 hours prior to surgery
How Supplied	Single use vial
Storage	Before reconstitution: 15°C to 30°C (59°F to 86°F) After reconstitution: 15°C to 30°C (59°F to 86°F) for no more than 24 hours.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 9, 2017, we searched the L:drive and AIMS using the terms, Gliolan to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 0 previous reviews.

Reference ID: 4097606

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Gliolan labels and labeling submitted by NX Development Corp. on December 6, 2016.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

Prescribing Information:

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Container Label:

(b) (4)

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[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

IDALIA E RYCHLIK
05/12/2017

HINA S MEHTA
05/12/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 24, 2017

To: Lisa M. Skarupa
Senior Regulatory Health Project Manager
Division of Medical Imaging Products (DMIP)

From: Zarna Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 208630**
Glioan® (5-aminolevulinic acid hydrochloride [5-ALA HCl]) for oral solution
"(b) (4)"

On April 18, 2017, DMIP consulted OPDP to review the (b) (4) (b) (4) for Gliolan® (5-aminolevulinic acid hydrochloride [5-ALA HCl] for oral solution) (Gliolan). Our review is based on the draft (b) (4) submitted on December 6, 2016, with the 505b2 NDA 208630 for Gliolan for use as an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery.

OPDP has reviewed the (b) (4) and considers it to be promotional labeling and should not be approved as part of approved product labeling.

If NX Development Corp would like OPDP to review (b) (4), we recommend that they submit a formal request for advisory comments to OPDP.

Thank you for the opportunity to comment on the proposed material. If you have any questions or concerns regarding this review, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
04/24/2017