Remind patient of scheduled arrival time at hospital. Patient must receive Gleolan 3 hours (range: 2 to 4 hours) in advance of induction of anesthesia.

Advise patient not to take any phototoxic drugs 24 hours prior to administration, such as St. John’s wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines, and topical preparations containing aminolevulinic acid (ALA).

Check patient’s weight, and advise pharmacy for calculation of volumetric dose.

Ensure that the reconstituted Gleolan from the pharmacy is stored at room temperature. Do not refrigerate.

Due to the risk of phototoxic reactions, reduce exposure to sunlight or room lights for 48 hours after administration of Gleolan. You may wish to consider securing a room with reduced light for use after Gleolan administration.

Please see full Prescribing Information.

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

The following checklist is a guide intended to assist you in the care of your patients pre- and post-surgery. This checklist does not replace surgical protocols. Please see the Important Safety Information on the reverse side, and the full Prescribing Information.

PRIOR TO PATIENT ARRIVAL FOR SURGERY

☐ Remind patient of scheduled arrival time at hospital. Patient must receive Gleolan 3 hours (range: 2 to 4 hours) in advance of induction of anesthesia.
☐ Advise patient not to take any phototoxic drugs 24 hours prior to administration, such as St. John’s wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines, and topical preparations containing aminolevulinic acid (ALA).

☐ Check patient’s weight, and advise pharmacy for calculation of volumetric dose.
☐ Ensure that the reconstituted Gleolan from the pharmacy is stored at room temperature. Do not refrigerate.
☐ Due to the risk of phototoxic reactions, reduce exposure to sunlight or room lights for 48 hours after administration of Gleolan. You may wish to consider securing a room with reduced light for use after Gleolan administration.

Gleolan administration:

☐ You may store reconstituted solution for up to 24 hours at room temperature. Do not refrigerate.
☐ Advise staff/anesthesiology that, as an exception to NPO status, the patient may have the appropriate weight-adjusted dose prior to anesthesia.
☐ Administer orally 3 hours (range: 2 to 4 hours) prior to induction of anesthesia.
☐ Ensure that patient drinks the entire amount, as prepared in the pharmacy based on patient weight.
☐ Place Gleolan wristband on patient, and mark timing of administration and end of light precautions (48 hours later).

☐ Place the patient in an area with reduced exposure to sunlight or room lights until surgery.
☐ Ensure that the patient is covered sufficiently if he/she leaves the light-protected area for any reason.
☐ Monitor for adverse events as well as hypersensitivity reactions. See Important Safety Information on the reverse side.
☐ Do not exceed 20 mg/kg dosing in preparation for each surgical case; consequences of repeat dosing of Gleolan have not been studied.

SURGICAL PROCEDURE

(MAINTAIN LOW-LIGHT PRECAUTIONS UNTIL PATIENT IS FULLY DRAPED)

☐ Advise full team of photosensitivity precautions and note in patient chart.
☐ Place Gleolan door hanger on patient’s room, and mark timing of administration and end of light precautions (48 hours later).
☐ Maintain reduced exposure to sunlight and room lights for 48 hours after administration.
☐ Drape patient to maintain reduced light precautions for transfer within the hospital (eg, transfer to recovery, for imaging, etc).

☐ Do not administer phototoxic drugs, such as St. John’s wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines, and topical preparations containing ALA for 24 hours after Gleolan administration.
☐ Advise patient to maintain reduced exposure to sunlight or room lights for 48 hours after administration of Gleolan due to risk of phototoxic reaction.
☐ Advise patient that it is possible to experience elevated liver enzymes (ALT and GGT) within the first week after surgery. This elevation may persist beyond 6 weeks.

QUESTIONS OR CONCERNS? CALL MEDEXUS AT 1-833-GLEOLAN (1-833-453-6526)

Please see full Prescribing Information.
Contraindications
Do not use Gleolan in patients with:
• Hypersensitivity to aminolevulinic acid (ALA) or porphyrins
• Acute or chronic types of porphyria

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

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

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

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

Nervous system disorders occurred in 29% of patients within the first week after surgery and events occurring in >1% of patients included: aphasia (8%), hemiparesis (7.8%), hemianopsia (3.2%), headache (2.7%), seizure (1.9%), hemiplegia (1.9%), monoparesis (1.3%) and hypoesthesia (1.1%). Brain edema occurred in <1% of patients in the first 6 weeks after surgery. In a randomized clinical trial, the numbers of serious neurologic adverse events in the post operative period were higher in patients randomized to ALA fluorescence arm compared to the control arm. An imbalance was notable for the adverse events aphasia, ataxia, convulsion and hemianopsia and is likely related to the higher amount of brain resection performed in the ALA arm. At longer follow-up periods, the numbers between the two arms appeared similar.

Worsening of >2 Common Toxicity Criteria grades in alanine aminotransferase and gamma-glutamyl transferase occurred in 15.8% and 11.6% of patients, respectively, within the first week after surgery. Absolute levels ranged from 2 times to greater than 10 times the upper limit of normal for each parameter. At 6 weeks, these measurements remained elevated in 2.9% and 7.5% of patients, respectively. There were no cases of liver failure.

Drug-Drug Interactions
See information under Warnings and Precautions regarding phototoxic reactions.

Please see the Important Safety Information above, and the full Prescribing Information.

QUESTIONS OR CONCERNS? CALL MEDEXUS AT 1-833-GLEOLAN (1-833-453-6526)
Gleolan® (aminolevulinic acid hydrochloride) for oral solution

**INDICATIONS AND USAGE**

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

**DOSEAGE AND ADMINISTRATION**

- **For oral use only**
  - **Recommended oral dose of Gleolan is 20 mg/kg.**
  - **Administer Gleolan to patient orally 3 hours (range 2 to 4 hours) before anesthesia.**
  - **See Full Prescribing Information for reconstitution information.**
  - **Use appropriate visualization techniques with appropriate surgical microscopes and light source filters.**

**FORMULATION AND STABILITY**

For oral solution: 1,500 mg aminolevulinic acid hydrochloride lyophilized powder, equivalent to 1,170 mg aminolevulinic acid per vial. The reconstituted solution (30 mg of Gleolan per ml) is clear and colorless to slightly yellowish in color. (3)

**CONTRAINDICATIONS**

- Hypersensitivity to aminolevulinic acid (ALA) or porphyrins. (4, 5.3, 6.2)
- Acute or chronic types of porphyria. (4)

**WARNINGS AND PRECAUTIONS**

- **Phototoxic reactions:** Do not administer phototoxic drugs (St. John’s wort, griseofulvin, thiazide diuretics, sulfonamides, phenothiazines, sulfonamides, quinolones, and tetracyclines), and topical preparations containing ALA for 24 hours during the perioperative period. Reduce exposure to sunlight or room lights for 48 hours after oral administration of Gleolan. (5.1, 7)
- **Risk of misinterpretation:** Non-fluorescing tissue in the surgical field does not rule out the presence of tumor. (5.2, 14)

**FULL PRESCRIBING INFORMATION CONTENTS**

1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
3. DOSAGE FORMS AND STABILITY
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
6. ADVERSE REACTIONS
7. CLINICAL STUDIES
8. USE IN SPECIFIC POPULATIONS
9. PREGNANCY
10. LACTATION

**ADVERSE REACTIONS**

- **Adverse reactions occurring in >1% of patients in the week following surgery were pyrexia, hypotension, nausea, and vomiting.** (6.1)
- **Adverse reactions occurring in < 1% of patients in the first 6 weeks after surgery were:** chills, phototoxic reaction, solar dermatitis, hypotension, abnormal liver function test, and diarrhea. (6.1)
- **Neurologic events related to the surgical procedure occurred in 29% of patients and included:** aphasia, hemiparesis, hemianopia, headache, seizure, hemiplegia, monopa-rosis, hypoesthesia, and brain edema. (6.1)
- **Elevated liver enzymes occurred in clinical studies. There were no cases of liver failure.** (6.1)

**ADVERSE REACTIONS**

- **Complete removal of the white cap and aluminum crimp seal from each vial.**
- **Remove and retain the rubber stopper from the vial.**
- **Using a disposable volumetric syringe, remove the administration volume of solution to be administered.**
- **Errors may occur with the use of Gleolan for intraoperative visualization of malignant glioma, including false negatives and false positives.**
- **Non-fluorescing tissue in the surgical field does not rule out the presence of tumor in patients with glioma.**

**CONTRAINDICATIONS**

- Hypersensitivity to aminolevulinic acid (ALA) or porphyrins. (4, 5.3, 6.2)
- Acute or chronic types of porphyria. (4)

**CONTRAINDICATIONS**

- **Use in patients with porphyrin abnormalities; exposure of the central nervous system or skin to photosensitizers increases the risk of photodermatitis.**

**ADVERSE REACTIONS**

- **Elevated Liver Enzymes**
  - Worsening of a common Toxicity Criteria (CTC) grade of alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) occurred in 15.8% and 11.6%, respectively within the first week after surgery. Absolute levels ranged from 2 times to greater than 10 times the upper limit of normal (ULN) for each parameter. At week 6, ALT remained elevated in 2.9% of patients (range 2 to greater than 5 X ULN), and GGT was elevated in 7.5% of patients (range 2 to greater than 10 X ULN). No cases of liver failure occurred.
Post Marketing Experience
The following adverse reactions are among those that have been identified during post-approval use of Gleolan outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

8.6 Patients with Renal Impairment
Because approximately one third of the ALA dose is excreted in urine as parent drug, ALA clearance may be reduced in patients with renal impairment; it is not known if dose adjustment is needed (see Clinical Pharmacology (12.3)).

8.7 Patients with Hepatic Impairment
The contribution of the liver to the elimination of ALA following Gleolan dosing is unknown. ALA clearance may be reduced in patients with hepatic impairment; it is not known if dose adjustment is needed (see Clinical Pharmacology (12.3)).

10 OVERDOSAGE
Overdosage has been associated with respiratory insufficiency and erythema. In the event of overdose, supportive measures should be provided as necessary, including protection from strong light sources.

11 DESCRIPTION
11.1 Chemical Properties
Gleolan (aminolevulinic acid hydrochloride) is an optical imaging agent for oral administration. The 50-mL clear, colorless, glass vial contains 1,500 mg of lyophilized aminolevulinic acid hydrochloride powder (equivalent to 1,770 mg aminolevulinic acid). After reconstitution, the product has a concentration of 30 mg aminolevulinic acid hydrochloride per mL (equivalent to 33.4 mg aminolevulinic acid per mL). The chemical name is 5-amino-4-oxo-pentanoic acid hydrochloride. The chemical formula for aminolevulinic acid hydrochloride is CH₂N₂O₃. Its molecular weight is 167.59 g/mol with the following structural formula:

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
ALA occurs endogenously as a metabolite that is formed in the mitochondria from succinyl-CoA and glycine. Exogenous administration of ALA leads to accumulation of the ALA metabolite Pp IX in tumor cells. The reason for the accumulation of Pp IX in neoplastic brain tissue is not known.

During glioma surgery, Gleolan is used with an operating microscope adapted with a blue emitting light source (power density 40-80 mW/cm²) and filters for excitation light of wavelength 375 to 440 nm, and observation at wavelengths of 620 to 710 nm. This allows tumor tissue to be visualized as red fluorescence. Tissue lacking sufficient Pp IX concentrations appears blue.

12.2 Pharmacodynamics
The effect of the timing of the Gleolan dosing on fluorescence intensity in brain tissue is unknown. The relationship between systemic ALA plasma concentrations at the time of visualization and fluorescence intensity in brain is also unknown. The dose of 20 mg/kg provided stronger ALA-induced fluorescence in glioma tissue by both visual and spectrophotometric assessment compared to lower doses tested.

12.3 Pharmacokinetics
In 12 healthy subjects, the mean half-life of ALA following the recommended dose of Gleolan solution was 9.9 ± 1.2 hours (mean ± std dev) with a range of 8.3 to 1.3 hours. Maximum concentrations of the Pp IX metabolite Tₘ₉₉ for Pp IX occurred with a median of 4 hours and a range of 1.2 to 7.8 hours. The elimination half-life of Pp IX was 3.6 ± 1.8 hours (mean ± std dev) with a range of 1.2 to 7.8 hours.

ABSORPTION
In 12 healthy subjects, the absolute bioavailability of ALA following the recommended dose of Gleolan solution was 100.0% ± 1.4 with a range of 78.5% to 113.2%. Maximum ALA plasma concentrations were reached with a median of 0.8 hours (range 0.5 – 1.0 hour).

DISTRIBUTION
In in vitro experiments using ALA concentrations up to approximately 25% of the maximal concentration that occurs in plasma following the recommended dose of Gleolan solution, the mean protein binding of ALA was 17.6%.

ELIMINATION
Metabolism
Exogenous ALA is metabolized to Pp IX, but the fraction of administered ALA that is metabolized to Pp IX is unknown. The average plasma AUC of Pp IX is less than 6% of that of ALA.

Excretion
In 12 healthy subjects, excretion of parent ALA in urine in the 12 hours following administration of the recommended dose of Gleolan solution was 34 ± 8% (mean ± std dev) with a range of 27% to 57%.

Specific Populations
The effect of renal or hepatic impairment on the pharmacokinetics of ALA following Gleolan administration is unknown.

Drug Interaction Studies
In vitro studies suggest that phenytoin and other anti-convulsants may decrease cellular Pp IX accumulation following Gleolan dosing.

ALA is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C7, 2D6, or 3A.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity studies have been conducted with Gleolan.

Mutagenesis
ALA HCI was not mutagenic in the Ames assay, Hprl-V79 mammalian cell mutagenicity test, the peripheral human lymphocyte chromosomal aberration assay and the in vivo mouse micronucleus test when studies were performed in the dark or under subdued lighting.

Impairment of fertility
No fertility studies have been conducted with Gleolan.

14 CLINICAL STUDIES
The efficacy of 20 mg/kg ALA HCI was evaluated in 3 clinical studies (Study 1-3) involving patients, ages 18 to 75 years old, who had a presurgical MR compatible with high-grade glioma (World Health Grade III or IV) and were undergoing surgical resection. Study 1 was an open-label study of 31 patients with newly diagnosed high-grade glioma and Study 2 was an open-label study of 36 patients with recurrent high-grade glioma. In Studies 1 and 2, after initial debulking was carried out under white light, biopsies were obtained under fluorescence 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 nonfluorescent biopsies are provided in Table 1.

Study 3 was a randomized, multicenter study in 415 patients with a presurgical diagnosis of high-grade glioma by MRI. Patients were randomized in 1:1 ratio to ALA fluorescence arm or to white light control arm. Biopsies were obtained from tumor-core, tumor-margin and regions just distant to the tumor margins. In 349 patients high grade glioma was confirmed by a blinded central read and histopathology. The remaining patients were diagnosed with metastatic disease, abscess, low-grade glioma or other conditions.

In patients with confirmed high-grade glioma randomized to the ALA fluorescence arm, presence of fluorescence at a biopsy level was compared to tumor status using histopathology as the reference standard (Table 1). In 4 patients with low-grade glioma (WHO Grade I or II) who received ALA HCI, 9 out of 10 biopsies were false negative.

The extent of resection among patients with confirmed high-grade glioma in the ALA 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 ‘completeness’ of resection was 64% in the ALA arm and 38% in the control arm, with the difference of 26% [95% CI: (16%, 36%)].

Table 1. Presence of Fluorescence Compared to Histopathology (biopsy level)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>%T</th>
<th>%F</th>
<th>%TN</th>
<th>%FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>31</td>
<td>71</td>
<td>29</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Study 2</td>
<td>36</td>
<td>72</td>
<td>28</td>
<td>32</td>
<td>70</td>
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<tr>
<td>Study 3</td>
<td>415</td>
<td>64</td>
<td>36</td>
<td>38</td>
<td>62</td>
</tr>
</tbody>
</table>

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Gleolan (IND 59137-231-01) is supplied as a 1,500 mg of lyophilized aminolevulinic acid hydrochloride powder (equivalent to 1,770 mg aminolevulinic acid), for oral solution in a 50-mL clear, colorless, glass vial with a rubber stopper and an aluminum/stamp seal.

16.2 Storage and Handling
Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F).

17 PATIENT COUNSELING INFORMATION

Advice patients that they may experience elevated liver enzymes (ALT and GGT) within the first week after surgery. This elevation may persist for 6 weeks. Advise patients to reduce exposure to sunlight or room lights for 48 hours after administration of Gleolan due to risk of phototoxic reactions.

Manufactured by: NX Development Corp. Lexington, KY 40503
Distributed by: Mediceus Pharm, Inc. Chicago, IL 60606
Product of Germany

Table 1. Presence of Fluorescence Compared to Histopathology (biopsy level)

<table>
<thead>
<tr>
<th>Number of Fluorescent Biopsies</th>
<th>False Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>31</td>
</tr>
<tr>
<td>Study 2</td>
<td>36</td>
</tr>
<tr>
<td>Study 3</td>
<td>415</td>
</tr>
</tbody>
</table>

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