PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrGLEOLAN

Aminolevulinic Acid Hydrochloride Powder for Oral Solution

1.5 g / vial

Imaging Agent

Medexus Inc.
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RECENT MAJOR LABEL CHANGES

None.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

Clinical effectiveness for this optical imaging agent is based on a high rate of fluorescence-positive biopsies with positive identification of tumour among all fluorescent-positive biopsies (true-positive rate) taken in three clinical studies.

Limitations of usefulness:
There was a high rate of non-fluorescence positive biopsies with positive identification of tumour among all non-fluorescent positive biopsies (false-negative rate) found in the three clinical studies (see WARNING AND PRECAUTIONS, *General, Risk of Misinterpretation* and CLINICAL TRIALS).

Special restrictions:
Gleolan should only be used by neurosurgeons who have completed a training program on use of fluorescence in surgery.

1.1 Pediatrics

Pediatrics (0 to 18 years old): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> *65* years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness. Greater sensitivity of some older individuals cannot be ruled out. (see SPECIAL POPULATIONS).

2 CONTRAINDICATIONS

Gleolan is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

- Hypersensitivity to porphyrins,
- Acute or chronic types of porphyria (see WARNING AND PRECAUTIONS)

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

The recommended oral dose of reconstituted Aminolevulinic Acid HCl is 20 mg / kg body weight.

The total number of vials needed to achieve the intended dose for the individual patient can be determined according to the equation below (rounded up to the nearest whole vial):

$$\text{Number of vials} = \frac{\text{Patient body weight (kg)}}{\text{75 kg/vial}}$$

No dose adjustment is needed for geriatric patients.

Health Canada has not authorized an indication for pediatric use.

The effect of renal or hepatic impairment on safety and efficacy of Aminolevulinic Acid HCl (ALA HCl) has not been studied. Safety issues might potentially occur, since ALA is excreted via the kidneys and porphyrins are metabolized in the liver. The use of Aminolevulinic Acid HCl in these populations is, therefore, not recommended unless medically justified.

3.2 Administration

The solution should be administered orally three hours (range 2-4 hours) before anaesthesia.

The administration volume needed to achieve the intended dose for the individual patent can be calculated according to the equation below:

$$\text{Administration volume (mL)} = \frac{\text{Patient body weight (kg) x 20 mg/kg}}{\text{30 mg/mL}}$$

If surgery is delayed by more than 12 hours, surgery should be re-scheduled for the next day or later. Another dose of this medicine can be taken 2-4 hours before anaesthesia.

Missed Dose:
This medicine is given once only at the day of surgery, 2 – 4 hours before start of anaesthesia. If it has not been taken during this time period, it is not advisable to take it just before start of anaesthesia. In this case, anaesthesia and surgery should be postponed for at least 2 hours, if possible.

3.3 Reconstitution

Oral Solutions: Gleolan powder must be reconstituted prior to administration by a healthcare provider. The oral solution is prepared by dissolving the amount of powder of one vial in 50 ml of drinking water.

Table 1 – Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
1.5 g / vial	50 mL drinking water	50 mL	30 mg Aminolevulinic Acid HCl per mL

The reconstituted solution is a clear and colourless to slightly yellowish fluid.

Gleolan is for single use only and any content remaining after first use must be discarded.

3.4 Imaging Instructions

During glioma surgery, Gleolan has to be used with an operating microscope adapted with a blue emitting light source (white light power density 40-80 mW/cm^2) and filters to allow for excitation light of wavelength 375 to 440 nm, and observation at wavelengths of 620 to 710 nm. This allows tumour tissue to be visualized as red (typically strong) fluorescence or pink (typically weak) fluorescence. Tissue lacking sufficient protoporphyrin IX (PpIX) concentrations appears blue.

4 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.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Lyophilized powder, 1.5 g / vial	None.

Gleolan powder is available in a 50 mL single-dose clear, colorless glass vial with a rubber stopper containing 1.5 g of lyophilized Aminolevulinic Acid HCl powder (1.17 g of Aminolevulinic Acid).

Gleolan is packaged in cartons of 1 vial.

6 WARNINGS AND PRECAUTIONS

General

Risk of new onset or worsening of neurological deficits post-operatively:
As with any tumour resection surgery, pre- or intraoperative measures should be used to maintain safety distances from areas of eloquence. Resection of fluorescing tissue should be

weighed up carefully against the neurological function of fluorescing tissue.

Some investigators reported that the use of ALA-fluorescent-guided resection of gliomas was associated with an increased risk of new onset or worsening of neurological deficits. Based on these results, special care must be taken in patients with a tumour in the immediate vicinity of an important neurological function and pre-existing focal deficits that do not improve on corticosteroid treatment.

Risk of misinterpretation:
False negative and false positive results may occur with the use of ALA HCl for intraoperative visualization of malignant glioma. Non-fluorescing tissue in the surgical field does not rule out the presence of tumour in patients with glioma. In the three clinical studies taken together, a total of 228 (79%) false-negative biopsies out of 288 biopsies from non-fluorescent tissue were identified. On the other hand, fluorescence may be seen in areas brain tissue without the presence of tumour cells. In the three clinical studies taken together, a total of 26 (3%) false-positive biopsies out of 858 biopsies from fluorescent tissue were identified. In none of these studies was it required to describe the histopathological findings of false-positive biopsies. (See CLINICAL TRIALS). Based on the scientific literature, fluorescence may be seen in areas of abnormal brain tissue (such as reactive astrocytes, atypical cells), necrotic tissue, inflammation, infections (such as fungal or bacterial infections and abscesses), CNS lymphoma or metastases from other tumour types.

Patients with porphyria:
Patients with acute or chronic types of porphyria were not included in any clinical study; therefore, potential efficacy and safety issues are not known. In patients with impaired heme metabolism, exogenous administration of Aminolevulinic Acid HCl might lead to unexpected reactions.

Cardiovascular
In patients with pre-existing cardiovascular disease, Gleolan should be used with caution due to possible risk of cardiovascular effects. Literature reports have shown decreased systolic and diastolic blood pressure, pulmonary artery systolic and diastolic pressure as well as pulmonary vascular resistance.

Hepatic/Biliary/Pancreatic
The contribution of the liver to the elimination of Aminolevulinic Acid following Gleolan dosing is unknown. Aminolevulinic Acid clearance may be reduced in patients with hepatic impairment. Within 24 hours after administration, hepatotoxic drugs should be avoided due to the potential risk of elevated liver enzymes.

Immune
In the post-marketing setting, hypersensitivity reactions, including serious hypersensitivity reactions have been observed. Hypersensitivity reactions might include: anaphylactic shock, swelling, and urticaria (see ADVERSE REACTIONS). Always have cardiopulmonary resuscitation personnel and equipment readily available and monitor all patients for hypersensitivity reactions.

Peri-Operative Considerations
Aminolevulinic Acid induces a photosensitizing agent (PpIX). Patients are to avoid direct sunlight and postoperatively reduce exposure to room lights for 48 h after administration of

Gleolan to avoid any skin sensitization.

In addition, due to the risk of possible phototoxic reactions, phototoxic agents (e.g., certain antibiotics [tetracyclines, sulfonamides, fluoroquinolones], hypericin extract) should not be used concurrently for up to 24 hours perioperatively after administration of Gleolan, unless medically justifiable (see DRUG INTERACTIONS). Concomitant exposure to any photosensitizing agent and Aminolevulinic Acid HCl should be avoided. One case of an increased phototoxic reaction (severe sunburn lasting for 5 days) has been reported in a breast cancer patient after co-administration of 40 mg/kg Aminolevulinic Acid HCl with a hypericin extract.

Renal
Because approximately one third of the Aminolevulinic Acid dose is excreted in urine as parent drug, Aminolevulinic Acid clearance may be reduced in patients with renal impairment. Use of Gleolan is not recommended in this population, unless medically justified.

6.1 Special Populations

6.1.1 Pregnant Women

Gleolan is not recommended during pregnancy. There are no available human data on Gleolan 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 Aminolevulinic Acid HCl administration to pregnant rabbits during organogenesis at doses 3 times the maximum recommended human oral dose.

6.1.2 Breast-feeding

There are no data on the presence of Aminolevulinic Acid 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. To decrease exposure to Gleolan to the breastfed infant, advise a lactating woman to pump and discard breast milk after the administration of Gleolan for 24 hours (i.e., 5 to 6 half-lives).

6.1.3 Pediatrics

Pediatrics (0 to 18 years old): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics

Of 527 subjects in clinical studies of Gleolan, 182 were 65 to < 75 years of age and 7 were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the older and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of Gleolan is supported by data from 6 clinical studies, which included 21 healthy male subjects and 527 patients with glioma who received at least one dose of 20 mg/kg bodyweight Aminolevulinic Acid HCl (including 36 patients with recurrent glioma). None of these studies included blinded assessment of adverse events.

Treatment Emergent Adverse Events (TEAEs) were reported in 317 patients (60.2%); 3.4% were considered drug-related. No patient discontinued the study due to nonfatal TEAEs. More patients experienced TEAEs in the first week after surgery (41.6%) as compared to 24.6% within 6 weeks of surgery, and 18.3% of patients after more than 6 weeks post-surgery.

The most common TEAEs, regardless of causality to Gleolan, pertained to nervous system disorders, which occurred in 29.4% of patients within the first week after surgery. Events occurring in > 1% of patients included aphasia (8.0%), hemiparesis (7.8%), hemianopia (3.2%), headache (2.7%), seizure (1.9%), hemiplegia (1.9%), monoparesis (1.3%) and hypoaesthesia (1.1%). In the randomized clinical trial (MC-ALS.3/GLI), 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. Other TEAEs that occurred in > 1% of patients in the week following surgery were pyrexia (1.9%), hypertension (1.3%), nausea (1.1%), and vomiting (1.1%).

TEAEs that were considered by the investigators to be drug-related, occurring in the first 6 weeks after surgery, were brain edema, hemianopia, hypoaesthesia, pyrexia, chills, photosensitivity reaction, solar dermatitis, hypotension, abnormal liver function test, diarrhea, and venous thrombosis. Each of these TEAEs occurred only in 1-2 patients (< 1% of patients). In addition, there was 1 case of respiratory failure reported due to drug overdose.

7.3 Less Common Clinical Trial Adverse Reactions

Please refer to section 7.2 for all TEAEs and their frequencies.

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Elevated Liver Enzymes
Overall, there was no clinically significant pattern of change in any laboratory parameter that was associated with Aminolevulinic Acid HCl. Across studies, patients experienced a worsening of ≥ 2 Common Toxicity Criteria (CTC) grades in alanine aminotransferase (ALT)

and gamma- glutamyl transferase (GGT) (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 6 weeks, 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).

Post-Market Adverse Reactions
The following adverse reactions have been sporadically identified during post-approval use of Gleolan outside of Canada. 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.

Immune System Disorders (possibly representing hypersensitivity reactions): anaphylactic shock, angioedema, drug eruption, urticaria, erythema.

Metabolism and Nutrition Disorders: metabolic/lactic acidosis.

There is one case described in the scientific literature of a patient who developed generalized edema including mucosal surfaces and required 4 days' monitoring in the intensive care unit after fluorescence assisted surgical intervention for brain tumour. The patient made a complete recovery.

8 DRUG INTERACTIONS

8.1 Overview

Aminolevulinic Acid is metabolized in the body into PpIX, which in the skin can lead to phototoxic reactions. Therefore, caution is advised for the administration of therapeutic agents that may also induce phototoxic reactions.

8.2 Drug-Drug Interactions

Patients exposed to a photosensitizing agent may experience a phototoxic skin reaction (severe sunburn). Due to the risk of possible phototoxic reactions, avoid administering phototoxic drugs (e.g. certain antibiotics [tetracyclines, sulfonamides, fluoroquinolones griseofulvin] thiazide diuretics, sulfonylureas, phenothiazines, topical preparations containing ALA HCl, and hypericin extract) for 24 hours before and after administration of Gleolan.

In vitro studies suggest that phenytoin and other anti-convulsants may decrease cellular PpIX accumulation following Gleolan dosing.

Aminolevulinic Acid HCl is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A.

Interactions with other drugs have not been established.

8.3 Drug-Herb Interactions

St. John's wort is considered phototoxic and should be avoided for 24 hours before and after administration of Gleolan.

8.4 Drug-Food Interaction

Drug-food interaction is not considered relevant in the clinical situation since for the visualization of glioma tissue, Aminolevulinic Acid HCl is administered 2 - 4 hours prior to anesthesia induction on an empty stomach.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Aminolevulinic Acid occurs endogenously as a metabolite that is formed in the mitochondria from succinyl-CoA and glycine. Exogenous administration of Aminolevulinic Acid leads to accumulation of the Aminolevulinic Acid metabolite PpIX in tumour cells. The reason for the accumulation of PpIX in neoplastic brain tissue is not known. PpIX is a fluorescent compound when excited with light of the appropriate wavelength.

9.2 Pharmacodynamics

Systemic administration of Aminolevulinic Acid HCl results in an overload of the cellular porphyrin metabolism and accumulation of PpIX in various epithelia and cancer tissues. Malignant glioma tissue has also been demonstrated to synthesise and accumulate porphyrins in response to Aminolevulinic Acid administration. Tissue surrounding the tumour and normal brain may also be affected. In a dose finding study in 21 patients, it was shown that the dose of 20 mg / kg body weight provided stronger Aminolevulinic Acid-induced fluorescence in glioma tissue by both visual and spectrophotometric assessment compared to lower doses tested. The relationship between systemic Aminolevulinic Acid plasma concentrations at the time of visualization and fluorescence intensity in brain is unknown. The effect of the timing of the Gleolan dosing on fluorescence intensity in brain tissue is not well defined after 10 h after administration, but at the recommended oral dose of 20 mg/kg body weight, tumour to normal brain fluorescence ratios are usually high and offer lucid contrast for visual perception of tumour tissue under violet-blue light for at least 9 hours.

Cardiac Electrophysiology
Administration of the approved recommended dose of Gleolan did not prolong the QT interval to any clinically relevant extent.

9.3 Pharmacokinetics

As determined in a dose-finding study in 21 patients, there is dose proportionality between $AUC_{0\text{-}inf}$. of Aminolevulinic Acid values and different oral doses of this medicinal product. In Table 3 the pharmacokinetic parameters after oral administration of the recommended dose in healthy volunteers are summarized.

Table 3- Summary of Pharmacokinetic Parameters for Aminolevulinic Acid and PpIX in healthy volunteers after a single oral dose of 20 mg/kg bodyweight (geometric mean)

	C_{max}	T_{max}	$t_{½}$ (h)	$AUC_{0\text{-}\infty}$
Aminolevulinic Acid	20.90 mg/L	0.76 h (median)	0.92 h	33.13 mg*h/L

	C_{max}	T_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$
PpIX	279 µg/L	4 h (median)	3.57 h	1,875.66 µg*h/L

Absorption: In 12 healthy subjects, the absolute bioavailability of Aminolevulinic Acid following the recommended dose of Gleolan solution was 100.0% + 1.1 with a range of 78.5% to 131.2%. Maximum Aminolevulinic Acid plasma concentrations were reached with a median of 0.8 hour (range 0.5 – 1.0 hour).

Distribution: In in vitro experiments using Aminolevulinic Acid 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 Aminolevulinic Acid was 12%.

Metabolism: Exogenous Aminolevulinic Acid is metabolized to PpIX, but the fraction of administered Aminolevulinic Acid that is metabolized to PpIX is unknown. The average plasma AUC of PpIX is less than 6% of that of Aminolevulinic Acid.

Elimination: In 12 healthy subjects, excretion of parent compound Aminolevulinic Acid 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%.

Special Populations and Conditions

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of Aminolevulinic Acid following Gleolan administration is unknown.

Renal Insufficiency: The effect of renal impairment on the pharmacokinetics of Aminolevulinic Acid following Gleolan administration is unknown.

10 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C - 30°C).

The reconstituted solution (in a re-stoppered vial) is stable for 24 hours at room temperature (15°C - 30°C).

Gleolan 1.5 g/vial is for single use only and any contents remaining after first use must be discarded.

Any unused Gleolan or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

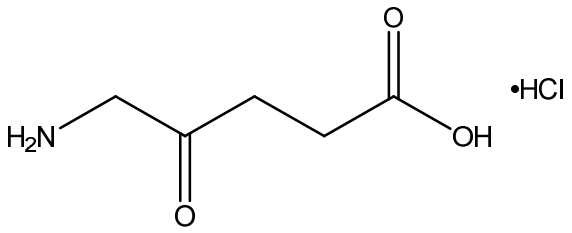
Drug Substance

Proper name: Aminolevulinic Acid Hydrochloride

Chemical name: 5-amino-4-oxo-pentanoic acid hydrochloride

Molecular formula and molecular mass: $C_5H_{10}ClNO_3$ 167.59 g/mol

Structural formula:



Physicochemical properties: Aminolevulinic Acid HCl is a white to off-white crystalline powder with a melting range of 150°C to 165°C. It is slightly soluble in ethanol and methanol and freely soluble in water. It has a UV maximum of 266.5 nm in water. In 1% solution, Aminolevulinic Acid HCl has a pH of 2.0 to 3.5.

12 CLINICAL TRIALS

12.1 Trial Design and Patient Demographics in Clinical Trials

The efficacy of 20 mg / kg Aminolevulinic Acid HCl as an adjunct for intraoperative visualization of malignant tissue was evaluated in 3 clinical studies (MC-ALS.28/GLI, MC-ALS.30/GLI, and MC-ALS.3/GLI) involving patients, ages 18 to 75 years old, who had a preoperative MRI compatible with high-grade glioma (WHO Grade III or IV) and were undergoing surgical resection. Primary efficacy assessment used biopsy-based positive predictive value (PPV), which was collected and analyzed (initially as a pre-specified secondary endpoint) in studies MC-ALS.28/GLI and MC-ALS.30/GLI, and was derived post-hoc in study MC-ALS.3/GLI. The negative predictive value (NPV) was derived post-hoc for all three studies.

Table 4 - Summary of trial design and patient demographics for clinical trials in malignant glioma surgery

Study #	Trial design	Dosage, route of administration and duration	Number of enrolled patients (Enrolled/ Full Analysis Set) (n)	Mean age (Range)	Sex Male /Female

Study #	Trial design	Dosage, route of administration and duration	Number of enrolled patients (Enrolled/ Full Analysis Set) (n)	Mean age (Range)	Sex Male /Female
MC-ALS.28/ GLI	Multicenter, single-arm, nonrandomized, rater- blinded, uncontrolled Phase 2 study	Patients were given a single oral dose of Aminolevulinic Acid HCl 20 mg/kg bodyweight 3 hours (range 2.5-3.5 hours) before anesthesia	36/33 Malignant glioma	56.8 yr (21-72)	19 M/17F
MC-ALS.30/ GLI	Multicenter, single-arm, nonrandomized, uncontrolled Phase 2 study	Patients were given a single oral dose of Aminolevulinic Acid HCl 20 mg/kg bodyweight 3 hours (range 2.5-3.5 hours) before anesthesia	40/36 Progressive / recurrent malignant glioma	52.2 (22-74)	28 M/12 F
MC-ALS.3/ GLI	Multicenter, 2-arm, randomized, parallel-group, group-sequential, rater- blinded, controlled Phase 3 study Objective: Efficacy and safety of fluorescence guided resection of malignant gliomas with 5-ALA (FL-group) were compared to conventional resection (WL-group)	Patients in the FL-group were given a single oral dose of Aminolevulinic Acid HCl 20 mg/kg bodyweight 3 hours (range 2-4 hours) before anesthesia	207/176 FL group and 208/173 in placebo group Malignant glioma	58.2 (19-73)	230 M/ 144 F

FL = fluorescent light, WL = white light

Study MC-ALS.28/GLI was an open-label study of 33 patients in the full analysis set with newly diagnosed high-grade glioma; and Study MC-ALS.30/GLI was an open-label study of 36 patients in the full analysis set with recurrent high-grade glioma. In both studies after initial

resection was carried out under white light and deemed by the surgeon as a complete resection, the light source was switched to blue-violet light to assess residual malignant tissue. Biopsies were obtained under fluorescent light from fluorescent and non-fluorescent sites. The presence of fluorescence (strong/weak) versus non-fluorescence (none) were compared to tumour status (positive = defined as tumour cells > 0%) using histopathology as the reference standard (assessed by blinded central independent histopathological review).

Study MC-ALS.3/GLI was a randomized, multicenter study in which 415 patients with a preoperative diagnosis of high-grade glioma by MRI were enrolled. Patients were randomized in 1:1 ratio to ALA and fluorescence light (FL) arm or to white light (WL) control arm. Biopsies were obtained from tumour-core, tumour-margin and regions just distant to the tumour margins. The primary endpoints of this study were the percentage of patients with a histopathologically confirmed malignant glioma (WHO grade III or IV) without definite residual contrast-enhancing tumour in the early post-operative control MRI (within 72 hours after surgery) and 6-month progression-free survival.

12.2 Study Results

For all three clinical studies, true positives and false positives among fluorescent biopsies and true negatives and false negatives among non-fluorescent biopsies are provided in Table 5.

Table 5 - Results of pivotal studies in malignant glioma surgery

	Study MC-ALS.28/GLI	***Study MC-ALS.30/GLI***	***Study MC-ALS.3/GLI***
Number of Fluorescent Biopsies	185	354	319
True Positives / all fluorescent biopsies (Positive predictive value)	178/185 (96.2%) (95% CI: 92.4% - 98.5%)	342/354 (96.6%) (95% CI: 94.2% - 98.2%)	312/319 (97.8%) (95% CI: 95.5% - 99.1%)
False Positives /all fluorescent biopsies	7/185 (3.8%)	12/354 (3.4%)	7/319 (2.2%)
Number of Non-Fluorescent Biopsies	112	16	160
True negatives /all non-fluorescent biopsies (Negative predictive value)	27/112 (24.1%)' (95% CI 16.5-33.1)	3/16 (18.8%) (95% CI 4.0-45.6)	30/160 (18.8%) (95% CI 13.0-25.7)
False negatives / all non-fluorescent biopsies	85/112 (75.9%)	13/16 (81.2%)	130/160 (81.2%)

In study MC-ALS.3/GLI, in 349 patients high-grade glioma was confirmed by blinded central independent histopathological review (Forty-one patients were excluded from the efficacy analysis because they did not meet the histology criteria (n=21 ALA FL arm and n=20 in the WL arm). These patients included those who were diagnosed with metastatic disease, abscess, low-grade glioma or other conditions. Of the excluded patients, there were 4 who were found to have low-grade glioma (WHO Grade I or II), in these patients only 1 area of fluorescence could be identified; 9 out of 10 biopsies did not fluoresce but showed tumour.

The extent of resection among patients with confirmed high-grade glioma in the ALA FL arm was compared to that among patient in the WL control arm, with the “completeness” of resection being determined by a centrally blinded neuroradiologists who reviewed the early post-surgical MRI. The percentage of patients who had “completeness” of resection was 64% in the ALA FL arm and 38% in the control arm, with a difference of 26% [95% CI: (16%, 36%)].

13 NON-CLINICAL TOXICOLOGY

General Toxicity
Single administration of high doses of Aminolevulinic Acid HCl to mice or rats leads to unspecific findings of intolerance without macroscopic abnormalities or signs of delayed toxicity. Repeat-dose toxicity studies performed in rats and dogs demonstrate dose-dependent adverse reactions affecting changes in bile duct histology (non-reversible within a 14 day recovery period), transient increase in transaminases, LDH, total bilirubin, total cholesterol, creatinine, urea and vomiting (only in dogs). Signs of systemic toxicity (cardiovascular and respiratory parameters) occurred at higher doses in the anaesthetised dog: at 45 mg/kg body weight intravenously a slight decrease in peripheral arterial blood pressure and systolic left ventricular pressure was recorded. Five minutes after administration, the baseline values had been reached again. The cardiovascular effects seen are considered to be related to the intravenous route of administration.

Carcinogenicity
No carcinogenicity studies have been conducted with Gleolan.

Genotoxicity
Aminolevulinic Acid HCl was not mutagenic in the Ames assay, HPRT-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.

Reproductive and Developmental Toxicology
No fertility studies have been conducted with Gleolan. Aminolevulinic Acid HCl was administered to pregnant 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 (MHRD), respectively based on AUC comparisons] from gestation days 6-18. The no-observed-adverse-effect level (NOAEL) for maternal toxicity was 50 mg/kg/day and the NOAEL for embryo-fetal developmental toxicity was 150 mg/kg/day.

Special Toxicology
Phototoxicity observed after Aminolevulinic Acid HCl treatment in vitro and in vivo is closely related to dose- and time-dependent induction of PPIX synthesis in the light exposed cells or tissues. Destruction of sebaceous cells, focal epidermal necrosis with a transient acute

inflammation and diffuse reactive changes in the keratinocytes as well as transient secondary oedema and inflammation of dermis are observed. Light exposed skin recovered completely except for a persistent reduction in the number of hair follicles. The compound potentially induces photogenotoxicity after subsequent light exposure which is also related to the induction of porphyrin synthesis. Accordingly, general light protective measures of eyes and skin are recommended for at least 48 hours after administration of this medicinal product.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrGLEOLAN
Aminolevulinic Acid Hydrochloride Powder for Oral Solution

Read this carefully before you start taking **Gleolan** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Gleolan**.

What is Gleolan used for?
Gleolan is used to help visualize certain brain tumours (called malignant glioma) during tumour surgery.

How does Gleolan work?
Gleolan contains a substance called Aminolevulinic Acid. This substance accumulates preferably in tumour cells where it is transformed into another similar substance. If the tumour is then exposed to blue light, this new substance emits a red-violet light. This helps to better see what is normal tissue and what is tumour tissue. This helps the surgeon to remove the tumour while sparing healthy tissue.

What are the ingredients in Gleolan?
Medicinal ingredients: Aminolevulinic Acid Hydrochloride (Aminolevulinic Acid HCl)

Gleolan comes in the following dosage forms:
Powder for oral solution, 1.5 g / vial

Do not use Gleolan if:
- you are allergic to Aminolevulinic Acid or any of the other ingredients in this drug or the container.
- you are allergic to porphyrins (parts of what form red blood cells pigments).
- you have known or suspected acute or chronic types of porphyria. This is a type of inherited or acquired disorders involved in making red blood pigment).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Gleolan. Talk about any health conditions or problems you may have, including if you:
- are pregnant, think you are pregnant, or plan to become pregnant
- are breast feeding. It is not known if Gleolan passes into breast milk. Your doctor may tell you to pump and throw away breast milk for a period of 24 hours after you are given Gleolan.
- have or had problems with your kidney
- have or had problems with your liver
- have a heart disease or had heart disease in the past.

Other warnings you should know about:
Gleolan can make your skin more sensitive to light. Reduce your exposure to sunlight or strong

room lights for 48 hours after you are given Gleolan.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Gleolan:
- phototoxic drugs (drugs that make your skin more sensitive to the sun) such as:
  - certain antibiotics (tetracyclines, sulfonamides, fluoroquinolones)
  - antifungals (such as Griseofulvin)
  - thiazide diuretics
  - diabetes drugs (such as sulfonylureas)
  - antipsychotic drugs (such as phenothiazines)
  - topical drugs containing Aminolevulinic Acid Hydrochloride
- St. John's wort

Do not take these for 24 hours before or after you are given Gleolan.

How to take Gleolan:
Gleolan will be prepared and given to you by a trained healthcare professional. Gleolan is a powder that will be first mixed with drinking water before use. Gleolan will be given to you 2-4 hours before anaesthesia (being put to sleep before the surgery).

If your surgery has been re-scheduled within less than 12 hours, your healthcare professional will not need to give you a new dose of Gleolan. If your surgery is delayed more than 12 hours, it should be re-scheduled to the next day or later. Your healthcare professional will give you another dose of Gleolan 2-4 hours before anaesthesia.

Usual dose:
The usual dose is 20 mg ofAminolevulinic Acid Hydrochloride per kilogram body weight. Your healthcare professional will calculate the exact dose you need and the amount of the solution (in mL) you have to drink.

Overdose:
Your healthcare professional will determine the right dose for you. If you have taken more Gleolan than you should, your healthcare professional will decide on any steps needed to avoid any problems. This includes protection from strong light (for example direct sunlight).

If you think you have received too much Gleolan, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Your healthcare professional will give you Gleolan only once at the day of your surgery, 2 – 4 hours before anaesthesia (being put to sleep). If you have not taken Gleolan in this time period, tell your healthcare professional immediately. Your surgery may be delayed until later.

What are possible side effects from using Gleolan?
These are not all the possible side effects you may feel when taking Gleolan. If you experience any side effects not listed here, contact your healthcare professional.

Some of the side effects are related to the surgery, while some of the side effects are related to Gleolan.

- Headache
- decrease of sense of touch
- fever
- chills
- nausea
- vomiting
- diarrhea
- red skin rash that may itch and burn after being exposed to the sun
- hives, skin redness

After you are given Gleolan, you may also have side effects of abnormal blood test results related to your liver.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
COMMON			
Nervous system problems: including: • aphasia (total or partial loss of ability to use or understand language). • hemiparesis (partial paralysis of one side of the body) • hemianopia (blindness for half the field of vision in one or both eyes) • Seizure • hemiplegia (total paralysis of one side of the body) • monoparesis (partial paralysis of (a part of) an arm or a leg)			√
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations. This symptom has only been seen in the week after surgery and is not related to taking Gleolan..		√	
UNCOMMON			

Brain edema (brain swelling): headache, nausea, dizziness, lack of coordination			√
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up). This symptom is related to taking Gleolan.		√	
Venous thrombosis (clot in a blood vessel): swelling and pain in one part of the body			√
UNKNOWN			
Anaphylactic shock (allergic reaction): difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			√
Angioedema (swelling of tissue under the skin): difficulty breathing; swollen face, hands and feet, genitals tongue, throat; Swelling of the digestive tract causing diarrhea, nausea or vomiting			√
Lactic Acidosis (high level of acid in the blood): nausea, vomiting, fatigue, abdominal pain, unusual muscle pain, dizziness, irregular heartbeat, shortness of breath		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Your healthcare professional will store this medication for you.

Store at room temperature (15°C - 30°C).

Keep out of reach and sight of children.

If you want more information about Gleolan:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website www.medexus.ca, or by calling 1-877-633-3987.

This leaflet was prepared by Medexus Inc.

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