ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gliolan 30 mg/ml powder for oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 1.17 g of 5-aminolevulinic acid, corresponding to 1.5 g 5-aminolevulinic acid hydrochloride (5-ALA HCl).

One ml of reconstituted solution contains 23.4 mg of 5-aminolevulinic acid, corresponding to 30 mg 5-aminolevulinic acid hydrochloride (5-ALA HCl).

3. PHARMACEUTICAL FORM

Powder for oral solution.
The powder is a white to off-white cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gliolan is indicated in adult patients for visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV).

4.2 Posology and method of administration

This medicinal product should only be used by experienced neurosurgeons conversant with surgery of malignant gliomas and in-depth knowledge of functional brain anatomy who have completed a training course in fluorescence-guided surgery.
The recommended dosage is 20 mg 5-aminolevulinic acid hydrochloride per kilogram body weight. The solution should be administered orally three hours (range 2-4 hours) before induction of anaesthesia. Use of 5-ALA under conditions other than the ones used in the clinical trials entail an undetermined risk.

Patients with renal or hepatic impairment
No studies have been performed in patients with clinically relevant hepatic or renal impairment. Therefore, this medicinal product should be used with caution in such patients.

Paediatric population
There is no experience in children.

Elderly patients
There are no special instructions for use in elderly patients with regular organ function.

4.3 Contraindications

- Hypersensitivity to 5-aminolevulinic acid hydrochloride or porphyrins.
- Acute or chronic types of porphyria.
- Pregnancy (see sections 4.6 and 5.3)

4.4 Special warnings and precautions for use

5-ALA-induced fluorescence of brain tissue does not provide information about the tissue's underlying neurological function. Therefore, resection of fluorescing tissue should be weighed up carefully against the neurological function of fluorescing tissue.

Special care must be taken in patients with a tumour in the immediate vicinity of an important neurological function and pre-existing focal deficits (e.g. aphasia, vision disturbances, paresis etc.) that do not improve on corticosteroid treatment. Fluorescence-guided resection in these patients has been found to impose a higher risk of critical neurological deficits. A safe distance to eloquent cortical areas and subcortical structures of at least 1 cm should be maintained independent of the degree of fluorescence.
In all patients with a tumour in the vicinity of an important neurological function, either pre- or intraoperative measures should be used to localise that function relative to the tumour in order to maintain safety distances.

After administration of this medicinal product, exposure of eyes and skin to strong light sources (e.g. operating illumination, direct sunlight or brightly focused indoor light) should be avoided for 24 hours. Co-administration with other potentially phototoxic substances (e.g. tetracyclines, sulfonamides, fluoroquinolones, hypericin extracts) should be avoided (see also section 5.3).

Within 24 hours after administration, other potentially hepatotoxic medicinal products should be avoided.

In patients with pre-existing cardiovascular disease, this medicinal product should be used with caution since literature reports have shown decreased systolic and diastolic blood pressures, pulmonary artery systolic and diastolic pressures as well as pulmonary vascular resistance.

4.5 Interaction with other medicinal products and other forms of interaction

One case of an increased phototoxic reaction (severe sunburn lasting for 5 days) has been reported in a patient after co-administration of 5-aminolevulinic acid and a hypericin extract (a known phototoxic agent).
Patients should not be exposed to any photosensitizing agent up to 2 weeks after administration of Gliolan.

4.6 Pregnancy and lactation

Use in pregnancy
There are no adequate data from the use of this medicinal product in pregnant woman. Some limited animal studies suggest an embryotoxic acitivity of 5-ALA plus light exposure (see section 5.3). Therefore, this medicinal product should not be used during pregnancy.

Use in lactation
It is unknown whether 5-ALA or its metabolite PPIX are excreted in human breast milk. The excretion of 5-ALA or PPIX in milk has not been studied in animals. Breast-feeding should be interrupted for 24 hours after treatment with this medicinal product.

4.7 Effects on ability to drive and use machines

Gliolan has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions observed after the use of this medicinal product for fluorescence-guided glioma resection are divided into the following two categories:

- immediate reactions occurring after oral administration of the medicinal product before induction of anaesthesia (= active substance-specific side effects)
- combined effects of 5-ALA, anaesthesia, and tumour resection (= procedure-specific side effects).

Very common (≥ 1/10)
Common (≥ 1/100, < 1/10)
Uncommon (≥ 1/1,000, < 1/100)
Rare (≥ 1/10,000, < 1/1,000)
Very rare (≤ 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Substance-specific side effects:

Cardiac disorders	Uncommon: Hypotension
Gastrointestinal disorders	Uncommon: Nausea
Skin and subcutaneous tissue disorders	Uncommon: Photosensitivity reaction, photodermatosis

Procedure-related side effects

The extent and frequency of procedure-related neurological side effects depend on the localisation of the brain tumour and the degree of resection of tumour tissue lying in eloquent brain areas (see section 4.4).

Blood and lymphatic system disorders	Very common: Anaemia, thrombocytopenia, leukocytosis
Nervous system disorders	Common: Neurological disorders (e.g. hemiparesis, aphasia, convulsions, hemianopsia) Very rare: Hypesthesia
Cardiac disorders	Uncommon: Hypotension
Vascular disorders	Common: Thromboembolism
Gastrointestinal disorders	Common : Vomiting, nausea Very rare: Diarrhoea
Hepatobiliary disorders	Very common: Blood bilirubin increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma glutamyltransferase increased, Blood amylase increased

In a single-arm study including 21 healthy male volunteers, erythema of the skin could be provoked by direct exposure to UVA light up to 24 hours after oral application of 20 mg/kg body weight 5-ALA HCl. Possibly drug-related mild nausea was reported in 1out of 21 volunteers.

In another single-centre study, 21 patients with malignant glioma received 0.2, 2, or 20 mg/kg body weight 5-ALA HCl followed by fluorescence-guided tumour resection. The only adverse reaction reported in this trial was one case of mild sunburn occurring in a patient treated with the highest dose.

In a single-arm study including 36 patients with malignant glioma, drug-related adverse events were reported in 4 patients (one patient: mild diarrhoea, one patient: moderate hypesthesia, one patient: moderate chills, and one patient: arterial hypotension 30 minutes after application of 5-ALA HCl). All patients received the medicinal product in a dose of 20 mg/kg body weight and underwent fluorescence-guided resection. Follow-up time was 28 days.

In a comparative, unblinded phase-III trial (MC-ALS.3/GLI), 201 patients with malignant gliomas received 5-ALA HCl in a dose of 20 mg/kg body weight and 176 of these patients underwent fluorescence-guided resection with subsequent radiotherapy. 173 patients received standard resection without administration of the medicinal product and subsequent radiotherapy. Follow-up time comprised at least 180 days after administration. At least possibly related adverse reactions were reported in 2/201 (1.0 %) patients: mild vomiting 48 hours after surgery, and mild photosensitivity 48 hours after study surgery. Another patient accidentally received an overdose of the medicinal product (3000 mg instead of 1580 mg). Respiratory insufficiency, which was reported in this patient, was managed by adaptation of ventilation and resolved completely. A more pronounced transient increase of liver enzymes without clinical symptoms was observed in the 5-ALA HCl- treated patients. Peak values occurred between 7 and 14 days after administration. Increased levels of amylase, total bilirubin, and leukocytes, but decreased levels of thrombocytes and erythrocytes were observed, however differences between treatment groups were not statistically significant.

4.9 Overdose

Within a clinical trial, a 63-year old patient with known cardiovascular disease was accidentally given an overdose of 5-ALA HCl (3000 mg instead of 1580 mg). During surgery he developed respiratory insufficiency, which was managed by adaptation of ventilation. After surgery the patient also displayed facial erythema. It was stated that the patient had been exposed to more light than permitted for the trial. Respiratory insufficiency and erythema completely resolved.

In the event of overdose, supportive measures should be provided as necessary, including sufficient protection from strong light sources (e.g. direct sunlight).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sensitisers used in photodynamic therapy, ATC code: L01XD04

5-aminolevulinic acid (5-ALA), the active substance of Gliolan, is a natural biochemical precursor of heme that is metabolised in a series of enzymatic reactions to fluorescent porphyrins, particularly protoporphyrin IX (PPIX). 5-ALA synthesis is regulated by an intracellular pool of free heme via a negative feedback mechanism.

Systemic administration of 5-ALA results in an overload of the cellular porphyrin metabolism and accumulation of PPIX in various epithelia and cancer tissues. Malignant glioma tissue (WHO-grade III and IV, e.g. glioblastoma multiforme, gliosarcoma or anaplastic astrocytoma) has also been demonstrated to synthesise and accumulate porphyrins in response to 5-ALA administration. The concentration of PPIX is significantly lower in white matter than in cortex and tumour. Tissue surrounding the tumour and normal brain may also be affected. However, 5-ALA induced PPIX formation is significantly higher in malignant tissue than in normal brain.

In contrast, in low-grade tumours (WHO-grade I and II, e.g. medulloblastoma, oligodendroglioma) no fluorescence could be observed after application of the active substance. Brain metastases revealed inconsistent or no fluorescence.

The phenomenon of PPIX accumulation in WHO grade III and IV malignant gliomas may be explained by higher 5-ALA uptake into the tumour tissue or an altered pattern of expression or activity of enzymes (e.g. Ferrochelatase) involved in haemoglobin biosynthesis in tumour cells. Explanations for higher 5-ALA uptake include a disrupted blood-brain barrier, increased neo-vascularisation, and the overexpression of membrane transporters in glioma tissue.

After excitation with blue light (λ=400-410 nm), PPIX is strongly fluorescent (peak at λ=635 nm) and can be visualised after appropriate modifications to a standard neurosurgical microscope.

Fluorescence emission can be classified as intense (solid) red fluorescence (corresponds to vital, solid tumour tissue) and vague pink fluorescence (corresponds to infiltrating tumour cells), whereas normal brain tissue lacking enhanced PPIX levels reflects the violet-blue light and appears blue.

In a phase I/II-trial including 21 patients, a dose-efficacy relationship between the dose levels and the extent and quality of fluorescence in the tumour core was detected: Higher doses of 5-ALA HCl enhanced the fluorescence quality and the fluorescence extent of the tumour core compared to demarcation of the tumour core under standard white illumination in a monotone, non-falling fashion. The highest dose (20 mg/kg body weight) was determined to be the most efficient.

A positive predictive value of tissue fluorescence of 84.8 % (90 % CI: 70.7 %-93.8 %) was found. This value was defined as the percentage of patients with positive tumour cell identification in all biopsies taken from areas of weak and strong fluorescence. The positive predictive value of strong fluorescence was higher (100.0 %; 90 % CI: 91.1 %-100.0 %) than of weak fluorescence (83.3 %; 90 % CI: 68.1 %-93.2 %). Results were based on a phase-II trial including 33 patients receiving 5-ALA HCl in a dose of 20 mg/kg body weight.

The resulting fluorescence was used as an intraoperative marker for malignant glioma tissue with the aim of improving the surgical resection of these tumours.

In a phase-III trial with 349 patients with suspected malignant glioma amenable to complete resection of contrast-enhancing tumour were randomised to fluorescence-guided resection after administration of 20 mg/kg body weight 5-ALA HCl or conventional resection under white light. Contrast-enhancing tumour was resected in 64 % of patients in the experimental group compared to 38 % in the control-group ($p<0.001$).
At the visit six months after tumour resection, 20.5 % of 5-ALA-treated-patients and 11 % of patients who underwent standard surgery were alive at the six-month visit without progression. The difference was statistically significant using the chi-square test ($p=0.015$).
No significant increase in overall survival has been observed in this study, however, the trial was not powered to detect such a difference.

5.2 Pharmacokinetic properties

General characteristics
This medicinal product shows good solubility in aqueous solutions. After ingestion, 5-ALA itself is not fluorescent but is taken up by tumour tissue (see section 5.1) and is intracellularily metabolised to fluorescent porphyrins, predominantly protoporphyrin IX (PPIX).

Absorption
5-ALA HCl as drinking solution is rapidly and completely absorbed and peak plasma levels of 5-ALA are reached 0.5–2 hours after oral administration of 20 mg/kg body weight. Plasma levels return to baseline values 24 hours after administration of an oral dose of 20 mg/kg body weight. The influence of food has not been investigated because this medicinal product is generally given on empty stomach prior to induction of anaesthesia.

Distribution and Biotransformation
5-ALA is preferentially taken up by the liver, kidney, endothelials and skin as well as by malignant gliomas (WHO grade III and IV) and metabolised to fluorescent PPIX. Four hours after oral administration of 20 mg/kg body weight 5-ALA HCl, the maximum PPIX plasma level is reached. PPIX plasma levels rapidly decline during the subsequent 20 hours and are not detectable anymore 48 hours after administration. 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.

Besides tumour tissue, faint fluorescence of the choroid plexus was reported. 5-ALA is also taken up and metabolised to PPIX by other tissues, e.g. liver, kidneys or skin (see section 4.4). Plasma protein binding of 5-ALA is unknown.

Elimination
5-ALA is eliminated quickly with a terminal half-life of 1-3 hours. Approximately 30 % of an orally administered dose of 20 mg/kg body weight are excreted unchanged in urine within 12 hours.

Linearity/non-linearity
There is dose proportionality between $AUC_{0\text{-inf.}}$ of 5-ALA values and different oral doses of this medicinal product.

Patients with renal or hepatic impairment
Pharmacokinetics of 5-ALA in patients with renal or liver impairment has not been investigated.

5.3 Preclinical safety data

Standard safety pharmacology experiments were performed under light protection in the mouse, rat and dog. 5-ALA HCl administration does not influence the function of the gastro-intestinal and central nervous systems. A slight increase in saluresis cannot be excluded.

Single administration of high doses of 5-ALA 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 cholesterin, 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.

Phototoxicity observed after 5-ALA HCl treatment *in vitro* and *in vivo* is obviously closely related to dose- and time- dependent induction of PPIX synthesis in the irradiated 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. Accordingly, general light protective measures of eyes and skin are recommended for at least 24 hours after administration of this medicinal product.

Although pivotal studies on the reproductive and developmental behaviour of 5-ALA have not been performed, it can be concluded that 5-ALA induced porphyrin synthesis may lead to embryotoxic activity in mouse, rat and chick embryos only under the condition of direct concomitant light exposure. This medicinal product should, therefore, not be administered to pregnant women. Excessive single dose treatment of rats with 5-ALA reversibly impaired male fertility for two weeks after dosing.

The majority of genotoxicity studies performed in the dark do not reveal a genotoxic potential of 5-ALA. The compound potentially induces photogenotoxicity after subsequent irradiation or light exposure which is obviously related to the induction of porphyrin synthesis.
Long-term *in vivo* carcinogenicity studies have not been conducted. However, considering the therapeutic indication, a single oral treatment with 5-ALA HCl might not be related to any serious potential carcinogenic risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

The reconstituted solution is physically-chemically stable for 24 hours at 25ºC.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted product see section 6.3.

6.5 Nature and contents of container

Colourless type II glass vial, with rubber stopper.
Pack sizes: 1, 2 and 10 vials of powder.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The oral solution is prepared by dissolving the amount of powder of one vial in 50 ml of tap water.
The reconstituted solution is a clear and colourless to slightly yellowish fluid.
Any unused product or waste material should be disposed of in accordance with local requirements.

Single use vial – discard any content remaining after first use.

7. MARKETING AUTHORISATION HOLDER

m e d a c
Gesellschaft für klinische
Spezialpräparate mbH
Fehlandtstraße 3
D-20354 Hamburg, Germany
Tel. + 49 4103 8006 0
Fax: +49 4103 8006 100

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

medac
Gesellschaft für klinische
Spezialpräparate mbH
Theaterstraße 6
D-22880 Wedel
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Gliolan should be used only by neurosurgeons who have attended a training course in accordance with the standards detailed below:

The Marketing Authorisation Holder in agreement with the competent authorities in the Member States shall implement, prior to launch:

– A training course for neurosurgeons which is aimed at risk minimisation and to support safe and effective use for the product. The training course will take place at qualified training centres using qualified trainers. This course shall consist of measures aiming to minimise adverse events associated with the Gliolan-fluorescence-guided surgery (in particular neurological serious adverse events) through adequate education about:

  a) Theory and core principles of Gliolan-fluorescence-guided surgery and malignant glioma resection, including methods of eloquent sites identification;
  b) On-site instructions on the use of the fluorescence-microscope, including pitfalls and recognition of problems;
  c) Differentiation of fluorescence intensity, maintaining safety distances from eloquent areas, etc.
  d) The practice of Gliolan-fluorescence-guided surgery (including participation in at least one cases using Gliolan-fluorescence-guided surgery in the operating room with on-site instructions on the use of the microscope or demonstration of a fluorescence-guided resection by video);
  e) The current understanding of the benefits and risks of cytoreductive surgery in the management of patients with malignant gliomas;
  f) The theoretical base for porphyrin accumulation in malignant gliomas;
  g) The technical principles behind fluorescence-guided resections using Gliolan;
  h) How to identify suitable candidates for fluorescence-guided resections using Gliolan;
  i) How to apply Gliolan in the correct dosage and timing regimen, and to understand the importance of concurrent corticosteroids;
  j) How to identify patients at risk for neurological deficits using fluorescence-guided resections with Gliolan with special focus on aphasias and other critical focal deficits;

k) Techniques for intraoperative risk reduction (microsurgical technique, neurophysiological monitoring, choice of approach) and how to implement them;
l) How to identify fluorescence for resection through using the operating microscope in a hands-on setting in the operating room;
m) The benefits and risks of fluorescence-guided resections using Gliolan;

Minimum requirements for a qualified trainer are:
- Board-certification as neurosurgeon according to local, national requirements;
- Previous successful participation at a training course, or equivalent course during the phase III trial;
- Experience with Gliolan-fluorescence-guided surgery in at least 20 cases.

Minimum requirements for a qualified training centre are:
- Microscope modified for fluorescence-guided resection;
- Sufficient case load (at least 10 patients per year) of malignant gliomas (WHO grade III and IV);
- Neurophysiological monitoring techniques for surgery in eloquent brain regions.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 2 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 5 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton/Vial label

1. NAME OF THE MEDICINAL PRODUCT

Gliolan 30 mg/ml powder for oral solution

5-aminolevulinic acid hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 1.17 g of 5-aminolevulinic acid, corresponding to 1.5 g 5-aminolevulinic acid hydrochloride (5-ALA HCl).

One ml of reconstituted solution contains 23.4 mg of 5-aminolevulinic acid, corresponding to 30 mg 5-aminolevulinic acid hydrochloride (5-ALA HCl).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution

Vial only:
1.5 g 5-aminolevulinic acid hydrochloride

Outer carton only:
1 vial
2 vials
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Single use vial – discard any content remaining after first use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische
Spezialpräparate mbH
Fehlandtstraße 3
D-20354 Hamburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gliolan 30 mg/ml powder for oral solution
5-aminolevulinic acid hydrochloride

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT GLIOLAN IS AND WHAT IT IS USED FOR

Gliolan is used for the visualisation of certain brain tumours (called malignant glioma) during tumour surgery.

Gliolan contains a substance called aminolevulinic acid hydrochloride (5-ALA). 5-ALA is taken up more by tumour cells where it is transformed into another similar substance. If then the tumour is put under blue light exposure this new substance emits a red-violet light which helps to see better what normal tissue is and what tumour tissue is. This helps the surgeon to remove the tumour more completely while sparing healthy tissue.

2. BEFORE YOU TAKE GLIOLAN

Do not take Gliolan
- If you are allergic (hypersensitive) to 5-aminolevulinic acid hydrochloride or porphyrins.
- In case of known or suspected acute or chronic types of porphyria (i.e. inherited or acquired disorders of certain enzymes in the synthesis pathway of red blood pigment).
- In case of known or suspected pregnancy.

Take special care with Gliolan
After administration of this medicine, avoid that your eyes and skin are under strong light (for example operating illumination, direct sunlight or brightly focused indoor light) for 24 hours.

If you have a heart disease or had heart disease in the past, you should tell your doctor. In this case, this medicine should be used with caution because the blood pressure may be decreased.

Patients with renal or hepatic impairment
No studies have been performed in patients with poor liver or kidney function. Therefore, this medicine should be used with caution in such patients.

Children and adolescents (< 18 years)
There is no experience with Gliolan in children. Therefore this medicine is not recommended in this age group.

Elderly patients
There are no special instructions for use in elderly patients with normal organ function.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, particularly medicines that may cause skin problems when the skin comes under strong light (for example some types of medicines called antibiotics), but also medicines obtained without prescription (for example hypericin or Saint John's wort extracts). One case of severe sunburn lasting for 5 days has been reported in a patient after having taken this medicine and a hypericin extract. You should not take any such products up to 2 weeks after you have taken Gliolan.
Within 24 hours after having taken Gliolan, avoid any other medicines that may harm the liver.

Taking Gliolan with food and drink
This medicine is generally used once only, namely 2-4 hours before anaesthesia for surgery for certain brain tumours called glioma. You should not drink or eat for at least 6 hours before starting anaesthesia.

Pregnancy and breast-feeding
Use in pregnancy
It is not known whether Gliolan will harm an unborn baby. Do not use this medicine if you are pregnant.

Use in lactation
It is not known whether this medicine enters breast milk. Breast-feeding mothers should not breast-feed for 24 hours after treatment with this medicine.

Driving and using machines
This medicine itself has no influence on the ability to drive and use machines.

3. HOW TO TAKE GLIOLAN

This medicine is a powder that must be first mixed with drinking water before use. This is always done by a pharmacist or a nurse and not by yourself. The usual dose is 20 mg per kilogram body weight. The pharmacist or nurse will calculate the exact dose you need. You have to drink the prepared solution 2-4 hours before start of anesthesia.

If the anesthesia/surgery is delayed by some hours, additional doses of this medicine must not be given. If the surgery is delayed by one or more days, another dose of this medicine can be taken 2-4 hours before start of anesthesia.

If you take more Gliolan than you should
If you have taken more Gliolan than you should, your doctor will decide on any necessary measures to avoid any problems, including sufficient protection from strong light (for example direct sunlight).

If you forget to take Gliolan
This medicine is given once only at the day of surgery, 2-4 hours before start of anesthesia. If you have forgotten to take this medicine during this time period, it is not advisable to take it just before start of anesthesia. In this case, anesthesia and surgery must be postponed for at least 2 hours, if possible.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Gliolan can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

After having taken Gliolan and before start of anaesthesia, the following side effects may occur:

Uncommon side effects (likely to occur in more than 1 of 1,000 patients but less than 1 of 100 patients):
Nausea (unsettled stomach), decrease of blood pressure, skin reactions (for example rash, looking like sunburn).

In combination with anaesthesia and tumour resection further side effects may occur:

Very common side effects (likely to occur in more than 1 of 10 patients):
Mild alterations of blood cell counts (red and white cells, platelets), slight increase of some enzymes (transaminases, γ-GT, amylase) or bilirubin (a bile pigment produced in the liver by breakdown of red blood pigment) in the blood. These changes peak between 7 and 14 days after surgery. The changes will completely resolve within a few weeks. Usually you will not experience any symptoms when these changes occur.

Common side effects (likely to occur in more than 1 of 100 patients but less than 1 of 10 patients):
Nausea (unsettled stomach), vomiting (sickness), neurological disorders (disorders that affect the nervous system like hemiparesis (partial paralysis of one side of the body), aphasia (total or partial loss of ability to use or understand language), convulsions (seizures) and hemianopsia (blindness for half the field of vision in one or both eyes), thromboembolism (blood clots that may obstruct blood vessels).

Uncommon side effects (likely to occur in more than 1 of 1,000 patients but less than 1 of 100 patients):
Decrease of blood pressure.

Very rare side effects (likely to occur in less than 1 of 10,000 patients), including isolated reports:
Hypesthesia (i.e. decrease of your sense of touch); diarrhoea (loose or watery stools).

5. HOW TO STORE GLIOLAN

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Keep the vial in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Gliolan contains
The active substance is 5-aminolevulinic acid hydrochloride. One vial contains 1.17 g of 5-aminolevulinic acid, corresponding to 1.5 g 5-aminolevulinic acid hydrochloride (5-ALA HCl). One ml of reconstituted solution contains 23.4 mg of 5-aminolevulinic acid, corresponding to 30 mg 5-aminolevulinic acid hydrochloride (5-ALA HCl).

What Gliolan looks like and contents of the pack
This medicine is a powder for oral solution. The powder is a white to off-white cake. The reconstituted solution is a clear and colourless to slightly yellowish fluid.
Gliolan is presented in packs of 1, 2 and 10 vials. Not all pack size may be marketed.

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