SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gliolan 30 mg/ml powder for oral solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One ml of reconstituted solution contains 23.4 mg of 5-ALA, corresponding to 30 mg 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 adults 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.

Posology

The recommended dose is 20 mg 5-ALA HCl per kilogram body weight.

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

$$\textit{Number of bottles} = \frac{\textit{Patient body weight (kg)}}{\textit{75 kg/bottle}}$$

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

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

Renal or hepatic impairment

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

Elderly

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

Paediatric population

The safety and efficacy of Gliolan in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Method of administration

The solution should be administered orally three hours (range 2-4 hours) before anaesthesia. Use of 5-ALA under conditions other than the ones used in the clinical trials entail an undetermined risk.

If the surgery is postponed 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.

Precautions to be taken before handling or administering the medicinal product

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance 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 and paresis) 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.

False negative and false positive results may occur with the use of 5-ALA for intraoperative visualisation of malignant glioma. Non-fluorescing tissue in the surgical field does not rule out the presence of tumour in patients with glioma. On the other hand 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.

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 pressure, pulmonary artery systolic and diastolic pressure as well as pulmonary vascular resistance.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should not be exposed to any photosensitising agent up to 2 weeks after administration of Gliolan.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of 5-ALA in pregnant women. Some limited animal studies suggest an embryotoxic activity of 5-ALA plus light exposure (see section 5.3). Therefore, Gliolan should not be used during pregnancy.

Breast-feeding

It is unknown whether 5-ALA or its metabolite protoporphyrin IX (PPIX) is excreted in human 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.

Fertility

There are no data available regarding the influence of 5-ALA on fertility.

4.7 Effects on ability to drive and use machines

Not relevant, the treatment itself will have an influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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 anaesthesia (= active substance-specific side effects)
- combined effects of 5-ALA, anaesthesia, and tumour resection (= procedure-specific side effects).

Most serious side effects include anaemia, thrombocytopenia, leukocytosis, neurological disorders and thromboembolism. Further frequently observed side effects are vomiting, nausea and increase of blood bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase and blood amylase.

Tabulated summary of adverse reactions

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <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 depends 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) Uncommon: brain oedema

	Very rare:	hypaesthesia
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

Description of selected adverse reactions

In a single-arm trial 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. An adverse drug reaction of mild nausea was reported in 1 out of 21 volunteers.

In another single-centre trial, 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 trial including 36 patients with malignant glioma, adverse drug reactions were reported in 4 patients (mild diarrhoea in one patient, moderate hypaesthesia in another patient, moderate chills in another patient, and arterial hypotension 30 minutes after application of 5-ALA in another patient). 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 trial surgery. Another patient accidentally received an overdose of the medicinal product (3,000 mg instead of 1,580 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-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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 (3,000 mg instead of 1,580 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: Antineoplastic agents, sensitisers used in photodynamic therapy, ATC code: L01XD04

Mechanism of action

5-ALA is a natural biochemical precursor of heme that is metabolised in a series of enzymatic reactions to fluorescent porphyrins, particularly PPIX. 5-ALA synthesis is regulated by an intracellular pool of free heme via a negative feedback mechanism. Administration of excess exogenous 5-ALA avoids the negative feedback control, and accumulation of PPIX occurs in target tissue. In the presence of visible light, fluorescence of PPIX (photodynamic effect) in certain target tissues can be used for photodynamic diagnosis.

Pharmacodynamic effects

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, 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. oligodendroglioma) no fluorescence could be observed after application of the active substance. Medulloblastomas or brain metastases revealed inconsistent results 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.

Clinical efficacy and safety

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 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 ($p<0.0001$).

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 trial; however, it 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 intracellularly metabolised to fluorescent porphyrins, predominantly PPIX.

Absorption

5-ALA 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 is 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.

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 administration does not influence the function of the gastrointestinal and central nervous system. A slight increase in saluresis cannot be excluded.

Single administration of high doses of 5-ALA 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.

Phototoxicity observed after 5-ALA 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 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

Unopened bottle

4 years.

Reconstituted solution

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

6.4 Special precautions for storage

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless type I glass bottle with butyl rubber stopper containing 1.5 g powder for reconstitution in 50 ml of drinking water.

Pack sizes: 1, 2 and 10 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The oral solution is prepared by dissolving the amount of powder of one bottle in 50 ml of drinking water. One bottle of Gliolan 30 mg/ml powder for oral solution reconstituted in 50 ml of drinking water corresponds to a total dose of 1,500 mg 5-aminolevulinic acid hydrochloride (5-ALA HCl). The reconstituted solution is a clear and colourless to slightly yellowish fluid.

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

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

7 MARKETING AUTHORISATION HOLDER

photonamic GmbH & Co. KG
Eggerstedter Weg 12
25421 Pinneberg
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 45451/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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