**Gliolan® Guidance**

**Introduction**

Gliomas are by far the most common type of primary brain tumours. In adults the most commonly encountered of these are high grade or malignant neoplasms of astrocytic and oligodendrocytic lineage, such as glioblastoma multiforme (GBM). Though the prognosis of GBM remains poor, treating patients in an attempt to improve quality of life is worthwhile. Available treatment options include surgery, radiotherapy and chemotherapy.

One goal of surgery is to remove as much of the tumour as possible without damaging the neighbouring healthy brain tissue. Resection can improve a patients’ quality of life by alleviating symptoms, improving progression free survival and bettering the chances for other treatments, such as radiotherapy or chemotherapy to be effective.

Even for experienced neurosurgeons, it is very difficult to define the margins of a high grade glioma tumour during surgery. In the vast majority of cases, there is no sharp demarcation between the tumour and normal tissue. This can result in unintentional removal of healthy tissue or failure to remove malignant tissue. Therefore a method that improves intraoperative visualisation of malignant tissue is desirable.

**5- Aminolevulenic acid (Gliolan®)**

Gliolan® is a powder for oral solution usually administered orally three hours (range 2-4 hours) before induction of anaesthesia.

Aminolevulenic acid hydrochloride (5-aminolevulinic acid HCL; 5-ALA) is a prodrug that is metabolised intracellularly to form the fluorescent molecule protoporphyrin IX (PPIX). The exogenous application of 5-ALA leads to a highly selective accumulation of PPIX in tumour cells and epithelial tissues. Following excitation with blue light, the PPIX, which is accumulated selectively in the malignant glioma tissue, emits a red-violet light. This phenomenon is exploitable to guide tumour resection.

5-ALA is licensed in adult patients for visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV).

A multicentre randomised controlled phase III trial of fluorescence-guided surgery with 5-aminolevulinc acid resection of malignant glioma concluded that the data showed benefit in patients in terms of increased tumour removal and progression free survival on removal of tumours by use of 5-ALA induced fluorescence guidance1. A further study of resection and survival in glioblastoma multiforme analysed patients from the 5-ALA trial and concluded that differences in survival depending on resection status, strongly support a causal influence of resection status on survival2.

NICE Brain tumour and metastases guidance July 2018 section 1.2.36 states ‘ if a person has a radiologically enhancing suspected high-grade glioma and the multi-disciplinary team thinks that surgical resection of all enhancing tumour is possible, offer 5-aminolevulinic acid (5-ALA)- guided resection as an adjunct to maximise resection at initial surgery.’3

**Adverse effects**

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

1) Immediate reactions occurring after oral administration of Gliolan® before induction of anaesthesia (=active substance side effects)

2) Combined effects of 5-ALA, anaesthesia, and tumour resection (=procedure specific side effects)

**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 rather than the effect of the drug. The use therefore should be restricted to fully trained oncological neurosurgeons who have received specific instructions in the use of the drug.

|  |  |
| --- | --- |
| Blood and lymphatic system disorders | Very common: anaemia, thrombocytopenia, leukocytosis |
| Nervous system disorders | Common: neurological disorders  Very rare: Hypoesthesia |
| 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 |

**Product Details**

Gliolan® is a white to off white powder cake. One vial contains 1.5g of 5-ALA HCl. A 30mg/ml oral solution is prepared by dissolving the amount of powder of one vial in 50ml of sterile water e.g. sterile water for irrigation. The reconstituted solution is a clear and colourless to slightly yellowish fluid.

The vial is a single use vial, and any remainder should be discarded after first use.

**Storage**

The vial must be kept in the outer carton in order to protect from light.

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

**Nominated Neurosurgeons**

Gliolan® 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.

## PATIENT SELECTION AND MONITORING

## Patient Selection Criteria

* Patient with suspected diagnosis of high grade glioma (WHO grade III and IV)
* Tumour should be in a location where the operating surgeon feels is suitable for radical resection.
* Operation is to be completed by a neurosurgeon trained in the use of Gliolan®

## Contra-Indications

* Hypersensitivity to 5-ALA or porphyrins
* Acute or chronic types of porphyria
* Pregnancy

## Precautions

In patients with pre-existing cardiovascular disease, Gliolan® 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.

No clinical studies have been performed in patients with clinically relevant hepatic or renal impairment, and therefore use in these patients should be with caution.

## Operative Procedure

The use of Gliolan® must only be under the direct involvement of a neurosurgeon specifically trained in its use.

# Dosage

The recommended dose is 20mg 5-ALA HCL per kilogram body weight. The number of mls of oral solution that should be administered to provide the required dose should be administered according to the dosing table (Appendix 1). Under local protocol, patients who weigh between 75kg -100kg, one vial is to be administered, (i.e. 1500 mg maximum dose or 50 ml of oral solution). For patients over 100kg, the dose should be confirmed after a discussion between the consultant and the pharmacist.

## Timing of dose

The solution should be administered orally 3 hours (range 2-4 hours) before induction of anaesthesia. In the event of an unexpected delay between administration of Gliolan®, further doses will not be given but fluorescence should be attempted as studies shows there is significant tumour to brain ratio for up to 9 hours after administration. Further doses could be given after 24 hours from the first dose provided informed consent has been obtained.

## Intra-Operative Precautions

# 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 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 1cm 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.

## Post-Operative care

After administration of Gliolan®, exposure of eyes and skin to strong light sources (e.g.: operating illumination, direct sunlight or brightly focused indoor lights) should be avoided for 24 hours. Advise patients to cover up in direct sunlight and avoid sun beds and sun lamps for 2 weeks. Co-administration with other potentially phototoxic substances should be avoided. (Appendix 2)

Potentially hepatotoxic medicinal products should be avoided for 24 hours after administration of Gliolan®.

**References**

1. Stummer et al; Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial; Lancet Oncol; 2006; 7; 392-401

2. Pichlmeier et al; Resection and survival in glioblastoma multiforme: An RTOG recursive partitioning analysis of ALA study patients; Neuro-Oncology; 2008; 10; 1025-1034

3. NICE; Brain tumours (primary) and brain metastases in adults; NG 99; July 2018; Available at: <https://www.nice.org.uk/guidance/ng99>; Accessed on: 16/11/18

**Contacts**

Contact the consultant Neurosurgeons Mr Critchlry, Mr Epaliyanage or Mr Bucur for further advice on using this drug.

**Appendix 1 – Dose and Volume of Gliolan® to be administered per body weight**

|  |  |  |
| --- | --- | --- |
| Body weight (Kg) | Dose of Gliolan® to be administered (mg) | Volume of (30mg/ml) solution to be administered (mls) |
| 50 | 1000 | 33 |
| 51 | 1020 | 34 |
| 52 | 1040 | 35 |
| 53 | 1060 | 35 |
| 54 | 1080 | 36 |
| 55 | 1100 | 37 |
| 56 | 1120 | 37 |
| 57 | 1140 | 38 |
| 58 | 1160 | 39 |
| 59 | 1180 | 39 |
| 60 | 1200 | 40 |
| 61 | 1220 | 41 |
| 62 | 1240 | 41 |
| 63 | 1260 | 42 |
| 64 | 1280 | 43 |
| 65 | 1300 | 43 |
| 66 | 1320 | 44 |
| 67 | 1340 | 45 |
| 68 | 1360 | 45 |
| 69 | 1380 | 46 |
| 70 | 1400 | 47 |
| 71 | 1420 | 47 |
| 72 | 1440 | 48 |
| 73 | 1460 | 49 |
| 74 | 1480 | 49 |
| 75 | 1500 | 50 |
| 75-100 | 1500 | 50 |
| 100+ | discuss with consultant and pharmacist | |

**Appendix 2 – Photosensitizing drugs to avoid**

Tetracyclines e.g. doxycycline

Sulfonamides e.g. co-trimoxazole (Septrin®), sulphonylureas e.g. Gliclazide, diuretics (particularly the thiazide type)

Fluoroquinolones e.g. ciprofloxacin

Hypericin or St. John’s Wort extracts

Amiodarone

Hydroxychloroquine, Chloroquine (antimalarial) and Quinine

Isotretinoin

Methotrexate

These drugs should be avoided where possible or the patient should be advised to take sun protective measures (covering up when outdoors) for up to two weeks after the operation.

This list contains the drugs most commonly seen and likely to cause a reaction and does not contain all photosensitizing agents. Please consult with a pharmacist for further information if required.

**Appendix 1: 5 ALA protocol** 

All patients in whom 5-ALA is being considered should be discussed in Neurosciences Multidisciplinary meeting.

MDM discussion confirms

1. Appearance of a newly diagnosed/recurrent high grade glioma

2. Maximal resection feasible (>90%)

3. No contraindications –known porphyria, hepatopathy, severe cardiovascular disease and renal insufficiency

4. Age over 18 years old

If yes – suitable for 5-ALA

If no – consider other surgical interventions

Patient to be reviewed/ consented in clinic by nominated neuro-oncology consultant neurosurgeon

Consultant only prescription

Must include patient`s weight and time/date of administration

Consultant to inform Pharmacist

Anaesthetic consultant to be informed in advance of operation date

Theatre staff to ensure microscopes with 400nm fluorescence filter is available in advance.

Site manager and Neurosciences Bed manager to be informed of surgery date and that surgery will need to proceed on basis of extended recovery and HDU bed to be found later.

Patient to be admitted to the ward day before surgery

Neurosurgeon to ensure patient is allocated a side room pre and post operatively.

Check patient`s weight. Reweigh accurately, without shoes.

Pharmacist to ensure delivery of Gliolan® to the ward

Consultant to ensure Gliolan® 20mg/kg is prescribed and indicate time of administration

Day of surgery

Gliolan® to be administered as prescribed 3 hours pre anaesthesia. Each vial to be reconstituted with 50ml of sterile water.

Patient transfer to recovery with light avoidance precautions – subdued lighting in recovery.

Surgeon to take required precautions regarding light exposure during surgery.

Post-operative care

Patient to be cared for away from direct light for 24 hours.

To avoid direct sunlight, sun beds and sun lamps for 2 weeks