RISK MANAGEMENT PLAN

Active substance(s) (INN or common name):	5-Aminolevulinic acid hydrochloride
Pharmaco-therapeutic group (ATC Code):	L01XD04
Name of Marketing Authorisation Holder or Applicant:	medac Gesellschaft für klinische Spezialpräparate mbH Theaterstrasse 6 D-22880 Wedel / GERMANY
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name[s]):	Gliolan 30 mg/ml powder for oral solution
Data lock point for this RMP:	07/03/2015
Version number:	10
Date of final sign off:	11/12/2015

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ABBREVIATIONS:

ADR	Adverse Drug Reaction
AED	Antiepileptic Drug
5-ALA	5-Aminolevulinic Acid
5-ALA*HCl	5-Aminolevulinic Acid Hydrochloride
ALAT (SGPT)	Alanine Transaminase
ASAT (SGOT)	Aspartate Transaminase
CTC	Common Toxicity Criteria
CTD/eCTD	(Electronic) Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FL	Fluorescence Light
GBM	Glioblastoma Multiforme
γGT	Gamma Glutamyltransferase
HLT	High Level Term
ICSR	Individual Case Safety Reports
IV	Intravenously
MRI	Magnetic Resonance Imaging
LDH	Lactate Dehydrogenase
PFS	Progression Free Survival
PIL	Patient Information Leaflet
PO	Per os
PPIX	Protoporphyrin IX
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
pts.	Patients
RMP	Risk Management Plan
SmPC	Summary of Product Characteristic
SOC	System Organ Class
TUR	Transurethral Resection
WHO	World Health Organisation
WL	White Light

PART I: PRODUCT OVERVIEW

Administrative information on the RMP

Part	Module/annex	Date last updated for submission (sign off date)	Version number of RMP when last submitted
Part II Safety Specification	**SI** Epidemiology of the indication and target population(s)	11/12/2015	10
	SII Non-clinical part of the safety specification	11/12/2015	10
	SIII Clinical trial exposure	11/12/2015	10
	SIV Populations not studied in clinical trials	11/12/2015	10
	SV Post-authorisation experience	11/12/2015	10
	SVI Additional EU requirements for the safety specification	11/12/2015	10
	SVII Identified and potential risks	11/12/2015	10
	SVIII Summary of the safety concerns	11/12/2015	10
Part III Pharmacovigilance Plan		11/12/2015	10
Part IV Plan for post-authorisation efficacy studies		11/12/2015	10
Part V Risk Minimisation Measures		11/12/2015	10
Part VI Summary of RMP		11/12/2015	10
Part VII Annexes	**ANNEX 1** EudraVigilance Interface	11/12/2015	10
	ANNEX 2 Current or proposed SmPC/PIL	11/12/2015	10
	ANNEX 3 Worldwide marketing status by country	11/12/2015	10
	ANNEX 4 Synopsis of clinical trial programme	11/12/2015	10
	ANNEX 5	11/12/2015	10

Part	Module/annex	Date last updated for submission (sign off date)	Version number of RMP when last submitted
	Synopsis of pharmacoepidemiological study programme		
	ANNEX 6 Protocols for proposed and on-going studies in Part III	11/12/2015	10
	ANNEX 7 Specific adverse event follow-up forms	11/12/2015	10
	ANNEX 8 Protocols for studies in Part IV	11/12/2015	10
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	11/12/2015	10
	ANNEX 10 Details of proposed additional risk minimisation activities	11/12/2015	10
	ANNEX 11 Mock up examples	11/12/2015	10
	ANNEX 12 Other supporting data	11/12/2015	10

QPPV name	Dr. med Hans-Jürgen Kühnel
QPPV signature	[redacted]
Contact person for this RMP	
E-mail address or telephone	
Number of contact person	1

Overview of versions:

Version number of last agreed RMP	
Version number:	9
Agreed within:	Central

Current RMP versions under evaluation:

RMP Version number	Submitted on	Submitted within
-		

Invented name in the European Economic Area (EEA)	Gliolan 30 mg/ml powder for oral solution
Authorisation procedure	Centralised
Brief description of the product	
Chemical class	Porphyrin precursor
Summary of mode of action	Aminolevulinic acid hydrochloride (5-aminolevulinic acid HCl; 5-ALA*HCl) is a prodrug that is metabolised intracellularly to form the fluorescent molecule protoporphyrin (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 (λ = 400 - 410 nm), the PPIX, which has accumulated selectively in the malignant tissue, emits a red-violet light. This phenomenon is exploitable to guide tumour resection.
Important information about its composition	None
Indication(s) in the EEA	
Current (if applicable)	Gliolan is indicated for visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV).
Proposed (if applicable)	Not applicable
Posology and route of administration in the EEA	
Current (if applicable)	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.
Proposed (if applicable)	Not applicable
Pharmaceutical form(s) and strengths	
Current (if applicable)	Powder for oral solution; One vial contains 1.17 g of 5-aminolevulinic acid, corresponding to 1.5 g 5-aminolevulinic acid hydrochloride (5-ALA*HCl). 1 ml of reconstituted solution contains 23.4 mg of 5-aminolevulinic acid, corresponding to 30 mg 5-aminolevulinic acid hydrochloride (5-ALA*HCl).
Proposed (if applicable)	Not applicable

Country and date of first authorisation worldwide: EU + NO, IS, LI 07/09/2007

Country and date of first launch worldwide	DE	15/01/2008
Country and date of first authorisation in the EEA	EU + NO, IS, LI	07/09/2007

Is the product subject of additional monitoring in the EU? No

PART II: SAFETY SPECIFICATION

MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Epidemiology of the disease

Gliomas comprise a heterogeneous group of neoplasms that differ in location within the central nervous system, age and sex distribution, growth potential, extent of invasiveness, morphological features, tendency for progression, and response to treatments. In adults, the most frequently encountered of these are high-grade or malignant neoplasms of astrocytic and oligodendrocytic lineage, such as anaplastic astrocytoma, anaplastic oligodendroglioma, and glioblastoma multiforme (GBM), respectively.

GBM represents the most frequent brain tumours in adults. In most European and North American countries, incidence is approximately 2-3 new cases per 100,000 people per year. They may occur at any age, but 60% of cases are seen in patients between 55 and 74 years of age. The disease often progresses rapidly over 2 to 3 months, is incurable, and median overall survival is approximately one year. Therefore, prevalence of the disease is surely not much larger than the double incidence rate, namely 4-6 per 100,000. However, exact data on this subject are lacking because of the rareness of this disease.

In spite of the incurability of the disease, quality and prolongation of the patient's life can usually be increased by surgery. However the removal of the tumour is complicated even for experienced neurosurgeons due to its location and its fuzzy demarcation to normal tissue. Optical markers for detection of the tumour aim to improve the result of the cancer surgery.

Indication	**Malignant glioma WHO grade III and IV**
Brand names of the concerned products (with this indication):	Gliolan 30 mg/ml powder for oral solution
Incidence and prevalence	Incidence: 2-3 new cases per 100,000 per year Prevalence: estimated 4-6 per 100,000
Demographics of the target population – age, sex, race/ethnic origin	60% of cases are seen in patients between 55 and 74 years of age; the disease is 1.5 times more common in men than in women. There are no hints in the literature with respect to specific inter-country variation of this disease.
Risk factors for the disease	Possible risk factors include therapeutic ionising radiation, employment in synthetic rubber manufacturing, petroleum refining or production work, and exposure to vinyl chloride or pesticides.[20]
Main treatment options	Surgery – Surgery is usually the first therapeutic modality. Removal of the tumour is often complicated by its nature and by its location. Sometimes only partial removal (debulking) of the tumour is possible. However, the treatment aims to improve quality and prolongation of life. Radiation therapy – Postoperative radiotherapy is a standard treatment for patients with malignant glioma. Chemotherapy – Clinical trials with chemotherapeutic agents showed only marginal significant results.

Mortality and morbidity (natural history)	The disease is incurable.

SI.2 Concomitant medication(s) in the target population

Indication	Concomitant medication(s)
Malignant glioma WHO grade III and IV	*Corticosteroids* All patients usually receive corticosteroids. *Antiepileptic drugs (AEDs)* All glioma patients undergoing fluorescence-guided surgery are frequently treated with AEDs to control concomitant epileptic seizures. *Anaesthetics* All patients receive anaesthetics during surgery. Gliolan 30 mg/ml should be administered approx. 3 hours prior to induction of anaesthesia.

SI.3 Important co-morbidities in the target population

Information is available from the randomised trial MC-ALS.3/GLI. Within this trial concomitant illnesses at baseline were documented in 64.2% of patients in a fluorescence light (FL)-group and in 65.9% of patients in a white light (WL)-group. The most frequent co-morbidities are listed below.

Indication	Important co-morbidities
Malignant glioma WHO grade III and IV	Cardiovascular disorders, general - Arterial hypertension Endocrine disorders Metabolic and nutritional disorders - Hypercholesterolaemia - Obesity Myo endo pericardial & valve disorders Musculo-skeletal system disorders Respiratory system disorders Urinary system disorders

The system organ classes (according to WHO) affected most frequently were general cardiovascular disorders (FL: 37.5% vs. WL: 35.8%), endocrine disorders (FL: 15.3% vs. WL: 17.3%), metabolic and nutritional disorders (FL: 15.3% vs. WL: 15.0%), musculo-skeletal system disorders (FL: 5.7% vs. WL: 6.9%), myo-, endo-, pericardial & valve disorders (FL: 7.4% vs. WL: 9.2%), respiratory system disorders (FL: 5.1% vs. WL: 6.9%) and urinary system disorders (FL: 2.8% vs. WL: 8.1%).

MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Toxicity studies - Single dose toxicity, repeat-dose toxicity, genotoxicity, local tolerance and phototoxicity experiments were performed by medac GmbH using 5-ALA*HCl. The experiments were done under light protection (except phototoxicity study), in order to exclude potential phototoxic reactions.

Long-term carcinogenicity studies have not been performed. However, the therapeutic indication considers a single oral treatment with 5-ALA*HCL only once before surgery and the prognosis of the target population is poor (median survival approximately 1 year).

Safety pharmacology - Safety pharmacology experiments have been performed by medac in order to evaluate the effects of 5-ALA*HCl on the gastro-intestinal, the central nervous, the renal and the cardiovascular systems in the guinea pig, mouse, rat and dog. The experiments have been conducted under light protection, in order to exclude potential phototoxic reactions.

Drug interactions - No special drug interaction studies have been performed by medac. From the literature it is known that melatonin and vitamin E protect against 5-ALA-induced oxidative toxicity in rat brain regions. L-tryptophan, reduced glutathione, N-acetylcysteine, melatonin, L-methionine, L-cysteine, mannitol and glycine are protective agents with regard to 5-ALA-induced photodamage in vitro. For more details see CTD 2.4.1.4.

Key safety findings (from non-clinical studies)	Relevance to human use
Toxicity including	
Single and repeat-dose toxicity	
Increase of bilirubin, transaminases	Yes; also observed in patients
Bile duct changes/lesions; intrahepatic cholestasis	No; not observed in patients
Increase of lactate dehydrogenase (LDH), cholesterol, creatinine, and calcium	No, not observed in patients
Ataxia, dyspnoea, and slow gait immediately after injection	No, not observed in patients
Emesis	Yes; also observed in patients
Reproductive toxicity	
Not done	
Developmental toxicity	
5-ALA combined with light exposure resulted in dose-dependent detrimental effects on pregnancies and resorption of early pregnancies in rats.	No; for photodynamic diagnosis of malignant glioma it is unlikely that tissues/organs with reproductive function are illuminated
Nephrotoxicity	
Not done	
Hepatotoxicity	
Not done	
Genotoxicity	

Key safety findings (from non-clinical studies)	Relevance to human use
Potential photogenotoxicity could not be excluded.	No. Considering the fact, that Gliolan is intended to be used only once before surgery, potential photogeno-toxicity is not an important issue for this substance.
Carcinogenicity	
Not done	
Phototoxicity	
Dose- and time-dependent phototoxic reactions	Yes. Phototoxic reactions have also been observed in patients.
General safety pharmacology	
Cardiovascular toxicity	
Hypotension	Yes; also observed in patients
Nephrotoxicity	
Slight increase in saluresis	No, not observed in patients
Mechanism of drug interactions	
Not done	
Other toxicity-related information or data	
Not done	

The company considers that further non-clinical studies are not required.

Conclusions on non-clinical data

The following table lists those safety concerns from non-clinical data that have
- been confirmed by clinical data,
- have not been adequately refuted by clinical data,
- which are of unknown significance,
- or where further research needed.

Safety concern from this module	
Important identified risks (confirmed by clinical data)	Increase of bilirubin, transaminases Emesis Phototoxic reactions Hypotension
Important potential risks (not refuted by clinical data or which are of unknown significance)	None
Missing information	None

MODULE SIII CLINICAL TRIAL EXPOSURE

SIII.1 Brief overview of development

Even for experienced neurosurgeons, it is very difficult to define the margins of a GBM tumour during surgery.[11] In many cases, there is no sharp demarcation between 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 would be helpful. In the past, numerous attempts have been made to develop optical markers for the detection of tumours in order to improve the clinical results of cancer surgery. The substances studied (tetracycline, methylene blue, semi-synthetic porphyrins like Photofrin®) showed low sensitivity as well as an unfavourable benefit/risk ratio due to side effects. The advantages of 5-ALA for making GBM tumours more visible are its endogenous origin (from heme metabolism) and good tolerability after local, oral or intravenous use.

In total, 6 clinical trials were performed addressing different objectives listed in the table below.

Study ID	Study title	Objectives	Study report location
MC-ALS. 20/BV	Single dose study on the absolute bioavailability of oral doses of 20 mg/kg b.w. 5-aminolevulinic acid in comparison to 2 mg/kg b.w. intravenous administration in healthy male subjects	Absolute bioavailability IV vs PO; Duration of photosensitisation	5.3.1.1
MC-ALS. 8-I/ GLI	Clinical phase I/II study on 5-aminolevulinic acid hydrochloride (5-ALA) for the fluorescence-guided resection of malignant gliomas	Detection of a dose-efficacy relationship between the dose levels and extent/quality of fluorescence in the tumour core	5.3.4.2
MC-ALS. 28/ GLI	Clinical Phase II Trial of 5-Aminolevulinic Acid Hydrochloride (5-ALA, 5-ALS) for Fluorescence-guided Resection of Malignant Gliomas	To determine the positive predictive value of tumour fluorescence for tumour cell identification	5.3.5.2
MC-ALS. 3/ GLI	Fluorescence-guided resection of malignant gliomas with 5-Aminolevulinic acid (5-ALA) vs Conventional resection	To determine how accurately contrast agent-accumulating tumour can be removed by primary surgery using 5-ALA and to assess the clinical benefit of this procedure	5.3.5.1
MC-ALS. 30/GLI	Clinical phase II trial of MC 506/1 for fluorescence-guided resection of malignant gliomas in progression therapy	To determine the positive predictive value of tissue fluorescence	5.3.5.2
MC-ALS. 32/GLI	Clinical investigation of fluorescence-guided resection of malignant gliomas with 5-amino-levulinic acid	To determine the incidence of adverse events after fluorescence-guided resection of malignant gliomas (WHO grade III or IV) using 5-aminolevulinic acid	5.3.5.2

MC-ALS.20/BV - The first clinical trial aimed primarily to determine the absolute bioavailability of the oral solution of 5-ALA*HCl in 12 healthy subjects. Furthermore, pharmacokinetic parameters of 5-ALA and its major metabolite PPIX were determined. The second part of this trial included additional 9 subjects and aimed to measure the extent and duration of skin photosensitisation after oral administration of 5-ALA*HCl. This was done by measuring the Minimal Erythema Dose and the corresponding PPIX plasma concentrations.

MC-ALS.8-I/GLI - The aim of this study was to discover the optimal dose of 5-ALA*HCl for oral use in fluorescence-guided brain tumour surgery. Three dose levels were investigated (0.2, 2, and 20 mg/kg b.w. 5-ALA*HCl). Optimal dose was chosen by comparing in each dose group the global fluorescence extent (how much of the tumour identified under white light conditions was fluorescent) and fluorescence quality (strong, weak or no fluorescence) of the tumour core at the end of operation after the tumour had been resected. As an objective control of the subjective assessment of the fluorescence quality, selected areas from the tumour core and margin with strong, weak or no fluorescence were measured spectrophotometrically. Furthermore, the histology of tumour samples taken from the selected areas were compared with the spectrometric fluorescence measurements. Finally, this study provided additional pharmacokinetic data for 5-ALA and its major metabolite PPIX.

MC-ALS.28/GLI – This trial's objective was to determine the positive predictive value of 5-ALA-induced tissue fluorescence for tumour cell detection. For this purpose, the percentage of patients showing positive tumour cell identification in all biopsies taken from areas of weak and strong fluorescence was registered. Additionally, the quality of the fluorescent and non-fluorescent tissue adjacent to fluorescent tissue areas as well as the tumour distant cortex was evaluated. Finally, residual fluorescence observed intraoperatively was compared with contrast enhancement in early postoperative magnetic resonance imaging (MRI).

MC-ALS.3/GLI – This trial aimed to assess the clinical usefulness of 5-ALA-guided brain tumour surgery. For this purpose, patients were randomised to receive or not receive 20 mg/kg 5-ALA*HCl prior to surgery. Efficacy was determined by measuring the completeness of tumour resection (percentage of patients with a histologically confirmed malignant glioma without definite residual contrast-enhancing tumour in the early post-operative control MRI) as well as the progression-free survival rate (PFS) at the 6 months-visit after primary surgical treatment.

Sample size was determined by assuming a 20% point increase in tumour-free resection (30% in the control group vs 50% in the 5-ALA group) and 15% point increase in progression-free survival rate at 6-months-visit (25% vs 40%). 350 patients were required in the Full-Analysis-Set to provide 80% power within experiment-wise type I error of 0.05. To allow for early stopping, an interim analysis for the second primary efficacy criterion was foreseen with 270 patients. A total of 415 patients were randomly assigned to undergo either fluorescence-guided resection (FL-group) or standard white light surgery (WL-group) in a 1:1 ratio to yield 349 patients qualifying for the Full-Analysis-Set.

All 4 trials described above provided important safety data for the oral use of 5-ALA*HCl. In total, the submitted data package includes safety data from 265 subjects or patients who have been treated with the proposed oral dose regimen (1 x 20 mg/kg b.w. 5-ALA*HCl).

Two additional trials were performed with Gliolan in glioma patients, MC-ALS.30/GLI and MC-ALS.32/GLI, subsequent to submission for approval. All patients were treated with the approved dose schedule.

MC-ALS.30/GLI – The trial aimed to determine the positive predictive value of 5-ALA-induced tissue fluorescence for tumour cell detection in patients with recurrent gliomas (similar to study MC-ALS.28/GLI which, however, was performed in newly diagnosed glioma patients).

MC-ALS.32/GLI – The trial was launched after recruitment to the phase III trial MC-ALS.3/GLI had been terminated. Primary objective was to determine the incidence of adverse events after 5-ALA-supported fluorescence-guided resection of newly diagnosed patients with malignant gliomas. Secondary objectives were the observance of the patient's Karnofsky Performance Score as well as the determination of the overall survival. This trial was launched instead of a "Compassionate Use" programme because the legal base for "Compassionate Use" in Germany was not yet defined.

5-ALA*HCL was used in patients with malignant glioma (WHO grade III/IV) to visualize the malignant tissue during surgery. The majority of patients (> 85%) included into the clinical studies suffered from WHO grade IV gliomas, and only a small percentage of patients had a diagnosis of a WHO grade III tumour. All patients were previously untreated for their brain tumour.

The selection of patients represent the typical population of patients with malignant gliomas as can be seen by a comparison with another recently published study in 573 glioma patients (mean age ≈ 57 years; ≈ two thirds of patients older than 50 years, males/females ≈ 2:1).[19]

SIII.2 Clinical trial exposure

In total, 541 glioma patients have been treated with 5-ALA*HCL within 5 clinical studies sponsored by medac. Generally, patients receive only 1 administration of Gliolan.

Table 1: Duration of exposure (by indication)

Indication 1: Visualisation of malignant tissue during surgery for malignant glioma

Duration of exposure (at least)	Persons	Person time
Cumulative up to 1m	541	1 day
Total person time	541	1 day

Table 3: By dose (by indication)

Indication 1: Visualisation of malignant tissue during surgery for malignant glioma

Dose of exposure	Persons	Person time
0.2 mg/kg	7	1 day
2 mg/kg	7	1 day
20 mg/kg	527	1 day
Total	541	1 day

Table 5: By age group and gender (by indication)

Indication 1: Visualisation of malignant tissue during surgery for malignant glioma				
Age group	**Persons**		**Person time**	
	M	F	M	F
18 – 80 years	336	205	1 day	1 day
Total	336	205	1 day	1 day

Table 8: By ethnic or racial origin (by indication)		
Indication 1: Visualisation of malignant tissue during surgery for malignant glioma		
Ethnic/racial origin	**Persons**	**Person time**
Caucasian	541	1 day
Total	541	1 day

Table 10: Special populations (by indication)		
Indication 1: Visualisation of malignant tissue during surgery for malignant glioma		
	Persons	**Person time**
Pregnant women	-	-
Lactating women	-	-
Renal impairment	-	-
Hepatic impairment	-	-
Cardiac impairment	-	-
Sub populations with genetic polymorphism	-	-
Immuno-compromised	-	-

MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Limitations of ADR detection common to clinical trial development programmes

Ability to detect ADRs	Limitation of trial programme	Discussions of implications for target population
Which are rare	541 patients were exposed over the whole clinical trial programme.	Adverse drug reactions (ADR) with a frequency greater than 1 in ~ 180 could be detected if there were no background incidence.
Due to prolonged exposure	Gliolan is only given once before surgery.	Not applicable
Due to cumulative effects	Gliolan is only given once before surgery.	Not applicable
Which have a long latency	Safety data were collected until a maximum of 18 months of follow-up.	Long-term studies have not been performed because 5-ALA*HCL is intended to be used only once before surgery and the prognosis of the target population is poor (median survival approximately 1 year).

SIV.2 Effect of exclusion criteria in the clinical trial development plan

Exclusion criteria which will remain as contraindications	
Criteria	**Implications for target population**
Porphyria	Acute and chronic types of porphyria are listed as contraindication in the SmPC.
Hypersensitivity to porphyrins	Hypersensitivity to the active substance or other porphyrins is listed in the SmPC as a contraindication.
Existing/planned pregnancy/lactation or inadequate contraception	Pregnancy is listed as contraindication in the SmPC.

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criteria**	**Justification for not being a contraindication**
Renal insufficiency (Creatinine > 2.0 mg/dL)	The effects of Gliolan on liver and kidney were not known when the clinical trials were started. In consequence no trials have been performed in patients with clinically relevant hepatic or renal impairment.	It is known that 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. Based on these results the SmPC does not list these criteria as contra-indications but includes the sentence: 'Therefore, this medicinal product should be used with caution in such patients.'
Hepatic insufficiency (Bilirubin > 3 mg/dL; Quick test < 60%; γ-GT > 100 U/L)		

Exclusion criteria which are NOT proposed to remain as contraindications		
Criteria	**Reason for being an exclusion criteria**	**Justification for not being a contraindication**
Other known malignancy (except basaliomas)	Standard exclusion criteria in oncological trails	Not applicable
More than one contrast-enhancing lesion unrelated to the primary tumour or extracerebral metastases	This exclusion criterion was only set in trial MC-ALS.3/GLI that determines how accurately contrast agent-accumulating tumours can be removed by primary surgery.	Not applicable
Tumour location in the midline, basal ganglia, cerebellum or brain stem	The tumour cannot be resected by surgery.	Not applicable
Dementia or mental condition making it impossible to understand the therapy and therefore prohibiting written consent	The patient information sheet, a data clarification form and consent form has to be understood and signed by the patient.	The treatment should be accessible also to patients with dementia or mental conditions.
Simultaneous participation or participation in another clinical trial within the preceding 30 days	Standard exclusion criteria in clinical trials to avoid influence from other treatment	Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Population group	**Comment**
Paediatric population	
Pre-term newborns	Malignant gliomas are not restricted to these age groups but are extremely rare. They account only for 7-9% of all paediatric intracranial tumours and 0.6-7.9% of all glioblastomas in all age groups.[10]
Neonate (birth to 27 days)	
Infants and toddlers (28 days to 23 months)	
Children (2 years to e.g. 11 years)	
Adolescents (e.g. 12 years to 17 years)	
Elderly population	
Use in different age ranges	Malignant gliomas are not restricted to the elderly population. *Stummer et al.* published a sub-analysis of an elderly cohort of the clinical trial MC-ALS.32/GLI and stated a comparable treatment benefit for elderly patients to that observed in younger patients with similar frequency of neurological adverse events.[17]
Need for laboratory screening prior to use	
Effect of multiple co-existing impairments	
ADRs of special concern	
Effect of multiple medications	

Population group	Comment
	No literature is known about any effect of co-existing impairments, effect of multiple medications or ADRs of special concerns. There is no necessity for any laboratory screening prior to use.
Pregnant or breast-feeding women	
Number of pregnancies and outcomes	No pregnancy case was reported or is known from the literature. Subsequently nothing is known about the outcome of pregnancy. Furthermore no literature is available about failed contraceptive measures. Pregnancy is listed as a contraindication for the use of Gliolan. Because it is a prescription medicine it is expected that pregnancy can be ruled out. As per SmPC breast-feeding women are advised to interrupt breast feeding for 24 hours after treatment with the medicinal product.
Analysis of why contraceptive measures failed – i.e. consideration of whether human error or an interaction between product and e.g. oral contraceptives	
Implications for use under less controlled conditions (i.e. if measures failed under the relatively strict conditions of a trial, what will happen in real life, and if necessary suggestions for improvement)	

Population group	Comment
Patients with hepatic impairment	Liver and renal impairments have not been investigated. The SmPC includes the following sentence: 'Pharmacokinetics of 5-ALA in patients with renal or liver impairment has not been investigated.'
Patients with renal impairment	
Patients with other relevant co-morbidity (e.g. cardiovascular or immunocompromised including organ transplant patients)	Relevant co-morbidities were excluded during the clinical trials performed by medac GmbH. The health care professional should decide on the individual background of each patient if the treatment with 5-ALA is reasonable.
Patients with disease severity different from the inclusion criteria in the clinical trial population	The population treated with Gliolan within the clinical trial programme was representative for the population suffering from malignant gliomas.
Sub-populations carrying known and relevant polymorphisms	There are no hints of a reduced efficacy or enhanced toxicity in patients with specific polymorphisms.
Patients of different racial and/or ethnic origin	The clinical trial programme included only Caucasian patients. However, there are no hints that Gliolan's efficacy or safety differs in populations with any other race or in patients with genetic polymorphisms.

SIV.4 Conclusions on the populations not studied and other limitations of the clinical trial development programme

Missing information

Safety concerns due to limitations of the clinical trial programme		Outstanding concern?
Safety concern	**Comment**	**Yes/No**
None	-	No

MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

A change to the reference safety information was requested by the European Medicines Agency (EMA/601086/2013). Brain oedema occurring with an uncommon frequency was added as a procedure-related side effect to the SmPC section 4.8.

The educational training programme for neurosurgeons which aims at reducing the risk for neurological adverse effects was continued. Several training courses for neurosurgeons have been performed since the start of the programme.

SV.2 Non-study post-authorisation exposure

SV.2.1 Method used to calculate exposure

Gliolan 30 mg/ml powder for oral solution is a prescription medicine and is only used once before surgery. Therefore patient exposure can be estimated from the sold number of vials. However a detailed presentation of the data by age and sex is not possible.

SV.2.2 Exposure

Cumulatively 38,942 vials of Gliolan have been sold by medac GmbH worldwide until 07. March 2015. In general, patients receive only one administration of Gliolan. Therefore, one vial is appropriate for one patient. The estimated cumulative patient number is therefore calculated as 38,942 patients. The tables below list the estimated number of persons treated with Gliolan per year within the EU and in Non-EU countries.

By country		
Indication: Visualisation of malignant tissue during surgery for malignant glioma		
2008	**Persons**	**Exposure**
EU Total	1,193	1 vial per patient
Non-EU Total	82	
2009	**Persons**	**Exposure**
EU Total	1,897	1 vial per patient
Non-EU Total	198	
2010	**Persons**	**Exposure**
EU Total	2,654	1 vial per patient
Non-EU Total	1,413	
2011	**Persons**	**Exposure**
EU Total	3,230	1 vial per patient
Non-EU Total	1,264	
2012	**Persons**	**Exposure**
EU Total	3,747	1 vial per patient
Non-EU Total	907	
2013	**Persons**	**Exposure**

By country		
Indication: Visualisation of malignant tissue during surgery for malignant glioma		
EU Total	4,616	1 vial per patient
Non-EU Total	4,629	
2014	**Persons**	**Exposure**
EU Total	5,303	1 vial per patient
Non-EU Total	4,338	
2015*until DLP	**Persons**	**Exposure**
EU Total	727	1 vial per patient
Non-EU Total	2,744	

SV.3 Post-authorisation use in populations not studied in clinical trials

Paediatric use

It is known from literature that 5-ALA*HCl was used in paediatric population.

Beez et al. investigated the feasibility of fluorescence-guided surgery with 5-ALA for resection of brain tumours in children. Sixteen patients (mean age 9 years, range 1-16 years) received a standardised 5-ALA dose according to the published protocol after informed parental consent.[1]

Preuß et al. retrospectively analysed the use of 5-ALA fluorescence guidance in resection of paediatric brain tumours of various entities. 18 patients (13 male, 5 female; age 3-18 years) were analysed.[14]

The European ALA Paediatric Brain Tumour Study Group conducted a survey among certified European Gliolan users to collect data on their experiences with children. Data on 78 patients <18 years of age were submitted by 20 centres.[18]

According to the studies published the use of 5-ALA*HCl in paediatric patients with high grade gliomas is useful and seems to be safe. However it is mentioned that very young children are at an increased risk of suffering from adverse reactions which might be related to differences in 5-ALA metabolism in young children.

Only small groups of children have been observed in these studies. Further studies need to be conducted to investigate the efficacy and safety of Gliolan in the paediatric population.

Elderly use

Elderly patients were included in the clinical trial programme. For example, the patient's age ranged between 23 and 73 in study MC-ALS.3/GLI. *Stummer et al.* published a sub-analysis of an elderly cohort of the clinical trial MC-ALS.32/GLI and stated a comparable treatment benefit for elderly patients to that observed in younger patients with similar frequency of neurological adverse events.[17]

Pregnant or breast feeding women

No cases of pregnant or breast feeding woman exposed to Gliolan are known. Pregnancy and breast feeding are listed as contraindications.

Hepatic impairment

No data is available on patients with hepatic impairment that were exposed to 5-ALA.

Renal impairment

No data is available on patients with renal impairment that were exposed to 5-ALA.

SV.4 Post-authorisation off-label use

EU off-label use		
Off-label category	**Country**	**Source of information**
Use in patients with neurological tumours other than high grade gliomas (non-authorised indication)	Austria (Medical University of Vienna)	Literature: *Millesi et al.* [13]
	Comment	
	Millesi et al. systematically investigated 5-ALA-induced fluorescence characteristics in different spinal tumour entities. Fifty-two patients with 55 spinal tumours were included in the study. The authors conclude that in cases of intramedullary tumours, 5-ALA-induced PPIX fluorescence is a useful tool for the detection of potential residual tumour foci.[13]	
	Country	**Source of information**
	Germany (Department of Neurosurgery, Heinrich-Heine-University)	Literature: *Eicker et al.*[5] , *Cornelius et al.*[2]
	Comment	
	Eicker et al. evaluated the impact of fluorescence-guided surgery in spinal tumour surgery. 26 patients with intradural spinal tumours were included in the study. The study demonstrated that spinal intramedullary gliomas and the majority of spinal intradural meningiomas are 5-ALA positive. As a surgical consequence, especially in intramedullary gliomas, the use of 5-ALA fluorescence seems to be beneficial.[5] *Cornelius et al.* retrospectively analysed the impact of 5-ALA fluorescence-guided surgery on the extent of resection of 31 meningiomas, with special regard to high-grade tumours.[2] This study shows a strong correlation between fluorescence intensity and WHO grade. 5-ALA fluorescence-guided surgery improved the extent of resection in meningiomas.	
Off-label category	**Country**	**Source of information**
Use in patients suffering from meningioma (non-authorised indication)	Italy (Department of Neurosurgery of Padua)	Literature: *Della Puppa et al.(2014)* [3]
	Comment	
	Data from 12 patients affected by bone-invading meningiomas (7 with skull base and 5 with convexity meningiomas) who had undergone surgery with the assistance of 5-ALA fluorescence and neuro-navigation between July 2012 and March 2013 at the Department of Neurosurgery of Padua were retrospectively analysed. *Della Puppa et al.* summarised that 5-ALA fluorescence represents a suitable and reliable technique for identifying and removing bone infiltration by meningiomas. However, further studies are needed to prove the clinical consequences of this promising technique in a larger population.[3]	
Off-label category	**Country**	**Source of information**
Use in patients with bladder cancer (non-authorised indication)	Germany (University of Regensburg)	Literature: *Denzinger et al.*[4]
	Comment	
	Both *in vitro* and *in vivo* studies have demonstrated a selective uptake of 5-ALA and its derivatives within bladder cancer cell lines. *Denzinger et al.* performed a prospective, randomised trial to investigate whether the	

EU off-label use

long-term tumour recurrence and residual tumour rates can be decreased using 5-ALA-fluorescence diagnosis. A total of 301 patients with suspected superficial bladder carcinoma were randomised to transurethral resection using conventional white light or fluorescence light. Of the 301 patients, 191 were available for the efficacy analysis. The residual tumour rate was 25.2% in the WL arm versus 4.5% in the fluorescence diagnosis arm ($P < 0.0001$). The recurrence-free survival rate after 2, 4, 6, and 8 years was 73%, 64%, 54%, and 45% in the WL group and 88%, 84%, 79%, and 71% in the fluorescence diagnosis group, respectively, revealing a statistically significant difference in favour of fluorescent transurethral resection (TUR) ($P = 0.0003$). *Denzinger et al.* concluded that an advantage of decrease bladder tumour recurrence risk was maintaining with high statistical significance for at least 8 years.[4]

Country	Source of information
Germany (Medical Centre of Eberhard Karls University, Tübingen)	Literature: *Stenzl et al.* [16]

Comment

Stenzl et al. conducted a prospective randomised, double-blind, placebo-controlled study in 370 patients with nonmuscle-invasive urinary bladder carcinoma who received either 5-ALA (n = 187) or a placebo (n = 183) intravesically before cystoscopy. The primary study objective was to evaluate the 12-month recurrence-free survival. Slightly more patients with tumours were detected by using 5-ALA than by using the placebo (88.5% vs. 84.7%). The mean numbers of tumour specimens per patient were 1.8 (5-ALA) and 1.6 (placebo). Intrapatient comparison of FL- versus WL-cystoscopy in patients randomised to receive 5-ALA showed a higher tumour detection rate with FL. In patients receiving 5-ALA cystoscopy, the percentage of lesions that would not have been detected in these patients by WL cystoscopy ranged between 10.9% (pT1) and 55.9% (atypia). In comparison to placebo, 5-ALA cystoscopy did not increase the rates of recurrence-free (64.0% vs. 72.8%; $P = 0.22$) or progression-free survival (89.4 vs. 89.0%; $P = 0.9$) 12 months after tumour resection.[16]

Although more tumours per patient were detected in the 5-ALA group, the higher detection rate did not translate into differences in long-term outcome.

Country	Source of information
Sweden (Department of Urology, Stockholm)	Literature: *Schumacher et al.* [15]

Comment

Schumacher et al. conducted a randomised, multicentre, observer- and pathologist-blinded, prospective phase 3 clinical trial in which 153 were randomised to FL cystoscopy and 147 to standard WL cystoscopy. All patients were first inspected under WL and all lesions were recorded. Patients randomised to FL underwent a second inspection. TUR was carried out in both groups. Control cystoscopy under WL was performed in all patients every 3 month during the first year after randomisation and biannually thereafter. At the first TUR, the mean number of resection specimens per patient was 2.5 (FL: 2.5; WL: 2.4; $P = 0.37$) and the resulting mean number of resected tumours was 1.7 with FL and 1.8 with WL ($P = 0.85$).[15]

More patients were diagnosed with carcinoma in situ in the WL group (13%) than in

EU off-label use		
	the FL group (4.2%). Within-patient comparison of FL patients only showed that FL detected more lesions than WL. Tumour lesions solely detected by FL cystoscopy that would not otherwise be detected by WL cystoscopy included 52% dysplasia, 33% CIS, 18% papillary neoplasms, 13% pT1, and 7% pTa. Outcome at 12 month did not show any difference between groups with regard to recurrence-free and progression-free survival rates.[15] This study did not find a clinical advantage of FL cystoscopy compared with WL cystoscopy and TUR.	
Off-label category	**Country**	**Source of information**
Use in paediatric population (non-autho-rised population)	Germany (University Hospital Leipzig, Leipzig)	Literature: *Preuß et al.* [14]
	Comment	
	Preuß et al. analysed retrospectively the use of 5-ALA fluorescence guidance in resection of paediatric brain tumours (18 patients; 13 male, 5 female; age 3-18 years). 5-ALA was administered according to the adult protocol, with 20 mg/kg, 2 h before induction of anaesthesia. Fluorescence guidance was most useful for recurrent glioblastoma resection. Medulloblastoma tissue displayed fluorescence only inconsistently, and most pilocytic astrocytoma remained without staining. Ganglioglioma showed partial staining in the central tumour areas, without allowing the use for circumferential resection.[14]	
	Country	**Source of information**
	Germany (Heinrich-Heine -Universität, Düsseldorf)	Literature: *Beez et al.* [1]
	Comment	
	Beez et al. reported on the use of 5-ALA in paediatric brain tumours. Sixteen patients (mean age 9 years, range 1-16 years) received a standardised 5-ALA dose according to the published protocol after informed parental consent. Histology revealed pilocytic astrocytoma (n = 7), classical medulloblastoma (n = 4), anaplastic astrocytoma (n = 1), glioblastoma (n = 3) and anaplastic ependymoma (n = 1). Positive fluorescence was observed in cases of anaplastic astrocytoma, glioblastoma, and medulloblastoma, respectively. Significant increases were registered for alanine aminotransferase (14.92 ± 1.106 U/L vs. 37.70 ± 3.795 U/L; P = 0.0020) and gamma glutamyl transpeptidase (12.69 ± 1.638 U/L vs. 39.29 ± 6.342 U/L, P = 0.0156), correlated with young age. No further adverse reactions were evident. Positive fluorescence was observed in two high-grade gliomas and one medulloblastoma after oral administration of 5-ALA. Thus, 5-ALA appears capable of inducing fluorescence in paediatric high-grade tumours. Adverse reactions observed in children were similar to those reported for adults, although very young children might be at increased risk.[1]	
	Country	**Source of information**
	Germany (Department of Neurosurgery, Universitätsklinikum Münster, Münster)	Literature: *Stummer et al.*[18]
	Comment	
	The European ALA Paediatric Brain Tumour Study Group conducted a survey	

EU off-label use	
	among certified European Gliolan users to collect data on their experiences with children. Data on 78 patients <18 years of age were submitted by 20 centres. Fluorescence was found useful in 12 of 14 glioblastomas (85%), four of five anaplastic astrocytomas (60%), and eight of ten ependymomas grades II and III (80%). Fluorescence was found inconsistently useful in PNETs (three of seven; 43%), gangliogliomas (two of five; 40%), medulloblastomas (two of eight, 25%) and pilocytic astrocytomas (two of 13; 15%).[18] Recursive partitioning analysis of pre-operative factors showed tumours with supratentorial location, strong contrast enhancement and first operation to have a likelihood of useful fluorescence of 64.3%, as opposed to infratentorial tumours with first surgery (23.1%).[18] This survey demonstrates that 5-ALA may be especially useful for contrast-enhancing supratentorial tumours. However, controlled studies in these patients are necessary.

SV.5 Epidemiological study exposure

There were no epidemiological studies performed or funded by medac GmbH. There were no important safety findings during the investigated time period in reports in the scientific and medical literature.

MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for harm from overdose

Since the drug is administered by the physician and since there is no narrow therapeutic margin, intentional overdosage is not a significant issue. In addition, Gliolan is sold in vials containing 1.5 g of the active substance which cannot lead to a significant overdosage.

Within the clinical study programme, one patient (# [redacted] of study MC-ALS.3/GLI) received accidentally a higher dose than planned. [redacted] received 3,000 mg 5-ALA*HCl (instead of 1,580 mg) which corresponds approximately to a dose of 40 mg/kg. During surgery, the patient developed respiratory insufficiency which was managed by adaptation of ventilation. The reaction resolved completely.

Two post-marketing cases of overdose have come to the knowledge of medac GmbH since the first launch of Gliolan in 2007. However, harm from overdosage is not estimated as a risk that has to be addressed particularly.

One case is known by a patient that accidently received 2 g instead of 1.5 g of 5-ALA before fluorescence-guided surgery. The patient suffered from mild redness on head (face and forehead) during the surgery procedure. The redness was attributed notably to exposure to light source during surgery. The not serious adverse event was classified as possibly related.

One post-marketing case is known by a patient who received 2.13 g of 5-ALA instead of the intended 1.278 g due to incorrect reconstitution of 5-ALA which was caused by a lack of communication between the prescriber and the heath professional administering the drug. This report did not lead to any changes regarding the benefit-risk assessment of 5-ALA-containing medac products as it was not accompanied by any symptoms.

SVI.2 Potential for transmission of infectious agents

There is no potential for the transmission of an infectious agent with the administration of 5-ALA*HCl.

SVI.3 Potential for misuse for illegal purposes

Misuse is unlikely since patients do not use or order 5-ALA*HCl themselves. The substance has no risk of addiction.

SVI.4 Potential for medication errors

The drug has to be prescribed by a physician and will be administered by a suitable health care professional. In addition, Gliolan is sold in vials containing 1.5 g active ingredient which does not allow for extreme overdosage. The potential for medical errors is therefore considered as very low.

SVI.4.1 Description of medication errors during the clinical trial programme

Product name(s)				
Description of error	**Number of occurrences**	**Analysis of cause**	**Steps taken to prevent**	**Comment**
Accidental overdose	1	unknown	none	Gliolan is provided in vials that prevent an extreme overdosage.

SVI.4.2 Preventive measures for the final product(s) being marketed

Gliolan 30 mg/ml powder for oral solution is a prescription drug which is an effective measure to prevent misuse for illegal purposes and a first step to reduce medical errors.

To decrease medical errors and to minimise adverse events associated with the Gliolan-fluorescence-guided surgery training courses for neurosurgeons were offered.

SVI.4.3 Effect of device failure

Not applicable

SVI.4.4 Reports of medication errors with the marketed product(s)

Product name(s)				
Description of error	**Number of occurrences**	**Analysis of cause**	**Steps taken to prevent**	**Comment**
Accidental overdose by incorrect reconstitution of 5-ALA	1	Lack of communication between the prescriber and the health professional administering the drug.	None	No adverse event was reported.
Accidental overdose	1	Not known	None	Adverse event: Erythema
Incorrect route of drug administration – Oral formulation was accidentally administered intravenously.	3	Not known	None	No adverse events were reported.

SVI.5 Potential for off-label use

Photodynamic diagnosis and therapy is a promising methodology for the diagnosis and treatment of many epithelial tumours. 5-ALA has been used in several trials in patients with bladder cancer, oesophageal cancer, gastrointestinal cancer, genitourinary cancer, endometriosis, skin cancer and others. Further indications for off-label use have been e.g. meningioma, brain metastases, other solid tumours or paediatric use (see also Part II Module SV.4). The potential for off-label use is estimated as high.

SVI.6 Specific paediatric issues

SVI.6.1 Issues identified in paediatric investigation plans

Not applicable

SVI.6.2 Potential for paediatric off-label use

Glioblastoma is a rare disease in children. The German registry for childhood cancer lists only 148 new cases of astrocytomas (low and high grade) for the year 2003.

However literature reviews and case studies published demonstrating that off-label use of 5-ALA*HCl is an important topic. These reports reveal no new safety concerns but support that the use of Gliolan 30 mg/ml powder for oral solution in paediatric patients with high grade gliomas is useful and seems to be safe.

SVI.7 Conclusions

Safety concern from this module (to be carried through to Part II Module SVIII)	
Safety concern	**Comment**
Use in paediatric population	Due to increased research in paediatric patients careful monitoring of this off-label use is needed. PRAC PSUR assessment report (Procedure no.: EMEA/H/C/PSUSA/00000009/201503) dated 08/10/2015.
Use in patients with brain tumours other than malignant gliomas	Due to increased research in patients with brain tumours other than malignant gliomas (such as meningiomas and metastasis) careful monitoring is needed. PRAC PSUR assessment report (Procedure no.: EMEA/H/C/PSUSA/00000009/201503) dated 08/10/2015.

MODULE SVII – IDENTIFIED AND POTENTIAL RISKS
Non-ATMP version

SVII.1 Newly identified safety concerns (since this module was last submitted)

Since the last submission of this document in October 2010 only one new safety concern was identified. The identified risk 'brain oedema' occurring with an uncommon frequency was added as a procedure-related side effect to the SmPC section 4.8.

Safety concern: Brain oedema	
Details	The European Medicines Agency requested a reference to this safety concern (EMA/601086/2013). Brain oedema with uncommon frequency was added to section 4.8 of the SmPC.
Source	Clinical trial MC-ALS.32/GLI
New studies proposed in pharmacovigilance plan?	No
New risk minimisation actions proposed?	No

SVII.2 Recent study reports with implications for safety concerns

No new study reports with implications for safety concerns are available.

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

Side effects observed after such treatment have to be discussed in two ways:

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

Substance-specific safety concerns

Identified risk	Hypotension
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = -0.58% [-3.2%; 1.3%]; Total frequency in 3 patient trials (SAS = 244 pts.): 0.82% [0.1%; 2.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	Low
Risk groups or risk factors	Cardiovascular disease
Potential mechanisms	Unknown
Preventability	No
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trial MC-ALS.28/GLI; literature; preclinical investigations
MedDRA terms	Hypotension (PT)

Identified risk	Nausea
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = -1.64% [-6.2%; 2.4%]; Total frequency in 3 patient trials (SAS = 244 pts.): 3.69% [1.7%; 6.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	12.3% of patients had nausea already at baseline (trial MC-ALS.3/GLI)
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	No
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trials; literature
MedDRA terms	Nausea (PT)

Identified risk	Photosensitivity reaction
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = -0.08% [-2.8%; 2.2%]; Total frequency in 3 patient trials (SAS = 244 pts.): 0.82% [0.1%; 2.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	-
Risk groups or risk factors	Sensitive skin
Potential mechanisms	Toxic radicals in the skin induced by light exposure damage the skin
Preventability	Avoid exposure of eyes and skin to strong light sources for 24 hours. Avoid co-administration of other phototoxic substances.
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trials; literature
MedDRA terms	Photosensitivity reaction (PT)

Identified risk	Photodermatosis
Frequency with 95% CI	1 case observed in trial MC-ALS.8-I/GLI; Total frequency in 3 patient trials (SAS = 244 pts.): 0.41% [0.01%; 2.3%]
Seriousness/outcomes	Nonserious; the patient recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	-
Risk groups or risk factors	-
Potential mechanisms	Toxic radicals in the skin induced by light exposure damage the skin
Preventability	Avoid exposure of eyes and skin to strong light sources for 24 hours. Avoid co-administration of other phototoxic substances.
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Trial MC-ALS.8-I/GLI (see Clinical Overview table 2.7.4.2.1.1-7)
MedDRA terms	Photodermatosis (PT)

Procedure-specific safety concerns

Identified risk	Anaemia
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 5.38% [-4.5%; 15.3%]; Total frequency in 3 patient trials (SAS = 244 pts.): 65.98% [59.7%; 71.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	Approx. 10% of patients with anaemia at baseline (trial MC-ALS.3/GLI)
Risk groups or risk factors	-
Potential mechanisms	Blood loss during surgery
Preventability	No
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	May rarely require blood transfusion
Evidence source	Clinical trials
MedDRA terms	Anaemia (PT)

Identified risk	Thrombocytopenia
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 3.69% [-2.9%; 10.2%]; Total frequency in 3 patient trials (SAS = 244 pts.): 15.98% [11.6%; 21.2%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	Approx. 2% of patients with anaemia at baseline (trial MC-ALS.3/GLI)
Risk groups or risk factors	-
Potential mechanisms	Blood loss during surgery
Preventability	No
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	May rarely require platelet transfusion
Evidence source	Clinical trials
MedDRA terms	Thrombocytopenia (PT)

Identified risk	Leukocytosis
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 2.47% [-9.9%; 5.1%]; Total frequency in 3 patient trials (SAS = 244 pts.): 81.15% [75.7%; 85.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	Approx. 62% of patients with anaemia at baseline (trial MC-ALS.3/GLI)
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	No
Impact on individual patient	No long-term effects on patient's quality of life

Potential public health impact	None
Evidence source	Clinical trials
MedDRA terms	Leukocytosis (PT)

Neurological disorders (hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)

Identified risk	Neurological disorders
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 0.88% [-5.9%; 7.5%]; Total frequency in 3 patient trials (SAS = 244 pts.): 12.3% [8.5%; 17.1%]
Seriousness/outcomes	May be serious; not all patients recovered
Severity and nature of risk	Mostly mild to moderate, but may be severe
Background incidence/prevalence	87.1% had neurological disorders already at baseline (MC-ASP.3/GLI).
Risk groups or risk factors	Tumour in the vicinity of brain areas with important neurological function
Potential mechanisms	Resection of eloquent areas; oedema
Preventability	Keep a safe distance of at least 1 cm to eloquent areas
Impact on individual patient	Neurological disorders can include paresis and changes in motor skills. The patient's behaviour, memory or cognition can be affected.
Potential public health impact	May require special care of the patient; corticosteroids / antiepileptics
Evidence source	Clinical trials
MedDRA terms	Nervous system disorders (SOC)

Identified risk	Hemiparesis
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 1.67% [-2.3%; 5.7%]; Total frequency in 3 patient trials (SAS = 244 pts.): 3.69% [1.7%; 6.9%]
Seriousness/outcomes	May be serious; not all patients recovered
Severity and nature of risk	Moderate to severe
Background incidence/prevalence	1 patient in the FL group of the Gliolan phase III trial had already a hemiparesis at baseline
Risk groups or risk factors	Tumour in the vicinity of brain areas with important neuromotor function
Potential mechanisms	Resection of eloquent areas; oedema
Preventability	Keep a safe distance of at least 1 cm to eloquent areas
Impact on individual patient	Hemiparesis can affect different body functions including paralysis of a limb, the loss of motor skills or loss of using or understanding speech.
Potential public health impact	Requires special care of the patient
Evidence source	Clinical trials
MedDRA terms	Nervous system disorders (SOC)

Identified risk	Aphasia
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 2.91% [-0.06%; 6.5%]; Total frequency in 3 patient trials (SAS = 244 pts.): 3.69% [1.7%; 6.9%]
Seriousness/outcomes	May be serious; not all patients recovered

Severity and nature of risk	Moderate to severe
Background incidence/prevalence	1 patient (0.6%) in the FL group of the Gliolan phase III trial had already a aphasia at baseline
Risk groups or risk factors	Tumour in the vicinity of speech centres
Potential mechanisms	Resection of eloquent areas; oedema
Preventability	Keep a safe distance of at least 1 cm to eloquent areas
Impact on individual patient	Aphasia affects the communication abilities of the patient including the ability to speak, read and write.
Potential public health impact	Requires special care of the patient
Evidence source	Clinical trials
MedDRA terms	Nervous system disorders (SOC)

Identified risk	**Convulsions**
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 3.08% [-1.3%; 7.7%]; Total frequency in 3 patient trials (SAS = 244 pts.): 6.15% [3.5%; 9.9%]
Seriousness/outcomes	May be serious; most patients recovered
Severity and nature of risk	Moderate to severe
Background incidence/prevalence	-
Risk groups or risk factors	Tumour in the vicinity of brain areas with important neuromotor function
Potential mechanisms	Resection of eloquent areas; oedema
Preventability	Keep a safe distance of at least 1 cm to eloquent areas
Impact on individual patient	The patient may suffer from uncontrollable shaking of the body that are possibly a symptom of an epileptic seizure.
Potential public health impact	Requires treatment with corticosteroids and/or antiepileptics
Evidence source	Clinical trials
MedDRA terms	Nervous system disorders (SOC)

Identified risk	**Hemianopsia**
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 5.92% [-0.4%; 12.2%]; Total frequency in 3 patient trials (SAS = 244 pts.): 14.75% [10.6%; 19.8%]
Seriousness/outcomes	Non serious; not all patients recovered completely
Severity and nature of risk	Mostly mild to moderate
Background incidence/prevalence	20.1% of patients had vision impairment at baseline (MC-ALS.3/GLI)
Risk groups or risk factors	Tumour in the vicinity of optical areas
Potential mechanisms	Resection of eloquent areas; oedema
Preventability	Keep a safe distance of at least 1 cm to optical areas
Impact on individual patient	The vision can be seriously decreased and therefore the patient may need assistance in daily life.
Potential public health impact	None
Evidence source	Clinical trials
MedDRA terms	Nervous system disorders (SOC)

Identified risk	Hypoaesthesia
Frequency with 95% CI	1 report of a drug-related AE only; Total frequency in 3 patient trials (SAS = 244 pts.): 0.41% [0.01%; 2.3%]
Seriousness/outcomes	Non serious; patient recovered
Severity and nature of risk	Moderate (common toxicity criteria CTC grade II)
Background incidence/prevalence	1 patient in the phase III trial had already partial hypoaesthesia at baseline
Risk groups or risk factors	Tumour in the vicinity of brain areas with important neurosensory function
Potential mechanisms	Resection of eloquent areas; oedema
Preventability	Keep a safe distance of at least 1 cm to eloquent areas
Impact on individual patient	The patient's sense of touch or sensation might be completely or partially lost which results in the necessity of assistance in daily life.
Potential public health impact	None
Evidence source	Trial MC-ALS.28/GLI
MedDRA terms	Nervous system disorders (SOC)

Identified risk	Brain oedema
Frequency with 95% CI	One patient in study MC-ALS.32/GLI (0.4%)
Seriousness/outcomes	May be serious / Can usually be resolve with adequate treatment.
Severity and nature of risk	Severe
Background incidence/prevalence	According to the Swedish National Cancer Registry, cerebral oedema is among the most prevalent conditions at diagnosis (Odds ratio 25.0, 95% CI 5.5-114).[7]
Risk groups or risk factors	Unknown
Potential mechanisms	Disturbance of blood-brain barrier
Preventability	Unknown
Impact on individual patient	May result in a significant limitation of the patient's quality of life.
Potential public health impact	Requires adequate treatment (e.g. dexamethasone) and often intensive care
Evidence source	Clinical trial MC-ALS.32/GLI
MedDRA terms	Nervous system disorders (SOC)

Identified risk	Hypotension
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = -0.58% [-3.2%; 1.3%]; Total frequency in 3 patient trials (SAS = 244 pts.): 0.82% [0.1%; 2.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	Low
Risk groups or risk factors	Cardiovascular disease
Potential mechanisms	Unknown
Preventability	No
Impact on individual patient	No long-term effects on patient's quality of life

Potential public health impact	None
Evidence source	Clinical trial MC-ALS.28/GLI; literature; preclinical investigations
MedDRA terms	Hypotension (PT)

Identified risk	**Thromboembolism**
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 5.31% [1.6%; 9.8%]; Total frequency in 3 patient trials (SAS = 244 pts.): 5.33% [2.9%; 8.9%]
Seriousness/outcomes	May be serious; not all patients recovered; some patients with fatal lung embolism (8 of 13 pts. with lung embolism died in the Gliolan trial)
Severity and nature of risk	Severe
Background incidence/prevalence	One patient in the Gliolan phase III trial had a deep vein thrombosis of leg at baseline. According to the Swedish National Cancer Registry, beginning 30 days after diagnosis, increased risks of incident deep vein thrombosis (hazard ratio [HR] 119.7, 95% CI 60.8-211.0) and pulmonary embolism (HR 92.4, 95% CI 48.3-176.6) were observed.[7]
Risk groups or risk factors	Prothrombotic risk factors
Potential mechanisms	Haemostasis because of immobilisation of the patient
Preventability	Early mobilisation of the patient; anticoagulation treatment
Impact on individual patient	May result in a significant limitation of the patient's quality of life.
Potential public health impact	Requires adequate treatment (fibrinolysis) and often intensive care
Evidence source	Clinical trials
MedDRA terms	Embolism (PT)

Gastrointestinal toxicity (nausea, vomiting, diarrhoea)

Identified risk	**Nausea**
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = -1.64% [-6.2%; 2.4%]; Total frequency in 3 patient trials (SAS = 244 pts.): 3.69% [1.7%; 6.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	12.3% of patients had nausea already at baseline (trial MC-ALS.3/GLI)
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	No
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trials; literature
MedDRA terms	Nausea (PT)

Identified risk	**Vomiting**
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = -1.40% [-5.3%; 1.8%]; Total frequency in 3 patient trials (SAS = 244 pts.): 2.87% [1.2%; 5.8%]

Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	8.6% of patients had vomiting already at baseline (trial MC-ALS.3/GLI)
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	No
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trials; literature
MedDRA terms	Vomiting (PT)

Identified risk	**Diarrhoea**
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = -0.66% [-3.7%; 1.7%]; Total frequency in 3 patient trials (SAS = 244 pts.): 0.82% [0.1%; 2.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	6.3% of patients had diarrhoea already at baseline (trial MC-ALS.3/GLI)
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	-
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trials
MedDRA terms	Diarrhoea (PT)

Hepatotoxicity (blood bilirubin increase, ALAT increase, ASAT increase, γ-GT increase)

Identified risk	**Blood bilirubin increased**
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 6.85% [-0.5%; 14.1%]; Total frequency in 3 patient trials (SAS = 244 pts.): 16.03% [11.6%; 21.3%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	7.8% of pts in the Gliolan phase III trial had elevated bilirubin at baseline
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	-
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trial
MedDRA terms	Liver function analyses (HLT)

Identified risk	ALAT increased
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 21.93%[12.1%; 31.3%]; Total frequency in 3 patient trials (SAS = 244 pts.): 51.6% [45.2%; 58.1%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	30.5% of pts in the Gliolan phase III trial had elevated ALAT at baseline
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	-
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trial
MedDRA terms	Liver function analyses (HLT)

Identified risk	ASAT increased
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 25.74%[17.9%; 33.4%]; Total frequency in 3 patient trials (SAS = 244 pts.): 35.66% [29.7%; 42.0%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Generally mild to moderate
Background incidence/prevalence	6.1% of pts in the Gliolan phase III trial had elevated ASAT at baseline
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	-
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trials
MedDRA terms	Liver function analyses (HLT)

Identified risk	γ-GT increased
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 16.94% [7.4%; 26.1%]; Total frequency in 3 patient trials (SAS = 244 pts.): 43.44% [37.1%; 49.9%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Mostly mild to moderate
Background incidence/prevalence	29.2% of pts in the Gliolan phase III trial had elevated γ-GT at baseline
Risk groups or risk factors	Alcohol addict
Potential mechanisms	Unknown
Preventability	-
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trials

MedDRA terms	Liver function analyses (HLT)

Identified risk	**Blood amylase increased**
Frequency with 95% CI	Absolute difference over control phase III trial: Δ = 5.43% [-4.1%; 14.8%]; Total frequency in 3 patient trials (SAS = 244 pts.): 34.8% [28.9%; 41.2%]
Seriousness/outcomes	Nonserious; all patients recovered without sequelae
Severity and nature of risk	Mostly mild to moderate
Background incidence/prevalence	9.9% of pts in the Gliolan phase III trial had elevated blood amylase at baseline
Risk groups or risk factors	-
Potential mechanisms	Unknown
Preventability	-
Impact on individual patient	No long-term effects on patient's quality of life
Potential public health impact	None
Evidence source	Clinical trials
MedDRA terms	Amylase increased (PT)

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Aminolevulinic acid hydrochloride is an endogenous intermediate of the porphyrin biosynthesis pathway. It is formed from glycine and succinyl-coenzyme A by the enzyme 5-ALA synthase. 5-ALA is metabolised to the fluorescent molecule PPIX which is a precursor for heme. As a prosthetic group heme has a substantial function in metalloproteins such as haemoglobin, myoglobin, peroxidases or catalases. Naturally mammalian cells have the capacity for synthesizing heme.

The natural origin of the intermediates 5-ALA and its metabolites results in a good tolerance after use and reduces the potential for interactions with other medications or with food.

SVII.4.2 Important identified and potential interactions

Only one drug interaction has been reported in the literature. A patient developed severe sunburn lasting for 5 days after coadministration of 5-ALA and a hypericin extract (a known photosensitising agent).[12] This case underlines the demand to avoid coadministration of 5-ALA and other photosensitising agents. Other photosensitising agents may cause similar photo-sensitivity reactions. The SmPC of Gliolan® encloses a wording about this interaction.

Since 5-ALA*HCL is administered to fasting patients prior to surgery, the influence of food on the bioavailability has not been studied.

SVII.5 Pharmacological class effects

SVII.5.1 Pharmacological class effects already included as important identified or potential risks

Not applicable

SVII.5.2 Important pharmacological class effects not discussed above

Not applicable

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

5-ALA*HCl alone is usually very well tolerated by the patients. The only observed adverse reactions that may be related to the use of this agent are gastrointestinal disorders (nausea), cardiac/vascular disorders (hypotension) especially in predisposed patients, and photosensitivity reactions/photodermatosis.

Most adverse events observed in the clinical studies refer to the treatment procedure related signs and symptoms, i.e. the combination of administration of 5-ALA*HCl, anaesthesia, and tumour resection. Not surprisingly, major side effects observed were of neurological origin. At the time of launch of the clinical studies, no detailed information was available whether the use of 5-ALA-supported fluorescence-guided resection of malignant gliomas with its expected more radical resection would lead to more neurological defects.

Taking into account that safety concerns result both from the substance and from the procedure the list of risks have been separated to substance-specific and procedure-related risks.

Substance-specific safety concerns

Important identified risks	Hypotension
	Nausea
	Photosensitivity reaction
	Photodermatosis
Important potential risks	None
Missing information	Use in paediatric population Use in patients with brain tumours other than malignant gliomas

Procedure-related safety concerns

Important identified risks	Anaemia
	Thrombocytopenia
	Leukocytosis
	Neurological disorders (e.g. hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)
	Hypotension
	Thromboembolism
	Gastrointestinal toxicity (nausea, vomiting, diarrhoea)
	Hepatotoxicity (blood bilirubin increased; ALAT increased; ASAT increased; γ-GT increased)
	Blood amylase increased
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN

The company will continue to collect and monitor all spontaneously reported adverse events and commits to a detailed assessment of each report as part of routine pharmacovigilance activities. All events reported to the company or published in the literature will be periodically assessed for trends and periodic safety update reports (PSURs) will be provided to the EU regulatory authorities in accordance with the relevant EU Directives.

The company's pharmacovigilance system including routine pharmacovigilance activities is described in its pharmacovigilance system master file (PSMF) and summarised in eCTD Module 1.8.1.

III.1 Safety Concerns and Overview of Planned Pharmacovigilance Actions

Substance-specific safety concerns

Safety concern: Hypotension		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Nausea		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Photosensitivity reaction		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Photodermatosis		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Use in paediatric population		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Safety of Gliolan in this age group	Routine pharmacovigilance activity	-

Safety concern: Use in patients with brain tumours other than malignant gliomas		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Safety of Gliolan in such patients	Routine pharmacovigilance activity	-

Product-specific safety concerns

Safety concern: Anaemia		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Thrombocytopenia		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Leukocytosis		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Neurological disorders (e.g. Hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity Educational training programme for neurosurgeons	Reducing the risk for neurological adverse events

Safety concern: Hypotension		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Thromboembolism		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Gastrointestinal toxicity (nausea, vomiting, diarrhoea)		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Hepatotoxicity (blood bilirubin increased, ALAT increased, ASAT increased, γ-GT increased)		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

Safety concern: Blood amylase increased		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
None	Routine pharmacovigilance activity	-

III.2 Additional Pharmacovigilance Activities to Assess Effectiveness of Risk Minimisation Measures

No additional pharmacovigilance activities to assess the effectiveness of applied risk minimisation measures are planned.

III.3 Studies and Other Activities Completed Since Last Update of the Pharmacovigilance Plan

No studies have been completed by the applicant since the last update of the pharmacovigilance plan.

III.4 Details of Outstanding Additional Pharmacovigilance Activities

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

No mandatory additional pharmacovigilance activities have been imposed on the applicant.

III.4.2 Mandatory additional pharmacovigilance activity (being a specific obligation)

There are no mandatory additional pharmacovigilance activities to be performed by the applicant.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

There are no additional pharmacovigilance activities required to be performed by the applicant to address a specific safety concern or to measure the effectiveness of risk minimisation measures.

III.4.4 Stated additional pharmacovigilance activities

No other safety-related activities have been requested. The applicant is also not aware of any safety studies performed with the reference product.

III.5 Summary of Pharmacovigilance Plan

III.5.1 Table of ongoing and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

There are no ongoing or planned additional pharmacovigilance studies or activities in the pharmacovigilance plan.

III.5.2 Table of completed studies/activities from the Pharmacovigilance Plan

There are no completed additional pharmacovigilance studies or activities in the pharmacovigilance plan.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV.1 Applicability of Efficacy to all Patients in the Target Population

Although controversy exists regarding the relationship between the extent of surgery and survival in patients with malignant gliomas, there is general consensus that optimal treatment should involve the resection of as much tumour as possible without causing neurological deficits. Surgery reduces the number of cancer cells requiring treatment and often removes the hypoxic core of the tumour that is relatively resistant to radiation and inaccessible to chemotherapy.[8]

There is no doubt that the use of fluorescence-guidance after oral administration of 5-ALA*HCl increases the tumour visualisation and the rate of radiological complete tumour resection as has been convincingly shown in study MC-ALS.3/GLI.[6]

Additionally, within this study it has been demonstrated for the first time in a large prospectively randomised (before surgery) phase III clinical trial that this more aggressive tumour debulking leads to a significant benefit with respect to the PFS rate.[6]

Compared to the control group, approximately twice as much patients in the experimental group were progression-free at 6 months. Supplemental time to event analyses with tumour progression defined according to the *Mcdonald* or *Stupp* criteria clearly show that this increase in progression-free survival in the FL arm is not counterbalanced by worsened neurological findings.[6]

Unfortunately, the prolongation of PFS was not followed by a significant increase in overall survival of patients which was similar in both groups. It might be speculated that postoperative adjuvant radiotherapy as well as chemotherapy and re-operation after tumour progression have compensated to some extent for the reduced tumour debulking in the control group and therefore blurred a possible survival benefit. Indeed, in the control arm more patients underwent one or two re-operations or received temozolomide. Furthermore, the time to such re-intervention after radiological progression was prolonged in patients of the FL-group compared to the control-group.

IV.2 Tables of Post-Authorisation Efficacy Studies

No post-authorisation efficacy studies are planned by the applicant.

IV.3 Summary of Post-Authorisation Efficacy Development Plan

There is no post-authorisation efficacy development plan in place.

IV.4 Summary of Completed Post-Authorisation Efficacy Studies

No post-authorisation efficacy studies have been completed.

PART V: RISK MINIMISATION MEASURES

V.1 Risk Minimisation Measures by Safety Concern

Substance-specific safety concerns

Safety concern: Hypotension	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Hypotension is listed as a cardiac disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of Individual Case Safety Reports (ICSRs) and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	This risk can be both substance- and procedure-related.

Safety concern: Nausea	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Nausea is listed as a gastrointestinal disorder with uncommon frequency.

Safety concern: Nausea	
	Patient Information Leaflet (PIL) The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concern: Photosensitivity reaction	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Photosensitivity reaction is listed as a skin and subcutaneous tissue disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	

Safety concern: Photosensitivity reaction	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concern: Photodermatosis	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Photodermatosis is listed as a skin and subcutaneous tissue disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concern: Use in paediatric population	
Objective(s) of the risk	To provide information to health care professionals and patients about the

Safety concern: Use in paediatric population	
minimisation measures	lack of data via the SmPC / via the PIL
Routine risk minimisation measures	*SmPC 4.2 Posology and method of administration:* *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. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The current measures are considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concern: Use in patients with brain tumours other than malignant gliomas	
Objective(s) of the risk minimisation measures	None proposed
Routine risk minimisation measures	This medicinal product should only be used by experienced neurosurgeons. The authorised therapeutic indication of Gliolan is explicitly listed in SmPC and PIL. *Justification* Experienced neurosurgeons are the target health care professionals. It is expected that they have knowledge about the authorised indication.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase

Safety concern: Use in patients with brain tumours other than malignant gliomas	
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Procedure-related safety concerns

Safety concern: Anaemia	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Anaemia is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concern: Thrombocytopenia	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Thrombocytopenia is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concern: Leukocytosis	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Leukocytosis is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None

Safety concern: Leukocytosis	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concerns: Neurological disorders (e.g. Hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine 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 provided by medac GmbH. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Neurological disorders are listed as undesirable effects. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to address this safety concern. However, to avoid additional neurological deficits caused by use of Gliolan, neurosurgeons must have adequate experience with this new treatment modality.
Additional risk minimisation measure(s)	*Training courses* Specific educational training courses for neurosurgeons that aim to reduce neurological adverse effects are offered frequently and in alternating locations. *Controlled distribution system* The department product management for Gliolan has established a file listing all physicians who have successfully taken part in a training course,

Safety concerns: Neurological disorders (e.g. Hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)	
	as well as with the clinic address where they are currently employed. This file is regularly updated. The customer service department has the instruction to verify each incoming Gliolan order against this file. Gliolan is only sent to hospitals were a neurosurgeon who has successfully completed the compulsory medac training course is registered. *Justification* To avoid additional neurological deficits caused by use of Gliolan, neurosurgeons must have adequate experience with this new treatment modality. These measures, in addition to the routine risk minimisation measures, are considered to sufficiently address this safety concern.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements *Training courses* Counting and filing of training courses arranged. Counting and filing of neurosurgeons who have taken part in a training course and got a certificate on successful graduation by the training centre *Controlled distribution system* Counting and filing the number of hospitals that accidentally received Gliolan although no neurosurgeon of this hospital participated in a training course.
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase *Training courses* Number of neurosurgeons that participated in a training course and got a certificate on successful graduation. *Controlled distribution system* Number of hospitals that received Gliolan although no training course participant is registered there, should be zero.
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update *Training courses* The number of arranged trainings courses as well as the number of participants is steady of over the last years. Number of training courses and number of participants per year:

Year	#Courses	#Participants
2008	14	88
2009	25	223
2010	22	155
2011	21	220
2012	28	241
2013	25	204

Safety concerns: Neurological disorders (e.g. Hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)	
	2014 23 221 2015 (until 07/03/2015) 5 42 *Controlled distribution system* No unregistered hospitals have received Gliolan.
Impact of risk minimisation	None
Comment	None

Safety concern: Hypotension	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Hypotension is listed as a cardiac disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	This risk can be both substance- and procedure-related.

Safety concern: Thromboembolism	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL

Safety concern: Thromboembolism	
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Thromboembolism is listed as a vascular disorder with common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concerns: Gastrointestinal toxicity (nausea, vomiting, diarrhoea)	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Gastrointestinal toxicities are listed with frequencies from common to very rare. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk	Evaluation of ICSRs and expedited reporting as per EU requirements;

minimisation measures for the safety concern will be measured	Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	Nausea is also listed as a substance-specific safety concern.

Safety concerns: Hepatotoxicity (Blood bilirubin increased; ALAT increased; ASAT increased; γ-GT increased)	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* Within 24 hours after administration, other potentially hepatotoxic medicinal products should be avoided. *SmPC 4.8 Undesirable effects:* Hepatotoxicity is listed with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

Safety concern: Blood amylase increased

Safety concern: Blood amylase increased	
Objective(s) of the risk minimisation measures	To provide information to health care professionals and patients about this risk via the SmPC / via the PIL
Routine risk minimisation measures	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* The increase of blood amylase is listed as a hepatobiliary disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language. *Justification* The information provided within the label is considered to sufficiently address this safety concern.
Additional risk minimisation measure(s)	None
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Evaluation of ICSRs and expedited reporting as per EU requirements; Periodic evaluation and reporting (PSUR) as per EU requirements
Criteria for judging the success of the proposed risk minimisation measures	No significant increase in the frequency and/ or severity of reported adverse events in PSURs and RMP updates prepared during the post-marketing phase
Planned dates for assessment	At the time of the next data lock point for a PSUR or RMP update
Results of effectiveness measurement	No significant increase in the frequency of reported adverse events since the last PSUR and RMP update
Impact of risk minimisation	None
Comment	None

V.2. Risk Minimisation Measure Failure (if applicable)

It is known that in Germany a significant number of hospital pharmacies order the active ingredient of Gliolan - 5-ALA - from various other companies which have no marketing authorisation for such a product. This includes also hospitals (at least 16) from which no neurosurgeon has taken part on one of the above mentioned training courses. Thus the RMP set up for a safe and effective use of Gliolan is bypassed by these hospitals.

V.2.1 Analysis of risk minimisation measure(s) failure

No detailed analysis of the risk minimisation measure failure has been performed.

V.2.2 Revised proposal for risk minimisation

None

V.3. SUMMARY TABLE OF RISK MINIMISATION MEASURES

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Substance-specific safety concerns		
Hypotension	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Hypotension is listed as a cardiac disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Nausea	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Nausea is listed as a gastrointestinal disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Photosensitivity reaction	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Photosensitivity reaction is listed as a skin and subcutaneous tissue disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Photodermatosis	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Photodermatosis is listed as a skin and subcutaneous tissue disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Use in paediatric population	*SmPC 4.2 Posology and method of administration:* *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. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Use in patients with brain tumours other than malignant gliomas	This medicinal product should only be used by experienced neurosurgeons. The authorised therapeutic indication of Gliolan is explicitly listed in SmPC and PIL.	None
Product-specific safety concerns		
Anaemia	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Anaemia is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Thrombocytopenia	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Thrombocytopenia is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Leukocytosis	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC 4.8 Undesirable effects: Leukocytosis is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	
Neurological disorders (e.g. Hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Neurological disorders are listed as undesirable effects. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	Specific educational training courses for neurosurgeons that aim to reduce neurological adverse effects are offered frequently and in alternating locations. A training manual is handed over to the participants. Gliolan is only delivered to hospitals from which at least one neurosurgeon had been successfully taken part on a training course. The product management of Gliolan has established a file listing of all physicians who had been successfully taken part on a training course, together with their respective clinic address. This file is regularly updated. The customer service department has the instruction to verify each incoming Gliolan order against this file. Since this information is also stored in the individual customer basic data set, this control procedure is also checked electronically. A predefined text is included in delivery documents to make the receiver (mostly a pharmacist) aware that Gliolan should only be delivered for neurosurgery.
Hypotension	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* In patients with pre-existing cardiovascular disease, this	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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. *SmPC 4.8 Undesirable effects:* Hypotension is listed as a cardiac disorder with uncommon frequency. Gliolan is available on prescription only. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	
Thromboembolism	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Thromboembolism is listed as a vascular disorder with common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Gastrointestinal toxicity (nausea, vomiting, diarrhoea)	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Gastrointestinal toxicities are listed with frequencies from common to very rare. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Hepatotoxicity (Blood bilirubin increased; ALAT increased; ASAT increased; γ-GT increased)	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* Within 24 hours after administration, other potentially hepatotoxic medicinal products should be avoided. *SmPC 4.8 Undesirable effects:* Hepatotoxicity is listed with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Blood amylase increased	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC 4.8 Undesirable effects: The increase of blood amylase is listed as a hepatobiliary disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements of Summary Tables in the EPAR

VI.1.1 Summary table of safety concerns

Substance-specific safety concerns

Important identified risks	Hypotension
	Nausea
	Photosensitivity reaction
	Photodermatosis
Important potential risks	None
Missing information	Use in paediatric population
	Use in patients with brain tumours other than malignant gliomas

Procedure-related safety concerns

Important identified risks	Anaemia
	Thrombocytopenia
	Leukocytosis
	Neurological disorders (e.g. hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)
	Hypotension
	Thromboembolism
	Gastrointestinal toxicity (nausea, vomiting, diarrhoea)
	Hepatotoxicity (blood bilirubin increased; ALAT increased; ASAT increased; γ-GT increased)
	Blood amylase increased
Important potential risks	None
Missing information	None

VI.1.2 Table of ongoing and planned studies in the post-authorisation pharmacovigilance development plan

There are no ongoing or planned additional pharmacovigilance studies in the pharmacovigilance plan.

VI.1.3 Summary of post-authorisation efficacy development plan

There are no ongoing or planed post-authorisation efficacy studies.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Substance-specific safety concerns		
Hypotension	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Hypotension is listed as a cardiac disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Nausea	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Nausea is listed as a gastrointestinal disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Photosensitivity reaction	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Photosensitivity reaction is listed as a skin and subcutaneous tissue disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	language.	
Photodermatosis	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Photodermatosis is listed as a skin and subcutaneous tissue disorder with uncommon frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Use in paediatric population	*SmPC 4.2 Posology and method of administration:* *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. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Use in patients with brain tumours other than malignant gliomas	This medicinal product should only be used by experienced neurosurgeons. The authorised therapeutic indication of Gliolan is explicitly listed in SmPC and PIL.	None
Product-specific safety concerns		
Anaemia	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Anaemia is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Thrombocytopenia	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Thrombocytopenia is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Leukocytosis	Prescription only medicine This medicinal product should only be used by	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Leukocytosis is listed as a blood and lymphatic system disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	
Neurological disorders (e.g. Hemiparesis, aphasia, convulsions, hemianopsia, hypoaesthesia, brain oedema)	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* 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. *SmPC 4.8 Undesirable effects:* Neurological disorders are listed as undesirable effects. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	Specific educational training courses for neurosurgeons that aim to reduce neurological adverse effects are offered frequently and in alternating locations. A training manual is handed over to the participants. Gliolan is only delivered to hospitals from which at least one neurosurgeon had been successfully taken part on a training course. The product management of Gliolan has established a file listing of all physicians who had been successfully taken part on a training course, together with their respective clinic address. This file is regularly updated. The customer service department has the instruction to verify each incoming Gliolan order against this file. Since this information is also stored in the individual customer basic data set, this control procedure is also checked electronically. A predefined text is included in delivery documents to make the receiver (mostly a pharmacist) aware that Gliolan should only be delivered for neurosurgery.
Hypotension	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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. *SmPC 4.8 Undesirable effects:* Hypotension is listed as a cardiac disorder with uncommon frequency. Gliolan is available on prescription only. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	
Thromboembolism	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Thromboembolism is listed as a vascular disorder with common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Gastrointestinal toxicity (nausea, vomiting, diarrhoea)	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.8 Undesirable effects:* Gastrointestinal toxicities are listed with frequencies from common to very rare. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Hepatotoxicity (Blood bilirubin increased; ALAT increased; ASAT increased; γ-GT increased)	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons. *SmPC 4.4 Special warnings and precautions for use:* Within 24 hours after administration, other potentially hepatotoxic medicinal products should be avoided. *SmPC 4.8 Undesirable effects:* Hepatotoxicity is listed with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Blood amylase increased	Prescription only medicine This medicinal product should only be used by experienced neurosurgeons.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC 4.8 Undesirable effects: The increase of blood amylase is listed as a hepatobiliary disorder with very common frequency. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Gliomas are heterogeneous brain or spine tumours originating from different types of glial cells. They embrace a wide range of tumours e.g. astrocytoma, oligodendroglioma or glioblastoma multiforme (GBM) that are highly diverse in matter of location, physiognomy, progression, occurrence in population and response to the treatment.

The most common and aggressive malignant gliomas in adults are GBMs with an occurrence of approximately 2 – 3 new cases per 100,000 in Europe and North America per year. GBMs may occur at any age, but 60% of cases are seen in patients between 55 and 74 years of age. Slightly more men than women are affected. The disease often progresses rapidly over 2 to 3 months, is incurable, and median overall survival is approximately one year. Possible risk factors may include therapeutic ionisation radiation and exposure to pesticides. Despite of intensive research, exact data on this subject are lacking because of the rareness of this disease.

VI.2.2 Summary of treatment benefit

Surgery is often the first treatment option targeting the complete remove of the tumour tissue. However, entire removal of the tumour is often complicated by its fuzzy demarcation to normal tissue. Optical markers such as the active substance in Gliolan staining the tumour help the surgeon to differentiate between the tumour and the healthy tissue. It is absorbed by cells in the body where it is converted by enzymes into the fluorescent molecule protoporphyrin IX (PPIX). Since glioma cells take up more of the active substance and convert it more rapidly into PPIX, higher levels of PPIX accumulate in the cancer cells than in normal tissue. When illuminated under blue light of a specific wavelength, the PPIX in the tumour glows an intense red, while the normal brain tissue appears blue. This enables the surgeon to see the tumour more clearly during brain surgery and to remove it more accurately, sparing healthy brain tissue.

It was shown that removal of the brain tumour by surgery was more complete when Gliolan was used. At 72 hours after the operation, 63.6% of the patients given Gliolan had no visible tumour on a brain scan, compared with 37.6% of those who did not receive Gliolan. After six months, 20.5% of the patients given Gliolan were still alive without progression, compared with 11.0% of those who did not receive the medicine.

VI.2.3 Unknowns relating to treatment benefits

There is no evidence to suggest that treatment benefits would be different in any specific patient populations.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Substance-specific risks		
Hypotension (low blood pressure)	Hypotension is an uncommon side effect that may affect up to 1 in 100 people. It can arouse both from the substance itself as well from the actual surgery procedure. Patients usually recover from this complication without further complications.	Patients suffering from hypotension should inform the responsible physician. Blood pressure values will be monitored regularly throughout the treatment.
Nausea (feeling sick)	1 out of 100 patients may potentially develop nausea after taking Gliolan. They recover from this complication without further complications.	Patients should not drink or eat for at least 6 hours before anaesthesia. This will decrease the risk of the patient for this side effect.
Photosensitivity reaction (skin reaction due to light sensitivity)	1 out of 100 patients may potentially undergo a photosensitive reaction that looks like sunburn. It is known from patients that received an overdose of Gliolan that all patients recovered from this reaction without further complications. This side effect is also known from other photoactive medications.	The patient should avoid strong light sources for 24 hours and co-administration of other phototoxic substances.
Photodermatosis (skin reaction due to light sensitivity)	Less than 1 out of 100 patients may potentially develop photodermatosis. Patients recover from this complication without further complications.	The patient should avoid strong light sources for 24 hours and co-administration of other phototoxic substances.
Procedure-specific risks		
Anaemia (Decrease of red blood cells)	The mild alteration of red and white blood cell counts is known as a very common risk occurring during surgery. 1 in 10 people are potentially at risk to suffer from this side effect. Patients usually recover without further complications.	Blood substitutes are usually in place during surgery. Consult your doctor if a self-blood donation is a convincing opportunity.
Thrombocytopenia (Decrease of white blood platelets)		
Leukocytosis (Increase of white blood cells)	Leukocytosis is part of a normal surgical response of the body. It is a very common side effect that occurs in 1 in 10 people. Patients usually recover without further complications.	It is unknown how to prevent this side effect.

Risk	What is known	Preventability
Neurological disorder (disorders that affect the nervous system) Including: Hemiparesis (partial paralysis of one side of the body) Aphasia (total or partial loss of ability to use or understand language) Convulsions (seizures) Hemianopsia (blindness for half the field of vision in one or both eyes) Hypoaesthesia (decrease of your sense of touch) Brain oedema (brain swelling)	The occurrence of neurological disorders after the treatment range from rare to very common depending on the side effect.	The neurosurgeon must only treat the patient with the medication if she/he participated in an educational training course. These training courses aim to reduce neurological side effects.
Hypotension (low blood pressure)	Hypotension is an uncommon side effect that may affect up to 1 in 100 people. It can arouse both from the substance itself as well from the actual surgery procedure. Patients usually recover without further complications.	Patients suffering from hypotension should inform the responsible physician. Blood pressure values will be monitored regularly throughout the treatment.
Thromboembolism (blood clots that may obstruct blood vessels)	Blood clots are a known complication during surgery and may potentially affect 1 in 10 people. Most patients recover without further complications.	Blood clotting values may be monitored regularly throughout the treatment. Preventive use of anti-thrombotic agents after surgery may be reasonable.
Gastrointestinal toxicity (digestive system disease) Including: Nausea (feeling sick) Vomiting (throwing up) Diarrhoea (loose or watery stools)	Nausea and vomiting are known as very common side effects and may potentially occur in 1 in 10 people while diarrhoea occurs only rarely (1 in 10,000 people). Patients usually recover without further complications.	Patients should not drink or eat for at least 6 hours before anaesthesia. This will decrease the risk of the patient for this side effect.
Hepatotoxicity (Liver reactions) Including: Rise of blood bilirubin (bilirubin is a bile pigment produced in the liver by breakdown of red blood cell pigments) Transaminases (ALAT and ASAT) and γ-GT increase (Rise in different liver enzyme levels)	Subsequently to surgery 1 in 10 patients experienced a slight increase of liver enzyme concentrations and the bilirubin concentration. 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.	Avoid the intake of medicinal products that are potentially toxic to the liver within 24 hours after the treatment.
Blood amylase increased (enzyme	Subsequently to surgery 1 in 10	It is unknown how to prevent this

Risk	What is known	Preventability
increase)	patients experience a slight increase of this enzyme. 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.	side effect.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
None	Not applicable

Missing information

Risk	What is known
Substance specific risk	
Use in paediatric patients	Isolated use of Gliolan in paediatrics was only retrospectively studied. There is not sufficient experience with Gliolan in children and adolescents. Therefore this medicine is not recommended in this age group.
Use in patients with brain tumours other than malignant gliomas	The active substance of Gliolan, 5-Aminolevulinic acid hydrochloride, is sometimes used in non-authorised indications such as meningioma and metastasis. However, efficacy was not clearly demonstrated for the use in these diseases.

VI.2.5 Summary of risk minimisation measures by safety concerns

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Gliolan can be found in the Gliolan EPAR page.

Gliolan has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Gliolan's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

Safety concern in lay terms (medical term)

Risk minimisation measure(s)
Objective and rationale
• Summary description of main additional risk minimisation measure – Specific educational training courses for neurosurgeons Safety concern: This risk minimisation measure addresses the risk of neurological disorders Objective and Rationale: To lower the rate of neurological adverse effects caused by the surgery using Gliolan

VI.2.6 Planned post authorisation development plan

There are no studies planned with Gliolan.

List of studies in post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation

None

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes of the Risk Management Plan over time

Version	Date	Safety concerns	Comment
10	18/12/2015	'Brain oedema' (neurological disease) was added as an important identified risk.	Already integrated in the respective SmPC and current CCDS.
		The safety concerns 'Use in paediatric population' and 'Use in patients with brain tumours other than malignant gliomas' were added as missing information to the list of safety concerns.	PRAC PSUR assessment report (Procedure no.: EMEA/H/C/PSUSA/00000009/201503) dated 08/10/2015.

ANNEX 7 - SPECIFIC ADVERSE EVENT FOLLOW-UP FORMS

Not applicable

ANNEX 10 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION MEASURES (IF APPLICABLE)

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 medicinal 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;
d) The practice of Gliolan-fluorescence-guided surgery (including participation in at least one case 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 dose 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.