HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 May 2010

GLIOLAN 30 mg/ml, powder for oral solution
B/1 vial containing 1.5 g (CIP: 573 225-1)

Applicant: MEDAC GESELLSCHAFT FÜR MEDIZINISCHE SPEZIALPRÄPARATE mbH

5-aminolevulinic acid

ATC code: L01XD04

List I
Medicinal product for hospital use only
Prescription restricted to neurosurgery specialists

Orphan drug status (13 November 2002)

Date of Marketing Authorisation (centralised procedure): 7 September 2007

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

5-aminolevulinic acid

1.2. Novel aspects

The active ingredient in GLIOLAN is 5-aminolevulinic acid (5-ALA), which is metabolised into fluorescent porphyrins. The tissue of malignant gliomas (grade III and IV) has been shown to synthesise and accumulate porphyrins in response to administration of 5-ALA. After excitation with blue light (λ = 400 - 410 nm), protoporphyrin IX (PPIX), which has been selectively accumulated in malignant tissues, is strongly fluorescent (red in colour) and can therefore be visualised after appropriate modifications to a standard neurological microscope. Conversely, PPIX levels do not increase in normal brain tissue, which reflects the violet-blue light and appears blue.

1.3. Indication

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

1.4. Dosage

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

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XD	Sensitizers used in photodynamic/radiation therapy
L01XD04	Aminolevulinic acid

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

None

2.3. Medicines in the same therapeutic category

None

Other comparators:
Methods used in order to improve visualisation of the tumour:

- MRI during surgery
- Neuronavigation
- Ultrasound

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and tolerance of GLIOLAN have been assessed in two clinical studies described below:
- a phase II non-comparative study (MC-ALS.28/GLI).
- a phase III comparative study (MC-ALS.3/GLI, pivotal study).

Study MC-ALS.28/GLI

Phase II non-comparative study with the primary aim of assessing the positive predictive value of tissue fluorescence after administration of GLIOLAN to patients undergoing surgery for treatment of a glioma suspected to be malignant following radiology.

The primary efficacy endpoint is the positive predictive value of tissue fluorescence, defined as the percentage of patients in whom tumour tissues are positively identified compared to all the biopsies performed in high-fluorescence and low-fluorescence zones.

Secondary endpoints:
- assessment of the positive predictive value at the scale of the biopsy,
- correlation between the tumour and residual fluorescence observed before and after surgery and residual tumour visible on the MRI performed after surgery.

Inclusion criteria
- radiological examination indicating that the glioma may be malignant: tumour structure with contrast enhancement during MRI showing a clear corona or demarcation and a hypodense central node (tumoral necrosis) but no extended hypodense tumoral zone (to rule out secondary gliomas),
- surgical resection indicated,
- primary surgical treatment of the tumour, no other specific pre-treatment of the tumour,
- Karnofsky score $\geq$ 60%,
- age 18 to 75

Results

The median age of the patients was 61. Most of the tumours (87.9%) were grade IV, primarily glioblastoma multiforme.

Efficacy results were obtained for 33 patients. Six biopsies (high- or low-fluorescent) were available for each of 29 patients. Three high-fluorescent or low-fluorescent biopsies were performed on each of four patients.

Primary endpoint:
Average tumoral cellularity per patient as shown by the high-fluorescent biopsies was 79.1% ± 20.1%, compared to 30.78% ± 27.88% per patient in the case of the low-fluorescent biopsies. Average tumoral cellularity for all the biopsies was 79.1% ± 19.8%.
The number of biopsies classified as “true positives” was higher when the quality of fluorescence was good (n=32) than when it was poor (n=25). Consequently, the positive predictive value was 100% (90%CI: 91.1% - 100.0%) for high fluorescence and 83.3% (90%CI: 68.1% - 93.2%) for low fluorescence. The positive predictive value of tissue fluorescence (all types of fluorescence) was 84.8%.

Secondary endpoints:
The positive predictive value of tissue fluorescence at biopsy level was 96.2%: 100% in the case of high fluorescence and 92.2% in the case of low fluorescence.
Seven of the 185 biopsy samples examined were found to have no tumour cells (false positives). The intensity of fluorescence in all the false-positive samples was low.

Approximately two-thirds of the non-fluorescent biopsy samples taken from adjacent normal tissue were found to contain tumour cells.
Post-operative MRI revealed the presence of residual tumours in two out of the ten patients who had undergone perioperative complete resection (this reflects failure of visualisation by this fluorescence technique).

Study MC-ALS.3/GLI

Phase III[1] open-label, randomised study comparing fluorescence-guided surgical resection following administration of GLIOLAN with conventional resection under white light in patients undergoing surgery after being found to have a glioma that was suspected to be malignant following radiology.

Inclusion criteria:
Patients aged 18 to 72 who had undergone a brain MRI and been diagnosed with a single-site malignant glioma (WHO grade III or IV) for whom surgery was indicated. The location of the tumour taking up the contrast agent had to be suitable for complete resection.

Exclusion criteria:
- tumours located on the median line, in the basal ganglion, the cerebellum or the brainstem,
- Karnofsky score < 70,
- porphyria, hypersensitivity to porphyrins,
- renal or hepatic insufficiency,
- malignant tumour other than basal cell carcinoma.

Two primary endpoints were defined in the protocol:
- percentage of patients with no tumour visible on a brain MRI performed 72 hours after surgery,
- progression-free survival at six months after surgery defined by the time from randomisation to progression or death from any cause.
Tumour progression was assessed by radiology and defined as the reappearance of the tumour lesion (volume > 0.175 cm^2) or an increase of more than 25% in the size of the residual tumour compared to the volume shown on the MRI performed 72 hours after the procedure.

The secondary endpoints were:
- residual tumour volume,
- progression-free survival at 9, 12, 15 and 18 months after surgery,
- overall survival,
- toxicity following oral administration of GLIOLAN,
- neurological state assessed at various dates: 7 days, 6 and 12 weeks, 6, 9, 12 and 18 months after surgery,
- comparison of the fluorescence diagnosis findings (perioperative residual tumour) and early post-operative MRI findings (residual tumour as shown by radiology).

[1] Stummer W, Pichlmeier U, Meinel T, Wiestler O et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma; a randomized controlled multicentre phase III trial. Lancet Oncol 2006; 7: 392-401.

Treatments investigated:
Patients were randomised to either receive or not receive 20 mg/kg of GLIOLAN by oral administration 3 ± 1 hours prior to anaesthesia.
It should be noted that before starting the study all the participating centres had to treat three patients according to the study protocol for the GLIOLAN group in order to familiarise themselves with the fluorescence-guided tumour resection technique.
Treatment for both study arms after administration of the study drug consisted of surgical removal of the tumour. The study protocol recommended that resection be as complete as possible. At the end of the procedure, the surgeon was required to assess whether all the tumour zones had been removed and, if not, how large the residual tumour was.

Results
The efficacy analysis was carried out on 349 of the 415 patients who were randomised (31 were excluded mainly because resection was not performed, consent had been withdrawn, the histological analysis was not available, or for other reasons). The median age of the patients was 60. Approximately three-quarters (77.7%) of patients were in good general condition (KPS score $\geq$ 90%).

Primary endpoints:
The percentage of patients found to have no residual tumour after undergoing an MRI check-up was 63.6% in the GLIOLAN group versus 37.6% in the control group ($p < 0.0001$).
The percentage of patients surviving without progression after six months was 20.5% in the GLIOLAN group versus 11.0% in the control group ($p = 0.0152$).

Secondary endpoints:
- volume of residual tumour
The median residual tumour volume was 0.0 cm^3 (0.0 – 45.1 cm^3) among patients in the GLIOLAN group versus 0.5 cm^3 (range: 0.0 – 32.6 cm^3) among patients in the control group. The residual volume figures for 75% of the patients in each group were ≤ 0.7 cm^3 in the GLIOLAN group versus ≤ 2.1 cm^3 in the group which underwent surgery under white light ($p < 0.0001$).

- progression-free survival at 9, 12, 15 and 18 months
No difference was observed between the two groups in respect of this criterion (at 9 months: 10.2% in the GLIOLAN group versus 5.2% in the control group, $p = 0.07$ and at 18 months: 2.3% versus 1.2%, $p = 0.68$).

- overall survival
The median overall survival rates were very similar in the two groups: 14.3 months in the GLIOLAN group versus 13.7 months in the group undergoing surgery under white light, $p = 0.9170$.
The one-year survival rate in both groups was 58%.

3.2. Adverse events

The overall incidence of serious adverse events was similar in both treatment groups, with at least one serious adverse event being reported for 29.9% of patients in the GLIOLAN group and 23.1% of patients in the group undergoing surgery under white light.
Most of the adverse events were neurological in nature, and occurred at similar rates in both treatment groups (12.4% in the GLIOLAN group and 11.6% in the control group). The most commonly reported neurological adverse event was convulsions, reported among 6.0% of patients in the GLIOLAN group and 2.9% of patients in the control group. Other serious neurological adverse events which were frequently reported were ‘grand mal’ convulsions (GLIOLAN group: 3.5%, control group: 2.9%), aphasia (GLIOLAN group: 3.5%, control group: 0.6%) and hemiparesis (GLIOLAN group: 4.0%, control group: 2.3%).

3.3. Conclusion

The efficacy and tolerance of GLIOLAN in the visualisation of malignant tissues during fluorescence-guided surgical resection were assessed in a phase III open-label randomised study performed on 349 patients undergoing surgery for glioma suspected to be malignant following radiology.
This study compared the results of surgery in patients who were given GLIOLAN and had surgery under blue light with those of surgery in patients who were not given any product that alters tumour visibility and had surgery under conventional white light.
The protocol specified two primary endpoints: the percentage of patients found by a brain MRI scan 72 hours after surgery to have no visible tumour, and progression-free survival at 6 months after surgery.

The percentage of patients found to have no residual tumour after undergoing an MRI check-up was 63.6% in the GLIOLAN group versus 37.6% in the control group ($p < 0.0001$).
The percentage of patients surviving without progression after six months was 20.5% in the GLIOLAN group versus 11.0% in the control group ($p = 0.0152$). This difference between the groups was not observed for this criterion 9, 12, 15 and 18 months after surgery.
No difference between the two groups was observed in terms of overall survival (the one-year survival rate was 58% in both groups).

Overall, the use of GLIOLAN is beneficial compared to surgery under white light in perioperative visualisation of high-grade gliomas, as shown by the percentage of patients found by an MRI check-up to have no residual tumour and by the 6-month progression-free survival rates. However, this advantage in terms of progression-free survival disappears at the next assessments conducted between 9 and 18 months after surgery, and GLIOLAN does not increase overall survival.
Data on the predictive value of tissue fluorescence obtained from the phase II study showed the limitations of this technique:
- approximately two-thirds of the non-fluorescent biopsy samples taken from adjacent normal tissue were found to contain tumour cells.
- post-operative MRI revealed the presence of residual tumours in two out of the ten patients who had undergone perioperative complete resection (this reflects failure of visualisation by this fluorescence technique).

The Committee emphasises that the use of GLIOLAN depends on neurosurgeons being specially trained in this technique and on the availability of a particular type of microscope capable of delivering blue light ($\lambda = 400 - 410$ nm).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Malignant gliomas are life-threatening;
This proprietary medicinal product is intended for use in perioperative diagnosis;
This proprietary medicinal product is a first-line medicinal product;
Public health benefit:

In public health terms, the burden which stage III and IV malignant gliomas represent is moderate. These are rare but rapidly-developing clinical conditions.

Improved screening for these cancers comes within the scope of the public health priority "improvement in cancer management" (GTNDO priority).

In the light of the data available, the proprietary medicinal product GLIOLAN, which allows gliomas to be removed by fluorescence-guided surgery, enables more complete removal of malignant tissue. However, the results of clinical studies do not show that GLIOLAN has any effect on the overall survival of patients suffering from malignant gliomas. Furthermore, no data describing the impact of GLIOLAN on quality of life is available.

It is difficult to predict how far these findings can be transposed into practice. This will limit the use of the technique because of the need for specially-adapted microscopes, which may take several years to become available, and as the procedure has to be carried out by neurosurgeons who have had special training.

Consequently, this proprietary product is not expected to benefit public health.

No alternative medicinal products exist;
The efficacy/adverse effects ratio is moderate;

The actual benefit of this medicinal product is moderate.

4.2. Improvement in actual benefit (IAB)

GLIOLAN offers a minor IAB (grade IV) in the management of high-grade malignant gliomas (grades III and IV in the WHO classification).

4.3. Therapeutic use [2 3 4]

Current treatment of high-grade malignant gliomas involves surgery, radiotherapy and chemotherapy (nowadays mainly temozolomide).
The primary aim of surgery is to remove as much malignant tissue as possible while avoiding the creation of a severe functional handicap or aggravating any existing handicap. It is generally accepted that median survival rates are linked to the quality of malignant tissue removal and the provision of radiotherapy and chemotherapy. For a median survival time of 12 months, it is thought that the additional survival time would be 8 to 14 weeks depending on the quality of surgery.
Particular techniques, such as MRI during surgery, neuronavigation and ultrasound, could improve the outcome of surgery.

2 Albert F-K, Forsting M, Sartor K, Adams HP, Kunze S. Early post-operative magnetic resonance imaging after resection of malignant glioma : objective evaluation of residual tumor and its influence on regrowth and prognosis. Neurosurgery 1994; 34: 45-61.
3 Hall WA. Extending survival in gliomas : surgical resection or immunotherapy ? Surg. Neurology 2004; 6 : 145-8
4 Laws ER. Detection of brain tumor invasion and micrometastasis in vivo by expression of enhanced green fluorescent protein. Neurosurgery 1998; 43: 1442.

GLIOLAN improves the visualisation of the tumour during the operation. There is at present no other equivalent product which has obtained marketing authorisation. The main advantage of this drug is therefore that it improves the ability of the surgeon to remove these malignant tumours more completely.

4.4. Target population

The target population for GLIOLAN is made up of adult patients suffering from a grade III or IV malignant glioma who are suitable for surgery.

In France, the incidence of malignant glioma is 3,000 patients a year[5], of whom approximately three-quarters are adults, giving a total of 2,300 adult patients.
Seventy-five per cent (75%) of gliomas are grade III or IV gliomas[6], giving a total of 1,730 patients.
In view of the need for neurosurgeons to be trained in this technique, and the need for a particular type of microscope capable of producing blue light (λ = 400 - 410 nm) to be used, the expert consensus is that between a quarter and a third of these adult patients might benefit from surgery with GLIOLAN, i.e. around 430 to 580 patients.

The target population for GLIOLAN is estimated at 430 to 580 patients a year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage in the marketing authorisation.

The Transparency Committee requests that a study be set up to monitor patients suffering from malignant gliomas who have undergone surgery in which GLIOLAN was used. The objectives of this study would be to document in a real-life setting:

- patient characteristics (gender, age, type of tumour, etc.)
- the characteristics of the surgeons treating these patients (experience, etc.)
- medical and/or surgical treatments administered following diagnosis
- patients' clinical progress after surgery (neurological after-effects, etc.)

The length of the study, decided on by the independent scientific committee, must be appropriate and sufficient to meet the Committee's need for information.
The Transparency Committee will reassess this proprietary medicinal product two years after the product is taken into clinical use.

5 Psimaras D, Delattre JY. Perspectives dans le diagnostic et la prise en charge des gliomes malins [Perspectives in the diagnosis and management of malignant gliomas]. Cancer Radiothérapie 2008; 12:695–700.
6 Fleury A, Menegoz F, Grosclaude P et al. Descriptive epidemiology of cerebral gliomas in France. Cancer 1997; 79: 1195-1202.