

**ANNEX**

**CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND  
EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED  
BY THE MEMBER STATES**

## **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES**

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

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

The Member States shall agree with the Marketing Authorisation Holder, prior to launch, measures for the implementation of the following:

- A training course for neurosurgeons which is aimed at risk minimisation and to support safe and effective use for the product. The training course will take place at qualified training centres using qualified trainers. This course shall consist of measures aiming to minimise adverse events associated with the Gliolan-fluorescence-guided surgery (in particular neurological serious adverse events) through adequate education about:
  - a) Theory and core principles of Gliolan-fluorescence-guided surgery and malignant glioma resection, including methods of eloquent sites identification;
  - b) On-site instructions on the use of the fluorescence-microscope, including pitfalls and recognition of problems;
  - c) Differentiation of fluorescence intensity, maintaining safety distances from eloquent areas, etc.
  - d) The practice of Gliolan-fluorescence-guided surgery (including participation in at least one cases using Gliolan-fluorescence-guided surgery in the operating room with on-site instructions on the use of the microscope or demonstration of a fluorescence-guided resection by video);
  - e) The current understanding of the benefits and risks of cytoreductive surgery in the management of patients with malignant gliomas;
  - f) The theoretical base for porphyrin accumulation in malignant gliomas;
  - g) The technical principles behind fluorescence-guided resections using Gliolan;
  - h) How to identify suitable candidates for fluorescence-guided resections using Gliolan;
  - i) How to apply Gliolan in the correct dosage and timing regimen, and to understand the importance of concurrent corticosteroids;
  - j) How to identify patients at risk for neurological deficits using fluorescence-guided resections with Gliolan with special focus on aphasia 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.