Direct Healthcare Professional Communication

Important information on Gliolan (5-aminolevulinic acid, 5-ALA): What to do in case of delayed surgery and information on fluorescence in non high-grade glioma.

Dear Healthcare Professional,

medac GmbH in agreement with the European Medicines Agency and the <national competent authority> would like to inform you of the following:

Summary

- **Occasionally, delays and postponement of surgery may occur despite 5-ALA having been administered. It is basically unknown for how long useful fluorescence persists in tumour cells beyond the defined window of lucid contrast. If the surgery is delayed by more than 12 hours, surgery should be re-scheduled for the next day or later. Another dose of this medicine can be taken 2 – 4 hours before anaesthesia. Re-administration of 5-ALA on the same day should be avoided as no data are available on the safety of a repeated dose of 5-ALA or the specificity of fluorescence with repeat same day administration.**
- **Neurosurgeons are reminded that fluorescence can be encountered in metastasis, inflammation, CNS infections (fungal or bacterial abscess), lymphoma, reactive changes or necrotic tissue, which does not indicate the presence of glioma cells. On the other hand, non-fluorescing tissue in the surgical field does not rule out the presence of tumour in the low density infiltration zone of patients with glioma.**

Background information

Gliolan (5-ALA) is indicated in adults for visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV). 5-ALA is a prodrug that is metabolised intracellularly to form the fluorescent molecule PPIX. As described in the SmPC, the maximum PPIX plasma level is reached four hours after oral administration of 20 mg/kg body weight 5-ALA HCl. PPIX plasma levels rapidly decline during the subsequent 20 hours and are not detectable anymore 48 hours after administration. At the recommended oral dose of 20 mg/kg body weight, tumour to normal brain fluorescence ratios are usually high and offer lucid contrast for visual perception of tumour tissue under violet-blue light for at least 9 hours.

In the clinical setting, delays can occur that prevent the patient entering the operating room and the brain may be exposed for tissue identification. This may lead to uncertainty whether the surgery can be performed within the window of lucid contrast described above. Due to this uncertainty, surgery should be completely rescheduled for the next day or later in case surgery is postponed for 12 hours or more, in which case another dose of 5-ALA can be administered 2-4 hours before anaesthesia. Re-administration of 5-ALA on the same day should not be considered as no information is available on the safety of early repeat dosing or on the specificity of fluorescence.

Please note that Gliolan should not be used as a tool for establishing the diagnosis of high-grade glioma, but is used as an aid to perform maximum safe resection. Some cases of fluorescence in non high-grade glioma cells have been reported in literature. Differential diagnosis, showing fluorescence when surgery for a suspected high-grade glioma was performed, included: inflammation, fungal or bacterial infection/abscess, necrotic tissue, multiple sclerosis, and neurodegenerative demyelinating disease (La Rocca et al., 2020).

The SmPC will be updated in section 4.2 (posology) in accordance with the current patient information leaflet:

If the surgery is delayed by more than 12 hours, surgery should be re-scheduled for the next day or later. Another dose of this medicine can be taken 2 – 4 hours before anaesthesia.

The following will be added to section 4.4 (warnings, precautions) of the SmPC:

False negative and false positive results may occur with the use of 5-ALA for intraoperative visualisation of malignant glioma. Non-fluorescing tissue in the surgical field does not rule out the presence of tumour in patients with glioma. On the other hand, fluorescence may be seen in areas of abnormal brain tissue (such as reactive astrocytes, atypical cells), necrotic tissue, inflammation, infections (such as fungal or bacterial infections and abscesses), CNS lymphoma or metastases from other tumour types.

The benefit-risk ratio of Gliolan remains positive.

The obligation of neurosurgeons to attend a training course prior to the use of Gliolan remains unchanged.

Call for reporting

Please report any suspected adverse reactions associated with the use of Gliolan (5-aminolevulinic acid) to the medac Pharmacovigilance Department at drugsafety@medac.de.

Alternatively, suspected adverse reactions should be reported in accordance with the national spontaneous reporting system <brief outline of the national reporting system and details on how to access it (e.g. name, postal address, fax number, website address).>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Yours sincerely/ Yours faithfully,

<names, titles, roles>

References

La Rocca G, Sabatino G, Menna G, Altieri R, Ius T, Marchese E, et al. 5-Aminolevulinic Acid False Positives in Cerebral Neuro-Oncology: Not All That Is Fluorescent Is Tumor. A Case-Based Update and Literature Review. World Neurosurg. 2020;137:187-193. PMID: 32058110

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Gliolan 30 mg/ml powder for oral solution (aminolevulinic acid hydrochloride)
Marketing authorisation holder(s)	medac GmbH
Safety concern and purpose of the communication	Safety concerns 1. Re-administration due to delayed surgery 2. Fluorescence in cells different from glioma and non-fluorescing tissue despite the presence of tumour. This DHPC is being disseminated to inform surgeons about the consolidation of the SmPC with existing information from the training courses and PL.
DHPC recipients	Board-certified neurosurgeons that previously attended a training course and are therefore qualified to receive Gliolan or who will attend the training course until the updated training manual can be distributed.
Member States where the DHPC will be distributed	In the following countries in the EEA Gliolan is on the market. Austria, Belgium, Croatia, Czechia, Denmark, Estonia, Finland, France, Germany , Greece, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.[1] If a registered neurosurgeon is located in one of these countries, the DHPC will be distributed there. Distribution should be further agreed upon with the national authorities

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP/CMDh	17 September 2020
Submission of translated DHPCs to the national competent authorities for review	20 November 2020
Agreement of translations by national competent authorities	27 November 2020
Dissemination of DHPC	1 December 2020

[1] As of 1.2.2020, the UK is no longer an EU Member State. However, EU law still applies to the UK during the transition period.