Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

1. Pneumocephalus:

Cumulatively, 51 cases of pneumocephalus were retrieved with carmustine implant. Accumulation of intracranial air is a normal finding following craniotomy and is usually asymptomatic and spontaneously absorbed. However it is to note that for 26 out of these 51 cases, pneumocephalus was reported with other events including brain oedema (27 reports), hemiplegia (10 reports), aphasia (4 reports) and seizures (7 reports). A possibility that the onset of pneumocephalus leads to serious AEs cannot be denied, and it is impossible to completely rule out the association of pneumocephalus with Gliadel. Therefore it is considered necessary to update sections 4.4 and 4.8 of Gliadel EU SmPC with the ADR of pneumocephalus, frequency "uncommon", based on data from interventional clinical trials.

2. Changes in the local blood vessels:

Among the 219 reports of adverse events associated with central nervous system hemorrhages and cerebrovascular accidents retrieved with carmustine implant, thirteen include information on vascular changes. Eight reports described effects that occurred in the aftermath of the surgery (vascular spasm (6), ischaemic stroke (1), vascular dissection (1)) and the remaining five reports described effect that developed more than 6 months after surgery (aneurysm (2), ischaemic stroke (2), vasculitis (1)). The two well documented cases of aneurysms reported a changed wall of blood vessel, very friable for one case and dissection of the intima for the second one.

Based on non-clinical data and available human data on pharmacokinetic properties, local inflammation due to carmustine may have some effects on proximate blood vessels. This is also in line with several clinical recommendations recommending to avoid carmustine wafer implantation at sites adjacent to large cerebral vessels.

Thus, in view of the seriousness of the events and considering the current body of evidence, it is recommanded to update section 4.4 of Gliadel EU SmPC in order to inform HCP about this potential risk of changes of wall of cerebral blood vessels located close to Gliadel wafer, including risk of aneurysm, that may contribute to the occurrence of cerebral haemorrhage or cerebrovascular accidents several months after Gliadel implantation and to recommend to avoid Gliadel wafers implantation adjacent to large cerebral vessels. In addition, it is noted that this potential risk can be minimised by avoiding implantation adjacent to large cerebral vessels.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for carmustine (implant) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing carmustine (implant) is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied.

To the extent that additional medicinal products containing carmustine (implant) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

The following changes to the product information of medicinal products containing the active substance carmustine implant are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Patients undergoing craniotomy for glioblastoma and implantation of GLIADEL Implant should be monitored closely in view of known complications of craniotomy which includes convulsions, intracranial infections, abnormal wound healing, ~~and~~ brain oedema **and pneumocephalus** (see section 4.8).

…//…

"Changes of wall of cerebral blood vessels located close to Gliadel wafer, including cases of aneurysms leading to cerebral bleeding several months after Gliadel wafer implantation, have been described. Gliadel wafers implantation adjacent to large cerebral vessels should be avoided."

- Section 4.8

The following adverse reaction "pneumocephalus" should be added under the SOC "Injury, poisoning and procedural complications" with a frequency **"uncommon".**

…//…

The following adverse events, not listed in the table above, were reported in patients treated with GLIADEL Implant in all studies. The events listed were either not present pre-operatively or worsened post-operatively. Whether GLIADEL Implant caused these events cannot be determined.

Adverse Events in patients receiving GLIADEL Implant

Class organ		Adverse events
…//…		
Injury, poisoning and procedural complications	**uncommon**	**"pneumocephalus"**
…//…		

"Cases of air accumulation at the implant site, sometimes associated with neurological symptoms (hemiplegia, aphasia, seizures) have been reported with Gliadel."

Package Leaflet

4. Possible side effects:

uncommon side effects (between 1 and 10 patients in every 1000)

Injury, poisoning and procedural complications

- **Pneumocephalus (air accumulation at the implant site)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 July 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 September 2019