Annex I

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

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for baclofen (oral), the scientific conclusions are as follows:

Further to a cumulative review of all case reports of central sleep apnoea syndrome with baclofen, the PRAC concluded that the provided dataset supports evidence of a causal relationship with baclofen. Whilst acknowledging that alcohol is a risk factor for “sleep apnoea syndrome”, the Committee agreed that amendments to section 4.8 of the SmPC are warranted with the inclusion of this ADR with frequency “unknown”, accompanied by an explanatory footnote.

In addition, the PRAC noted that a cumulative critical analysis of cases of rhabdomyolysis and related terms provided evidence of causal relationship in the context of both baclofen overdose and abrupt baclofen withdrawal. Hence, the Committee is of the view that amendments to sections 4.4 and 4.9 are required with the addition of “rhabdomyolysis” as a possible consequence of abrupt baclofen withdrawal and baclofen overdose respectively.

Finally, based on the review of cases of toxic encephalopathy with baclofen, the PRAC noted that the majority of the reported cases occurred due to the administration of baclofen to patients with end stage renal disease or compromised renal function at a dose in excess of that recommended in the SmPC; the patients presented with symptoms of baclofen overdose, the majority of which were neurological in nature. Hence, the Committee is of the view that an amendment to the section 4.4 is required to optimise the warnings and precautions for use in the population with renal impairment.

Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing oral baclofen, were warranted.

The CMDh agrees with the scientific conclusions made by the PRAC.

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

On the basis of the scientific conclusions for baclofen (oral) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing baclofen (oral) 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 baclofen (oral) are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

Annex II

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

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

A warning should be revised as follows:

Abrupt withdrawal:

"Treatment should always, (unless serious adverse effects occur), be gradually discontinued by successively reducing the dosage over a period of about 1-2 weeks. Anxiety and confusional state, delirium, hallucinations, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, **rhabdomyolysis** and temporary aggravation of spasticity as a rebound phenomenon have been reported with abrupt withdrawal of Lioresal, especially after long term medication."

- Section 4.4

A warning should be revised as follows:

Renal impairment:

"Baclofen should be used with caution in patients with renal impairment and should be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk (See section 4.2 Posology and method of administration). **Neurological signs and symptoms of overdose including clinical manifestations of toxic encephalopathy (e.g. confusion, disorientation, somnolence and depressed level of consciousness) have been observed in patients with renal impairment taking oral baclofen at doses of more than 5mg per day. Patients with impaired renal function should be closely monitored for prompt diagnosis of early symptoms of toxicity.**

Particular caution is required when combining baclofen to drugs or medicinal products that can significantly impact renal function. Renal function shall be closely monitored and baclofen daily dosage adjusted accordingly to prevent baclofen toxicity."
[....]

- Section 4.8

The following adverse reaction "**sleep apnoea syndrome*** " should be added under the SOC Nervous System disorders with a frequency "unknown".

The adverse reaction should be accompanied by the following explanatory footnote: "*** Cases of central sleep apnoea syndrome have been observed with baclofen at high doses (≥ 100 mg) in patients who are alcohol dependent**".

- Section 4.9

The wording should be revised as follows:

[….]

“Also liable to occur are: confusion, hallucinations, agitation, convulsion, abnormal electroencephalogram (burst suppression pattern and triphasic waves), accommodation disorder, impaired pupillary reflex; generalised muscular hypotonia, myoclonia, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension or hypertension, bradycardia or tachycardia, or cardiac arrhythmia; hypothermia; nausea, vomiting, diarrhoea, salivary hypersecretion; increased hepatic enzymes, SGOT and AP values, **rhabdomyolysis.”**

Package Leaflet

- Section 4 “Possible side effects”

Also reported (frequency unknown)

Trouble breathing during sleep (sleep apnoea syndrome)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 August 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 October 2017