

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:

Suicide and suicide-related events

One MAH identified 302 cases pertaining to suicidality/suicidal ideation with baclofen. Of these 302 cases, there were 56 cases of completed suicide (including one case of suicide attempt co-reported with completed suicide) 193 cases of suicide attempt/suicidal behaviour/intentional overdose, 40 cases of suicidal ideation and 13 cases of poisoning deliberate. Despite the presence of additional risk factors for suicide in a considerable proportion of cases, a contributory role of baclofen to the events observed cannot be excluded.

One of the common side effects of baclofen is depression. In addition, as outlined in section 4.4 of the SmPC, psychotic disorders, schizophrenia, depressive or manic disorders and alcoholism may be exacerbated by treatment with baclofen. Moreover, both suicidal ideation and suicide attempt are listed uncommon side effects for intrathecal baclofen. In view of the pharmacological properties of baclofen and considering the severe and potentially life-threatening consequences of baclofen overdose, particularly when other substances are co-ingested, it is considered that the product information should be updated to include a warning in section 4.4 of the SmPC under the existing heading "Psychiatric and nervous system disorders", to alert healthcare professionals and patients/carers to this risk. The package leaflet is updated accordingly.

Misuse, abuse and dependence

A cumulative review of drug abuse and related terms with baclofen identified 216 relevant cases. Of these 216 cases, 152 cases described intentional overdose, 53 cases reported drug abuse/unspecified abuse/unspecified and 11 were categorised as drug dependence. Seven pertinent literature case reports were also identified.

Euphoria mood and sedation are common and very common side effects of baclofen respectively. This mood elevating property and perhaps to a lesser extent the sedative effect, are both suggested as potential motivating factors for baclofen abuse, as illustrated by both the literature case reports and the cases identified in the MAH's database.

In view of the high potential for abuse and misuse with baclofen in the context of pre-existing or medical history of substance abuse or comorbid psychiatric illness, as evidenced by the pharmacological properties of baclofen, the well documented literature case reports, largely in patients with additional risk factors for substance use disorders, the accumulation of relevant cases of abuse, misuse and dependence identified by the MAH in the safety database, the signal of disproportionality for the Preferred Term 'Drug abuse' in Europe and the existing warning in the product information on the need to gradually discontinue baclofen due to the potential for the induction of a withdrawal syndrome, it is considered that the product information should be updated to include a warning on this risk as outlined below to alert healthcare professionals and patients to this safety concern. The package leaflet is updated accordingly.

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 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 baclofen (oral) are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

Warnings should be added under the existing heading of "Psychiatric and nervous system disorders" as follows:

Psychiatric and nervous system disorders

Porphyria, history of alcoholism, hypertension, psychotic disorders, schizophrenia depressive or manic disorders, confusional states or Parkinson's disease may be exacerbated by treatment with Lioresal. Patients suffering from these conditions should therefore be treated cautiously and kept under close surveillance.

Suicide and suicide-related events have been reported in patients treated with baclofen. In most cases, the patients had additional risk factors associated with an increased risk of suicide including alcohol use disorder, depression and/or a history of previous suicide attempts. Close supervision of patients with additional risk factors for suicide should accompany drug therapy. Patients (and caregivers of patients) should be alerted about the need to monitor for clinical worsening, suicidal behaviour or thoughts or unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Cases of misuse, abuse and dependence have been reported with baclofen. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of baclofen misuse, abuse or dependence e.g. dose escalation, drug-seeking behaviour, development of tolerance.

Package Leaflet

- Section 2 "Before you take baclofen"

Talk to your doctor or pharmacist before taking baclofen if you:

.....

- have a history of alcoholism, or you drink alcohol to excess **or you have a history of drug abuse or dependence**

Some people being treated with baclofen have had thoughts of harming or killing themselves or have tried to kill themselves. Most of these people also had depression, had been using alcohol excessively or were prone to having thoughts of killing themselves. If you have thoughts of harming or killing yourself at any time, speak to your doctor straightaway or go to a hospital. Also, ask a relative or close friend to tell you if they are worried about any changes in your behaviour and ask them to read this leaflet.

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