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 gabapentin, the scientific conclusions are as follows:

In view of the available data, including post-marketing reports and the literature review, there is sufficient evidence for a causal relation between in-utero exposure to gabapentin and the occurrence of neonatal withdrawal syndrome. Furthermore, in-utero co-exposure to gabapentin and opioids may increase the risk of neonatal withdrawal syndrome. The PRAC therefore proposes to update the product information.

In view of the available data, including post-marketing reports; abuse and dependence of gabapentin may also occur in patients without a history of substance use disorder and in context of therapeutic doses of gabapentin. It is therefore considered necessary to strengthen the warning on abuse and dependence. The proposed update to the information for gabapentin is consistent with the previous updates for pregabalin PI in this regard (please refer to EMEA/H/C/000546/LEG/057 and EMEA/H/C/003880/LEG/009).

Gabapentinoid withdrawal has been described as similar to benzodiazepines and alcohol withdrawal in recent literature. Gabapentinoids can lead to substantial physical dependence (tolerance and withdrawal) and signs of psychological dependence i.e. craving, loss of control of use, drug-seeking behavior - all representing core features of addiction (Evoy et al. 2021, Bonnet et al. 2022). Upon review of 161 cases in patients without a history of psychiatric or substance use disorder, the MAH Pfizer concluded that withdrawal symptoms have been reported after discontinuation of short-term and long-term treatment.

Withdrawal symptoms might be indicative of drug dependence and are of clinical significance. However, as an explicit warning on possible withdrawal symptoms is currently not included in SmPC section 4.4, the PRAC is of the opinion that the current labelling is insufficient and proposes to add information to SmPC sections 4.4 and 4.8, in line with the pregabalin product information, including the additional withdrawal symptoms that were described in literature and spontaneous case reports.

Reports of toxic epidermal necrolysis have been reported in the literature and the MAH's safety database for which a contributory role of gabapentin cannot be excluded. Steven-Johnson-Syndrome is listed as an ADR with unknown frequency in the product information of gabapentin-containing medicinal products. Steven-Johnson syndrome and toxic epidermal necrolysis represent a clinical entity with flowing transitions in their expression; the pathophysiologic mechanism and clinical characteristics are the same, but TEN involves a larger body surface area (> 30 %). From a clinical point of view, a clear differentiation between SJS and TEN is not considered reasonable, as a transition to TEN can occur during the course. An SJS-TEN overlap case has also been reported for gabapentin. The PRAC is therefore of the opinion that the risk of SJS/TEN should be adequately labelled in the product information and should be brought in line with the recently updated product information (signal procedure) of the gabapentinoid pregabalin

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 gabapentin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing gabapentin 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 gabapentin 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)

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 4.6 Fertility, pregnancy and lactation

Pregnancy

…

Neonatal withdrawal syndrome has been reported in newborns exposed *in utero* to gabapentin. Co-exposure to gabapentin and opioids during pregnancy may increase the risk of neonatal withdrawal syndrome. Newborns should be monitored carefully.

- Section 4.4:

Misuse, a~~A~~buse **potential** and dependence

Gabapentin can cause drug dependence, which may occur at therapeutic doses. Cases of abuse and misuse have been reported. Patients with a history of substance abuse may be at higher risk for gabapentin misuse, abuse and dependence, and gabapentin should be used with caution in such patients. Before prescribing gabapentin, the patient's risk of misuse, abuse or dependence should be carefully evaluated.

Patients treated with gabapentin should be monitored for symptoms of gabapentin misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

~~Cases of abuse and dependence have been reported in the post-marketing database. Carefully evaluate patients for a history of drug abuse and observe them for possible signs of gabapentin abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance.~~

- Section 4.8:

The following adverse reaction should be added under the SOC Psychiatric disorders with a frequency not known: **Drug dependence**

- Section 4.4 below the subsection 'Abuse and dependence'

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed. Withdrawal symptoms may occur shortly after discontinuation, usually within 48 hours. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise. The occurrence of withdrawal symptoms following discontinuation of gabapentin may indicate drug dependence (see section 4.8). The patient should be informed about this at the start of the treatment. If gabapentin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see section 4.2).

- Section 4.8

General disorders and administration site conditions	
Very Common	fatigue, fever
Common	peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon	generalized oedema
Not known	*withdrawal reactions*[*] ~~*(mostly anxiety, insomnia, nausea, pains, sweating)*~~*, […]*

- Description under the ADR table:

Description under the ADR table:

[*]**After discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed. Withdrawal symptoms may occur shortly after discontinuation, usually within 48 hours. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise (see section 4.4). The occurrence of withdrawal symptoms following discontinuation of gabapentin may indicate drug dependence (see section 4.8). The patient should be informed about this at the start of the treatment. If gabapentin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see section 4.2).**

- Section 4.4 :

~~Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)~~
~~Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking antiepileptic drugs including gabapentin (see section 4.8).~~
~~It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.~~

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug rash with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with gabapentin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, gabapentin should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of gabapentin, treatment with gabapentin must not be restarted in this patient at any time.

- **Section 4.8**

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders in the modified order as indicated:

Frequency 'not known': Stevens-Johnson-syndrome, **toxic epidermal necrolysis**,
drug rash with eosinophilia and systemic symptoms (see section 4.4), erythema multiforme, angioedema, alopecia

Package Leaflet

- Section 2:

Pregnancy

[…]

If used during pregnancy, gabapentin may lead to withdrawal symptoms in newborn infants. This risk might be increased when gabapentin is taken together with opioid analgesics (drugs for treatment of severe pain).

- Section 2:

Warnings and precautions

Talk to your doctor or pharmacist before taking <product name>
- […]

- **Before taking this medicine, tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines or illegal drugs; it may mean you have a greater risk of becoming dependent on <product name>.**

[…]

Dependence

Some people may become dependent on <product name> (a need to keep taking the medicine). They may have withdrawal effects when they stop using <product name> (see section 3, "How to take <product name>" and "If you stop taking <product name>"). If you have concerns that you may become dependent on <product name>, it is important that you consult your doctor.

If you notice any of the following signs whilst taking <product name>, it could be a sign that you have become dependent.

- You feel you need to take the medicine for longer than advised by your prescriber

- You feel you need to take more than the recommended dose

You are using the medicine for reasons other than prescribed

- You have made repeated, unsuccessful attempts to quit or control the use of the medicine

- When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again

If you notice any of these, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to do this safely.

[…]

3. How to take <product name>

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. **Do not take more medicine than prescribed.**

4. Possible side effects

Not known: frequency cannot be estimated from the available data

- **Becoming dependent on <product name> ('drug dependence')**

- Section 3:

If you stop taking <product name>

~~Do not stop taking Neurontin unless your doctor tells you to.~~ **Do not suddenly stop taking <product name>. If you want to stop taking <product name>, discuss this with your doctor first. They will tell you how to do this.** If your treatment is stopped it should be done gradually over a minimum of 1 week. ~~If you stop taking Neurontin suddenly or before your doctor tells you, there is an increased risk of seizures~~. **After stopping a short or long-term treatment with <product name>, you need to know that you may experience certain side effects, so-called withdrawal effects. These effects can include seizures, anxiety, difficulty sleeping, feeling sick (nausea), pain, sweating, shaking, headache, depression, feeling abnormal, dizziness, and feeling generally unwell. These effects usually occur within 48 hours after stopping <product name>. If you experience withdrawal effects, you should contact your doctor.**

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

PL section 4:

- Section 4:

4. Possible side effects

Not known: frequency cannot be estimated from the available data

- becoming dependent on <product name> ('drug dependence')

After stopping a short or long-term treatment with <product name>, you need to know that you may experience certain side effects, so-called withdrawal effects (see "If you stop taking <product name>").

- **Section 2**

~~A small number of people taking Neurontin get an allergic reaction or potentially serious skin reaction, which may develop into more serious problems if they are not treated. You need to know the symptoms to look out for while you are taking <product name>.~~

Serious skin rashes including Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with gabapentin. Stop using gabapentin and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

The following wording should be added as first paragraph to PL section 4, under the below heading:

- **Section 4**

Stop using <product name> and seek medical attention immediately if you notice any of the following symptoms:

- **reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious**

skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson-syndrome, toxic epidermal necrolysis).

- **Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).**

After marketing <product name> the following side effects have been reported:

- ~~A group of side effects that could include swollen lymph nodes (isolated small raised lumps under the skin), fever, rash, and inflammation of liver occurring together~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October / 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 November 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 January 2023