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 levetiracetam, the scientific conclusions of the CHMP are as follows:

Acute kidney injury

Following the review of the signal assessment report (SSAR), the Innovator MAH confirmed the possible association between levetiracetam and acute kidney injury. Therefore the undesirable effect “Acute kidney injury” should be added under the MedDRA System Organ Class (SOC) Renal and urinary disorders (frequency ‘rare’) as well as a warning in the Product Information of all levetiracetam-containing products.

Rhabdomyolysis/Blood creatine phosphokinase increased

Four case reports (2 published) with very suggestive causal association were issued during the reporting period regarding rhabdomyolysis in association with levetiracetam use. The statistical analysis in Eudravigilance based in proportional reporting ratio (PRR) was significant for a signal. Therefore, the MAHs should add the undesirable effect “Rhabdomyolysis” under the SOC Musculoskeletal and connective tissue disorders (frequency ‘rare’) in the Product Information of all levetiracetam-containing products. Moreover, as it is associated with rhabdomyolysis, the undesirable effect “Blood creatine phosphokinase increased” should also be added to the Product Information under the SOC Musculoskeletal and connective tissue disorders (frequency ‘rare’).

Encephalopathy

The safety report prepared by the Innovator MAH contained several cases very suggestive of a causal association between levetiracetam and encephalopathy. The statistical disproportionality analysis performed by the Innovator MAH in its own database was suggestive of a safety signal for ‘encephalopathy’ associated with levetiracetam. This statistical signal was also confirmed in Eudravigilance, based on PRR analysis. Based on the above, it is considered justified to document that cases of “encephalopathy” have been observed rarely in the Product Information of all levetiracetam-containing products.

Therefore in view of the data presented in the PSURs the PRAC considers that changes to the product Information of medicinal products containing levetiracetam were warranted.

The CHMP 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 levetiracetam the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing levetiracetam is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.
Annex II
Amendments to the product information of the nationally authorised medicinal product(s)
Amendments to be included in the relevant sections of the Summary of Product Characteristics (new text underlined and in bold, deleted text strike through)

- Section 4.4
A warning on acute kidney injury should be added as follows:

**Acute kidney injury**
The use of levetiracetam has been very rarely associated with acute kidney injury with a time to onset ranging from a few days to several months.

A warning on blood dyscrasias should be added as follows:

**Blood cell counts**
Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections or coagulation disorders (section 4.8).

- Section 4.8
The following adverse reactions should be added:

  - “**Rhabdomyolysis**” under the SOC Musculoskeletal and connective tissue disorders (frequency: rare). A footnote is proposed to highlight that the prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.
  
  - “**Blood creatine phosphokinase increased**” under the SOC Musculoskeletal and connective tissue disorders (frequency: rare). A footnote is proposed to highlight that the prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.
  
  - “**Acute kidney injury**” under the SOC Renal and urinary disorders (frequency rare).
  
  - “**Encephalopathy**” (not listed as an independent ADR in the table of undesirable effects from the section 4.8, but as a footnote at the bottom of the table).

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Rash</th>
<th>Alopecia, eczema, pruritus,</th>
<th>Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscular weakness, myalgia</td>
<td><strong>Rhabdomyolysis and blood creatine phosphokinase increased</strong></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia/fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td>Injury</td>
<td></td>
</tr>
</tbody>
</table>

*(at the end of the Table):*
* Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.

Cases of encephalopathy have rarely been observed after levetiracetam administration. These undesirable effects generally occurred at the beginning of the treatment (few days to a few months) and were reversible after treatment discontinuation.

Amendments to be included in the relevant sections of the Package Leaflet (new text underlined and in bold, deleted text strike through)

Section 4 of the package leaflet should be updated to add adverse reactions such as acute kidney injury, encephalopathy, rhabdomyolysis and blood creatine phosphokinase increase. In addition the section was brought in line with the latest QRD template for the ADRs angioedema, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis.

Section 4: Possible side effects

Tell your doctor immediately, or go to your nearest emergency department, if you experience:

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- swelling of the face, lips, tongue and throat (Quincke’s oedema)
- flu-like symptoms and a rash on the face followed by an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes (Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]).
- symptoms such as low urine volume, tiredness, nausea, vomiting, confusion and swelling in the legs, ankles or feet, as this may be a sign of sudden decrease of kidney function
- a skin rash which may form blisters and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme)
- a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
- a more severe form of rash causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis)
- signs of serious mental changes or if someone around you notices signs of confusion, somnolence (sleepiness), amnesia (loss of memory), memory impairment (forgetfulness), abnormal behaviour or other neurological signs including involuntary or uncontrolled movements. These could be symptoms of an encephalopathy.

(...)

Rare: may affect 1 to 10 users in 10,000 people

- liver failure, hepatitis;
- sudden decrease in kidney function;
- skin rash, which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme), a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), and a more severe form causing skin peeling in more than 30% of the body surface (toxic epidermal necrolysis).
- rhabdomyolysis (breakdown of muscle tissue) and associated blood creatine phosphokinase increase. Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients.