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 tramadol, the scientific conclusions are as follows:

Based on the review of data available from literature, and taking into account the inputs provided by the Pharmacogenomics working party (PGWP) and the Paediatric Committee (PDCO), the PRAC recommends the addition of a strong warning in section 4.4 of the SmPC on the metabolism of tramadol via CYP2D6, as well as on its use in children in post-operative settings and with compromised respiratory function. In addition, as the risks of dependence and withdrawal symptoms have been better characterised through the evaluation of the available literature and post-marketing surveillance, section 4.4 of the SmPC should be updated accordingly. Since new information emerged from literature with regards to the presence of tramadol in milk of breastfed infants, the PRAC considered that the information contained in section 4.6 with regards to breastfeeding should be amended. The Package leaflet is updated accordingly.

For a better reflection of the risk of tolerance to tramadol and of the information available on drug-drug interactions of tramadol, sections 4.4 and 5.2 should be updated, respectively; no updates of the Package Leaflet are necessary in these regards, since patient-specific information is not affected by these changes to the SmPC.

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 tramadol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing tramadol 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 tramadol 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 4.4

A warning should be added as follows:

CYP2D6 metabolism

Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing <side effects> of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	**Prevalence %**
African/Ethiopian	**29%**
African American	**3.4% to 6.5%**
Asian	**1.2% to 2%**
Caucasian	**3.6% to 6.5%**
Greek	**6.0%**
Hungarian	**1.9%**
Northern European	**1% to 2%**

Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function

Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. <These factors may worsen symptoms of opioid toxicity>.

The following phrase of section 4.4 should be amended as detailed:

~~On long-term use~~ Tolerance, psychic and physical dependence may develop**, especially after long-term use.**

The following phrase should be added in section 4.4:

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Where present, the following phrase of section 4.4 should be removed as detailed:

~~Tramadol has a low dependence potential~~

- Section 4.6

The following paragraph should be added, or amended as detailed:

Breast-feeding

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

- Section 5.2

The following paragraph should be amended as detailed:

[….]

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. ~~Up to now, clinically relevant interactions have not been reported.~~

Package Leaflet

- Section 2

Warnings and precautions

Tramadol is transformed in the liver by an enzyme. Some people have a variation of this enzyme and this can affect people in different ways. In some people, they may not get enough pain relief but other people are more likely to get serious side effects. If you notice any of the following side effects, you must stop taking this medicine and seek immediate medical advice: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite.

Children and adolescents

Use in children with breathing problems

Tramadol is not recommended in children with breathing problems, since the symptoms of tramadol toxicity may be worse in these children.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding

Tramadol is excreted into breast milk. For this reason, you should not take <product name> more than once during breast-feeding, or alternatively, if you take <product name> more than once, you should stop breast-feeding.

- Section 3

If you stop taking tramadol:

You should not suddenly stop taking this medicine unless your doctor tells you to. If you want to stop taking your medicine, discuss this with your doctor first, particularly if you have been taking it for a long time. Your doctor will advise you when and how to stop, which may be by lowering the dose gradually to reduce the chance of developing unnecessary side effects (withdrawal symptoms).

[……]

- Section 2 or Section 4

Where present, any statement relating to tramadol having a low dependence potential, such as the following or similar should be removed:

~~If [XX] is taken over a long period of time dependence may occur, although the risk is very low.~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 March 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 May 2018