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 tianeptine, the scientific conclusions are as follows:

Based on the review of literature and data from case reports, the PRAC considers that a causal relationship between tianeptine dose decrease (including gradual decrease) and occurrence of withdrawal symptoms is probable and therefore recommends an update of sections 4.2 and 4.4 of the of the summary of product characteristics to add a warning on withdrawal symptoms of tianeptine containing medicinal products. The package leaflet is updated accordingly.

Given that hyponatremia is a known risk associated to tianeptine treatment and in order to advice for caution about populations at risk especially elderly patients based on the review of literature and data from case reports and safety databases, the PRAC recommends that a warning on hyponatremia should be added to section 4.4 of the summary of product characteristics of tianeptine containing medicinal products.

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 tianeptine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing tianeptine 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 tianeptine 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 4.2

Abrupt discontinuation of the treatment should be avoided. The dosage should be gradually reduced over a period of 7 to 14 days in order to reduce the risk of withdrawal reactions (see sections 4.4)

- Section 4.4

A warning should be added/revised as follows:

Abuse/dependence and withdrawal syndrome:

If there is a history of drug dependence or alcohol dependence, the patients must be kept under very close surveillance in order to avoid any increase in dosage.

After discontinuation of treatment with tianeptine, withdrawal symptoms have been observed in some patients. The following events have been observed: Anxiety, Muscle pain, abdominal pain, Insomnia, Joint pain. When the treatment is started, the patient should be informed on the risk of withdrawal syndrome at discontinuation.

~~As with all psychotropic agents, I~~If the treatment is to be interrupted the dosage should be gradually reduced over a period of 7 to 14 days in order to reduce the risk of withdrawal reactions **(see sections 4.2)**.

[…]

Hyponatraemia

Hyponatraemia probably due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH) has been reported with the use of tianeptine. The majority of cases were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution should be exercised in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients or those treated with diuretics.

Package Leaflet

- **Section 2. What you need to know before you take [brand name]**

Warning and precaution

Precautions

Do not stop treatment abruptly; dosage should be reduced gradually for 7 to 14 days. **After stopping tianeptine treatment, you need to know that you may experience certain side effects. These include anxiety, muscle pain, abdominal pain, insomnia, joint pain.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February /2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 April 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	12 June 2019