Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

1. Risks after intrauterine exposure:

Results from a large cohort study of approximately 3,400 exposed pregnancies do not suggest an increased risk of overall birth defects. However, a small increase in the risk of cardiac malformations associated with intrauterine exposure to methylphenidate in the first trimenon was identified (pooled relative risk, 1.28; 95%CI, 1.00-1.64). Taking into account the limitations of the study and the non-significance, the SmPC was updated with information that data from a large study does not indicate an increased risk of overall birth defects and cautious wording that risk of cardiac malformation could however not be ruled out.

2. Incontinence:

A literature and database search identified 28 cases of incontinence / enuresis, of which 12 cases showed evidence for a causal association of incontinence with methyphenidate. Of these, seven cases showed a close temporal relationship between drug intake and incontinence, 11 cases reported positive dechallenge, five cases reported a positive rechallenge and in five cases no other plausible alternative reason for the onset of incontinence / enuresis than MPH could be identified. Overall, causality was classified as possible in seven cases, probable in four cases and certain in one case. Consequently, the SmPC was updated.

3. Trismus:

A literature and database search identified 67 cases of trismus, of which 12 cases showed evidence for a causal association of trismus with methyphenidate. Of these, six cases showed a close temporal relationship between drug intake and trismus, six cases reported positive dechallenge without confounding corrective treatment, four cases reported a positive rechallenge and in five cases no other plausible alternative reason for the onset of trismus than MPH could be identified. Overall, causality was classified as possible in fourteen cases and probable in seven cases. Consequently, the SmPC was updated.

4. Bruxism:

A literature review on bruxism associated with methylphenidate revealed evidence for a causal association including cases with close temporal relationship, positive dechallenge, positive rechallenge and no other plausible alternative reason for the onset of bruxism. Consequently, the SmPC was updated.

5. Hyperhidrosis:

In studies performed with methylphenidate in Adults, the frequency of hyperhidrosis varied between 1.3% to 8.8% of treated patients. Thus, the frequency of the event hyperhidrosis in Adults was updated to common.

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

All MPH products:

SmPC Section 4.6

~~There is limited amount of data from the use of methylphenidate in pregnant women.~~

Data from a cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a small increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

In **SmPC Section 4.8** it should be added:

- SOC "Psychiatric disorders": bruxism (frequency: *common*)
- SOC "Renal and urinary disorders": incontinence (frequency: *unknown*)
- SOC "Musculoskeletal and connective tissue disorders": trismus (frequency: *unknown*)

MPH products with indication(s) in Adults:

The frequency of "hyperhidrosis" should be updated to: common*

***ADR from clinical trials in adult patients that was reported with a higher frequency than in children and adolescents**

Package Leaflet

All MPH products:

2. What you need to know before you take [TRANDNAME]

Pregnancy, breast-feeding and contraception

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

~~It is not known if methylphenidate will affect an unborn baby.~~

Available data do not suggest an increased risk of overall birth defects, whilst a small increase in the risk of malformations of the heart when used during the first three months of pregnancy could not be ruled out. Your doctor will be able to give you more information about this risk. Tell your doctor or pharmacist before using methylphenidate if you or your daughter:

- is sexually active. Your doctor will discuss contraception.
- is pregnant or think might be pregnant. Your doctor will decide whether methylphenidate should be taken.

4. Possible side effects

Common:

- **excessive teeth grinding (bruxism)**

Not known (frequency cannot be estimated from the available data):

- **inability to control the excretion of urine (incontinence)**
- **spasm of the jaw muscles that makes it difficult to open the mouth (trismus)**

MPH products with indication(s) in Adults:

- 4. Possible side effects

Frequency of “excessive sweating” updated to “common”

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 August 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 October 2019