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 morphine, morphine/cyclizine, the scientific conclusions are as follows:

Based on postmarketing reporting and literature data, PRAC considered it relevant to update the Product Information (PI) by adding warnings on acute chest syndrome in patients with sickle cell disease, adrenal insufficiency, hypogonadism after long-term use, potentially fatal interactions with benzodiazepines, interactions with rifampicin (leading to reduced analgesic effects) and hyperalgesia observed particular in high doses.

Furthermore, the available data also supported the inclusion of anaphylactoid reaction, anxiety and dysphoric mood (as symptoms of drug withdrawal), hyperhidrosis, dry mouth, dependence, drug withdrawal syndrome, as well as allodynia and hyperalgesia as adverse events in the PI.

Based on non-clinical data indicating reduced fertility and risk of chromosomal damage, an update of the relevant sections of the product information is also considered warranted.

As neonatal abstinence syndrome in newborns of mothers treated with opioids has been observed, relevant information has been reflected in the relevant sections of the PI.

In addition, in the light of the available data on dependence, abuse and withdrawal the respective recommendations and warnings in the PI have been strengthened to reflect relevant risk factors and symptoms. The risks of death and aspiration pneumonia have further been added in the relevant PI sections addressing overdose.

Precipitate formation with 5-Fluorouracil has been observed in products authorised for injection/infusion, therefore this incompatibility is reflected in relevant sections of the PI for these 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 morphine, morphine/cyclizine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing morphine, morphine/cyclizine 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 morphine, morphine/cyclizine 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 MAHs

Summary of Product Characteristics

- Section 4.2:

Discontinuation of therapy

An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore the dose should be gradually reduced prior to discontinuation.

- Section 4.4

A warning should be added as follows:

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)

Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

For SmPCs that do not already have information on the topic, the following text should be included in section 4.4:

Adrenal insufficiency

Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

For SmPCs that do not already have information on the topic, the following text should be included in section 4.4:

Decreased Sex Hormones and increased prolactin

Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

A warning should be added as follows:

Hyperalgesia that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

A warning should be added as follows:

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of <product name> and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe <Product name> concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

For SmPCs that do not already have the below wording on the topic, the following warning should be included:

Morphine has an abuse potential similar to other strong agonist opioids, and should be used with particular caution in patients with a history of alcohol or drug abuse.

For SmPCs that do not already have the below wording on the topic, the following warning should be included:

Dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. The risk increases with the time the drug is used, and with higher doses. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

A warning should be added as follows:

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

- Section 4.5

A warning should be added as follows:

Sedative medicines such as benzodiazepines or related drugs:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

- Section 4.6

Fertility

Animal studies have shown that morphine may reduce fertility (see 5.3. preclinical safety data).

Pregnancy

Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. Treatment may include an opioid and supportive care.

- Section 4.8

MAHs with the below terms already included in their product information section 4.8 should maintain their calculated frequency for all the below listed adverse reactions.

The following adverse reaction(s) should be added under the SOC Immune system disorders with frequency unknown: **anaphylactoid reactions**

The following adverse reaction(s) should be added under the SOC Nervous system disorders with frequency unknown: **allodynia, hyperalgesia (see section 4.4)**

The following adverse reaction(s) should be added under the SOC Nervous system disorders with frequency unknown: **hyperhidrosis**

The following adverse reaction(s) should be added under the SOC Gastrointestinal disorders with frequency unknown: **dry mouth**

The following symptoms should be added as symptoms of drug withdrawal symptoms, e.g. in a section 4.8c) Description of selected adverse reactions below the adverse drug reaction table: **dysphoric mood, anxiety**

The following adverse reaction(s) should be added under the SOC Psychiatric disorder with frequency unknown: **dependence**

The following adverse reaction(s) should be added under the SOC General disorders and administration site conditions with frequency unknown: **drug withdrawal (abstinence) syndrome**

The following text should be included in section 4.8c), Description of selected adverse reactions, or in a similar section below the adverse drug reaction table.

drug dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered, or can sometimes be experienced between doses. For management, see 4.4.

Physiological withdrawal symptoms include: Body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, "drug craving" is often involved.

- Section 4.9

The following symptoms of overdose should be added to section 4.9:

Symptoms

Death may occur from respiratory failure.

Pneumonia aspiration.

- Section 5.3

The following information should be added:

In male rats, reduced fertility and chromosomal damage in gametes have been reported.

Package Leaflet

- 2. What you need to know before you <take> <use> X

Warnings and precautions

Talk to your doctor <or> <pharmacist> <or nurse> if you experience any of the following symptoms while <taking> <using> X:

- **Increased sensitivity to pain despite the fact that you are taking increasing doses (hyperalgesia). Your doctor will decide whether you will need a change in dose or a change in strong analgesic ("painkiller"), (see section 2).**
- **Weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. This may be a symptom of the adrenals producing too little of the hormone cortisol, and you may need to take hormone supplement.**
- **Loss of libido, impotence, cessation of menstruation. This may be because of decreased sex hormone production.**
- **If you have once been dependent on drugs or alcohol. Also tell if you feel that you are becoming dependent on X while you are using it. You may have started to think a lot about when you can take the next dose, even if you do not need it for the pain.**
- **Abstinence symptoms or dependence. The most common abstinence symptoms are mentioned in section 3. If this occurs, your doctor may change the type of medicine or the times between doses.**

Other medicines and X

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

This is especially important if you are taking any of the medicines mentioned below or medicines for:

- **Rifampicin to treat e.g. tuberculosis**
- **Concomitant use of X and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However if your doctor does prescribe X together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.**

Pregnancy <and> <,> breast-feeding <and fertility>

If X is used for a long time during pregnancy, there is a risk of the new-born child having drug withdrawal (abstinence) symptoms which should be treated by a doctor.

- 3. How to <take> <use> X

The following information should be added as appropriate:

<If you <take> <use> more X than you should>

People who have taken an overdose may **get pneumonia from inhaling vomit or foreign matter, symptoms may include breathlessness, cough and fever.**

People who have taken an overdose may also have **breathing difficulties leading to unconsciousness or even death.**

If you stop using X

Do not stop treatment with X unless agreed with your doctor. If you want to stop the treatment with X, ask your doctor how to slowly decrease the dosis so you avoid abstinence symptoms. Abstinence symptoms may include body aches, tremors, diarrhoea, stomach pain, nausea, flu-like symptoms, fast heartbeat and large pupils. Psychological symptoms include an intense feeling of unsatisfaction, anxiety and irritability

- 4. Possible side effects

In accordance with the QRD-template the following information should be added in the beginning of the section since it is considered to be important.
For PLs that do not already have information on the topic, the following text should be included:

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Important side effects or symptoms to look out for and what to do if you are affected:

- **Serious allergic reaction which causes difficulty in breathing or dizziness.**

If you are affected by these important side effects contact a doctor immediately.

The following adverse reaction(s) should be added with a frequency unknown, MAHs with similar wording already included in their package leaflet should maintain their calculated frequency:

- **An increased sensitivity to pain**
- **Sweating**
- **Dry mouth**
- **Abstinence symptoms or dependence (for symptoms see section 3: If you stop taking X).**

Morphine containing products authorised for injection/infusion

Summary of Product Characteristics

- Section 6.2

A warning should be added as follows:

Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulphate and 5- fluorouracil.

Package Leaflet

The following information is intended for healthcare professionals only:

Physicochemical incompatibility (formation of precipitates) has been demonstrated between solutions of morphine sulphate and 5- fluorouracil.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 August 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 October 2018