# Part VI: Summary of the risk management plan

## Summary of risk management plan for Sixmo (buprenorphine)

This is a summary of the risk management plan (RMP) for Sixmo. The RMP details important risks of Sixmo, how these risks can be minimised, and how more information will be obtained about Sixmo's risks and uncertainties (missing information).

Sixmo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Sixmo should be used.

This summary of the RMP for Sixmo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Sixmo's RMP.

## I. The medicine and what it is used for

Sixmo is authorised for substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment. Sixmo should be used as part of a complete treatment program, to include counselling and psychosocial support (see SmPC for the full indication). It contains buprenorphine as the active substance and it is an implant inserted subcutaneously in the inner side of the upper arm.

Further information about the evaluation of Sixmo's benefits can be found in Sixmo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/sixmo.

## II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Sixmo, together with measures to minimise such risks and the proposed studies for learning more about Sixmo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Sixmo, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

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In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Sixmo is not yet available, it is listed under 'missing information' below.

## *II.A List of important risks and missing information*

Important risks of Sixmo are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Sixmo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | <u>Safety concerns related to the subcutaneous (SC) implant:</u><br>Protrusion or expulsion of the SC implant<br>Infection at the insertion or removal site<br><br><u>Safety concerns related to the active substance:</u><br>Respiratory depression / respiratory failure<br>Hepatitis, hepatic events, use in patients with hepatic failure<br>Dependence<br>Precipitation of opioid withdrawal syndrome<br>Use during pregnancy and lactation (effects on newborn and infant)<br>CNS depression (including effects on driving ability)<br>Hypersensitivity<br>Risk of fatal outcome in patients with a history of polysubstance misuse/dependence who self-administer psychoactive substances while using Sixmo |
| Important potential risks | <u>Safety concerns related to the SC implant:</u><br>Damage to nerves or blood vessels during insertion and/or removal procedure<br>Implant migration and/or missing implant or partial implant<br><br><u>Safety concerns related to the active substance:</u><br>Use in patients with head injury and increased intracranial pressure<br>Peripheral edema |
| Missing information | <u>Safety concerns related to the SC implant:</u><br>Long-term use (greater than 12 months)<br><br><u>Safety concerns related to the active substance:</u><br>Patients >65 years old |

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## *II.B Summary of important risks*

| **Important identified risk:** Protrusion or expulsion of the SC implant | |
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| Evidence for linking the risk to the medicine | Implant protrusion and expulsion were reported infrequently in the clinical development program for Sixmo. |
| Risk factors and risk groups | The risk of protrusion or expulsion is increased by improper insertion of the implant, manipulation by the patient after insertion, and infection at the insertion site. |
| Risk minimization measures | Routine risk minimization measures:<br>Routine risk communication:<br>SmPC sections 4.2, 4.4, and 4.8<br>PL sections 2 and 3<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>Insertion and removal of the Sixmo implants must be performed by a physician or other qualified healthcare professional who is competent in minor surgery and has been trained to conduct the insertion and removal procedure, SmPC, section 4.2<br>Detailed instructions describing a step by step process for implant insertion / removal are provided in the SmPC, section 4.2<br>The same removal technique is employed for the removal of protruding or partially expelled implants. Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged, SmPC, section 4.2.<br>Recommendation to examine the insertion site one week following implant insertion for signs of any problems with wound healing, including evidence of implant extrusion from the skin is included in the SmPC, section 4. 2<br>Instructions for the healthcare professional on how to proceed in the case of spontaneous expulsion are included in the SmPC, section 4.4<br>Recommendation to confirm proper placement by palpation immediately after insertion is included in the SmPC, section 4.4<br>Instructions for the patient on what to do in the case of spontaneous expulsion are included in the PL, section 2 |

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| | Other routine risk minimization measures beyond the Product Information:<br><br>Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures:<br><br>Live training for healthcare professionals, including lecture slides, followed by a knowledge assessment proper insertion and removal techniques reduce the risk of protrusion or expulsion of the SC implant |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>MOLTeNI-2019-01 - A prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in routine clinical care.<br><br>PRO-816 - Prospective descriptive observational study of insertion-, localization-, and removal-related events and their sequelae associated with the use of Probuphine.<br><br>See section II.C of this summary for an overview of the post-authorisation development plan. |

| **Important identified risk:** Infection at the insertion or removal site | |
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| Evidence for linking the risk to the medicine | During the clinical development program for Sixmo, there were reports of infections occurring at the site of implant insertion or removal. In rare cases, the infections led to expulsion of the implant. |
| Risk factors and risk groups | The risk of infection is increased with poor wound care and excessive palpitation post-insertion. |
| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication:<br><br>SmPC sections 4.4 and 4.8<br><br>PL sections 2, 3, and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Recommendation to examine the insertion site one week following implant insertion for signs of infection is included in the SmPC, section 4.2<br><br>Recommendation to avoid excessive palpation shortly after insertion of the implants is included in the SmPC, section 4.4 |

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| | Recommendation to examine the incision site for infection if spontaneous expulsion occurs is included in the SmPC, section 4.4<br><br>Other routine risk minimization measures beyond the Product Information:<br><br>Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures:<br><br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>MOLTeNI-2019-01 - A prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in routine clinical care.<br><br>PRO-816 - Prospective descriptive observational study of insertion-, localization-, and removal-related events and their sequelae associated with the use of Probuphine.<br><br>See section II.C of this summary for an overview of the post-authorisation development plan. |

| **Important identified risk:** Respiratory depression / respiratory failure | |
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| Evidence for linking the risk to the medicine | In the clinical development program for Sixmo, reports of respiratory depression or failure were rare and the incidence was similar across the Sixmo, placebo implant, and SL buprenorphine groups. In the pivotal studies, there were no SAEs associated with respiratory failure reported for subjects on Sixmo.<br><br>Nevertheless, a number of cases of death due to respiratory depression have been reported while on buprenorphine, particularly when buprenorphine was used in combination with benzodiazepines or when buprenorphine was not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other depressants such as alcohol or other opioids. |
| Risk factors and risk groups | Patients administered buprenorphine in combination with benzodiazepines or other CNS depressants (including alcohol) and patients who misuse buprenorphine by self-injection are a greater risk of respiratory depression and death. |
| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication: |

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| | SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9<br><br>PL sections 2, 3, and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Recommendation to monitor elderly and persons with hepatic impairment for signs and symptoms of toxicity or overdose in the SmPC, section 4.2<br><br>Recommendation to monitor all patients receiving Sixmo for conditions indicative of diversion, or progression of opioid dependence and addictive behaviours suggesting the need for more intensive and structured treatment for substance use in the SmPC, section 4.4<br><br>Recommendation to warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking Sixmo, and should also be cautioned to use benzodiazepines concurrently with Sixmo only as directed by their healthcare professional, in the SmPC, section 4.5<br><br>Other routine risk minimization measures beyond the Product Information:<br><br>Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures:<br><br>Patient alert card |

| **Important identified risk:** Hepatitis, hepatic events, use in patients with hepatic failure | |
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| Evidence for linking the risk to the medicine | Cases of hepatitis and hepatic events have been observed in individuals receiving SL buprenorphine and in the Sixmo clinical development programme. As buprenorphine is extensively metabolized by the liver, plasma levels can be expected to be higher in patients with severe hepatic impairment; Sixmo is not suitable for use in patients with severe hepatic impairment. |
| Risk factors and risk groups | Patients with pre-existing liver impairment or with conditions that make them more susceptible to liver impairment (e.g., through disease or alcohol abuse). |
| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication:<br><br>SmPC sections 4.2, 4.3, 4.4, and 4.8<br><br>PL sections 2, 3, and 4 |

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| | Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Recommendations that patients with mild to moderate hepatic impairment should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity, or overdose caused by increased levels of buprenorphine, in the SmPC, sections 4.2 and 4.4<br><br>Recommendation that when a hepatic event is suspected, a liver function evaluation is required, including whether to discontinue treatment with Sixmo and if the treatment is continued, hepatic function should be monitored closely, in the SmPC, section 4.4<br><br>Other routine risk minimization measures beyond the Product Information:<br><br>Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures:<br><br>None |

| **Important identified risk:** Dependence | |
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| Evidence for linking the risk to the medicine | Studies in animals, as well as clinical experience, have demonstrated that buprenorphine may produce dependence, but at a lower level than a full agonist, such as morphine. |
| Risk factors and risk groups | All patients are at risk of developing dependence on Sixmo and every patient is anticipated to experience withdrawal symptoms when implants are removed. |
| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication:<br><br>SmPC sections 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Recommendations for monitoring and treating patients if Sixmo implants are discontinued in the SmPC, section 4.4<br><br>Other routine risk minimization measures beyond the Product Information:<br><br>Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures: |

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| **Important identified risk:** Precipitation of opioid withdrawal syndrome | |
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| Evidence for linking the risk to the medicine | Opioid withdrawal symptoms necessitating SL buprenorphine use at a level warranting a fifth implant were seen in approximately 20% of subjects in Studies PRO-805 and PRO-806. In Study PRO-814, in clinically stable patients and in which a fifth implant was not an option, a smaller percentage of subjects required supplemental SL buprenorphine. |
| Risk factors and risk groups | All patients beginning treatment with Sixmo are at risk of developing opioid withdrawal syndrome. |
| Risk minimization measures | Routine risk minimization measures:<br>Routine risk communication:<br>SmPC sections 4.2, 4.4, and 4.8<br>PL sections 2 and 4<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>Instructions for the induction of *de novo* patients before Sixmo insertion, SmPC, section 4.2<br>Other routine risk minimization measures beyond the Product Information:<br>Legal status: restricted and special medical prescription<br>Additional risk minimization measures:<br>None |

| **Important identified risk:** Use during pregnancy and lactation (effects on newborn and infant) | |
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| Evidence for linking the risk to the medicine | The potential for buprenorphine to induce effects on embryo-fetal development and/or effects on pre- and postnatal development is described in the literature, indicating that buprenorphine is embryotoxic at maternal toxic dosages, but is not teratogenic. Effects were also noted with respect to developmental milestones in pups from buprenorphine-treated dams.<br>Due to the lack of safer alternatives, there is considerable clinical experience on the use of buprenorphine in the treatment of opioid dependence during pregnancy. As reviewed by Farid et al (2008), clinical retrospective and prospective studies on buprenorphine maintenance for pregnant opioid-dependent women indicated that it is well tolerated and safe. Neonatal outcomes are not conclusive, |

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| | as studies are limited. Nevertheless, most pregnancies lack complications with neonatal outcomes, including birth weight, APGAR scores, head circumference and body length, being within normal ranges. Notwithstanding the benefits of managing pregnant opioid-dependent women with buprenorphine, caution is needed as adverse effects have been associated with this treatment.<br><br>The use of buprenorphine during pregnancy is known to cause neonatal abstinence syndrome in the infant (Johnson et al, 2003).<br><br>Buprenorphine and its metabolites are excreted in human breast milk (Lindemalm et al, 2009). Therefore, breastfeeding should be discontinued during treatment with buprenorphine. |
| Risk factors and risk groups | Neonates born to women using opioids or breast-fed by women using opioids. |
| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication:<br><br>SmPC sections 4.6 and 5.3<br><br>PL section 2<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Recommendation for neonatal monitoring at the end of pregnancy is included in the SmPC, section 4.6<br><br>Recommendation that breastfeeding should be discontinued during treatment with Sixmo, SmPC, section 4.6<br><br>Other routine risk minimization measures beyond the Product Information:<br><br>Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures:<br><br>None |

| **Important identified risk:** CNS depression (including effects on driving ability) | |
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| Evidence for linking the risk to the medicine | Cases of events related to CNS depression (e.g., fatigue, hypotension, and vertigo) have been reported in clinical studies and post-marketing sources for SL buprenorphine products and also in the clinical development program for Sixmo. |

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| Risk factors and risk groups | Concurrent use of buprenorphine with other CNS depressants (such as alcohol or benzodiazepines). |
| Risk minimization measures | Routine risk minimization measures:<br>Routine risk communication:<br>SmPC sections 4.4, 4.5, 4.7, 4.8, and 4.9<br>PL sections 2 and 4<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>Patients may experience somnolence, especially in the first week following insertion of the implants and should be cautioned in this respect in the SmPC, section 4.4<br>Recommendation to prescribe Sixmo with caution to patients taking benzodiazepines or other drugs that act on the CNS in the SmPC, section 4.5<br>Recommendation to caution patients about driving or operating hazardous machinery until they are reasonably certain that Sixmo does not adversely affect their ability to engage in such activities, in the SmPC, section 4.7<br>Other routine risk minimization measures beyond the Product Information:<br>Legal status: restricted and special medical prescription<br>Additional risk minimization measures:<br>None |

| **Important identified risk:** Hypersensitivity | |
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| Evidence for linking the risk to the medicine | Hypersensitivity events have been reported for other products containing buprenorphine in clinical trials and post-marketing experience and were also reported during Sixmo clinical trials. |
| Risk factors and risk groups | Patients with hypersensitivity to the active substance or any of the excipients in Sixmo. |
| Risk minimization measures | Routine risk minimization measures:<br>Routine risk communication:<br>SmPC sections 4.3 and 4.8<br>PL sections 2 and 4<br>Routine risk minimization activities recommending specific clinical measures to address the risk: |

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| | None.<br>Other routine risk minimization measures beyond the Product Information:<br>Legal status: restricted and special medical prescription<br>Additional risk minimization measures:<br>None |

| **Important identified risk: Risk of fatal outcome in patients with a history of polysubstance misuse / dependence who self-administer psychoactive substances while using Sixmo** | |
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| Evidence for linking the risk to the medicine | There were no reports of deaths associated with non-prescribed psychoactive substances during the Sixmo clinical development program. However, the combination of buprenorphine with other psycho-active substances, such as benzodiazepines or other CNS depressants (including alcohol) could increase the risk of adverse events. |
| Risk factors and risk groups | Patients who self-administer psychoactive substances |
| Risk minimization measures | Routine risk minimization measures:<br>Routine risk communication:<br>SmPC sections 4.4 and 4.5<br>PL section 2<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>Prior to initiating Sixmo therapy, the patient's medical history and treatment history, including use of non-opioid psychoactive substances, needs to be reviewed, in order to ensure that Sixmo treatment can be safely initiated.<br>Other routine risk minimization measures beyond the Product Information:<br>Legal status: restricted and special medical prescription<br>Additional risk minimization measures:<br>None |

| **Important Potential risk:** Damage to nerves or blood vessels during insertion and/or removal procedure | |
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| Evidence for linking the risk to the medicine | Cases of nerve injury have been reported during insertion and, in particular, during the removal of contraceptive implants. There were reports of possible damage to nerves |

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| | or blood vessels in the clinical development program for Sixmo; all were non-serious and did not lead to study drug discontinuation. |
| Risk factors and risk groups | Improper insertion, excessive palpitation or manipulation of the implants post-insertion, or significant weight gain post-insertion may make the implants more difficult to locate, increasing the risk of damage to the nerves or blood vessels during removal. |
| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication:<br><br>SmPC sections 4.2, 4.4, and 4.8<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Insertion and removal of the Sixmo implants must be performed by a physician or other qualified healthcare professional who is competent in minor surgery and has been trained to conduct the insertion and removal procedure, SmPC, section 4.2<br><br>Detailed instructions describing a step by step process for implant insertion / removal are provided in the SmPC, section 4.2<br><br>The same removal technique is employed for the removal of protruding or partially expelled implants. Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged, SmPC, section 4.2.<br><br>Other routine risk minimization measures beyond the Product Information:<br><br>Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures:<br><br>Live training for healthcare professionals, including lecture slides, followed by a knowledge assessment. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>MOLTeNI-2019-01 - A prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in routine clinical care.<br><br>PRO-816 - Prospective descriptive observational study of insertion-, localization-, and removal-related events and their sequelae associated with the use of Probuphine. |

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| | See section II.C of this summary for an overview of the post-authorisation development plan. |

| **Important potential risk:** Implant migration and/or missing implant or partial implant | |
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| Evidence for linking the risk to the medicine | In rare cases, Sixmo implants or partial implants could not be localized at the time of removal. No cases of distant migration have been reported with Sixmo. However, there have been isolated reports of other types of SC implant (contraceptive implants) that have migrated in the vasculature and to the lungs. |
| Risk factors and risk groups | Incorrect insertion.<br><br>Implants may be more difficult to find if the patient manipulates them under the skin or if the patient gains a lot of weight after insertion. |
| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication:<br><br>SmPC sections 4.2, 4.3, 4.4, and 4.8<br><br>PL sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Ultrasound and MRI facilities need to be available to the clinical site at which the insertion and removal of Sixmo occurs, SmPC, section 4.2<br><br>Suitable methods for the location of non-palpable implant(s) or fragment(s) include ultrasound with a high frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI). Sixmo implants are not radiopaque and cannot be seen by X-ray or CT scan, SmPC, section 4.2<br><br>If implant(s) or implant fragment(s) are not removed during a removal attempt, the patient should undergo imaging for localisation as soon as is feasible with the subsequent removal attempt performed on the same day as localisation, SmPC, section 4.2<br><br>Patients who have contraindications for MRI should not be allowed to receive Sixmo, SmPC, section 4.3<br><br>Recommendation to confirm proper placement by palpation immediately after insertion is included in the SmPC, section 4.4<br><br>Other routine risk minimization measures beyond the Product Information: |

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| | Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures:<br><br>Live training for healthcare professionals, including lecture slides, followed by a knowledge assessment. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>MOLTeNI-2019-01 - A prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in routine clinical care.<br><br>PRO-816 - Prospective descriptive observational study of insertion-, localization-, and removal-related events and their sequelae associated with the use of Probuphine.<br><br>See section II.C of this summary for an overview of the post-authorisation development plan. |

| **Important potential risk:** Use in patients with head injury and increased intracranial pressure | |
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| Evidence for linking the risk to the medicine | Opioids may elevate cerebrospinal fluid pressure, which may cause seizures, so opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure. Such events were not seen in the clinical development program for Sixmo. |
| Risk factors and risk groups | Patients with head injury, intracranial lesions, and other circumstances where cerebrospinal pressure may be increased. |
| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication:<br><br>SmPC sections 4.4 and 4.8<br><br>PL section 2<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Recommendation to use with caution in patients with head injury, intracranial lesions, and other circumstances where cerebrospinal pressure may be increased in the SmPC, section 4.4<br><br>Other routine risk minimization measures beyond the Product Information: |

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| | Legal status: restricted and special medical prescription<br>Additional risk minimization measures:<br>Patient alert card |

| **Important potential risk:** Peripheral edema | |
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| Evidence for linking the risk to the medicine | Reports of peripheral edema have been received for other products containing buprenorphine in clinical trials and post-marketing experience and were also reported during Sixmo clinical trials. |
| Risk factors and risk groups | Unknown |
| Risk minimization measures | Routine risk minimization measures:<br>Routine risk communication:<br>SmPC section 4.8<br>PL section 4<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>None<br>Other routine risk minimization measures beyond the Product Information:<br>Legal status: restricted and special medical prescription<br>Additional risk minimization measures:<br>None |

| **Missing information:** Long-term use (greater than 12 months) | |
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| Risk minimization measures | Routine risk minimization measures:<br>Routine risk communication:<br>SmPC section 4.2<br>PL section 3<br>Routine risk minimization activities recommending specific clinical measures to address the risk: none<br>Other routine risk minimization measures beyond the Product Information:<br>Legal status: restricted and special medical prescription<br>Additional risk minimization measures: |

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| Additional pharmacovigilance activities | Additional pharmacovigilance activities: none |

| **Missing information:** Patients >65 years old | |
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| Risk minimization measures | Routine risk minimization measures:<br><br>Routine risk communication:<br><br>SmPC section 4.4<br><br>PL section 2<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br><br>Recommendation that opioids should be administered with caution to elderly or debilitated patients in the SmPC, section 4.4<br><br>Due to lack of data in this population, use of Sixmo is not recommended in patients over 65 years, SmPC section 4.4<br><br>Other routine risk minimization measures beyond the Product Information:<br><br>Legal status: restricted and special medical prescription<br><br>Additional risk minimization measures:<br><br>None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br><br>MOLTeNI-2019-01 - A prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in routine clinical care.<br><br>PRO-816 - Prospective descriptive observational study of insertion-, localization-, and removal-related events and their sequelae associated with the use of Probuphine.<br><br>See section II.C of this summary for an overview of the post-authorisation development plan. |

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## *II.C Post-authorisation development plan*

### II.C.1 Studies which are conditions of the marketing authorisation

**Study short name:** MOLTeNI-2019-01 - A prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in routine clinical care.

**Purpose of the study:** The primary objectives are to evaluate the rate of breakage of Sixmo implants and to evaluate implant site treatment-emergent adverse events. The safety concerns addressed are: Protrusion or expulsion of the SC implant, Infection at the insertion or removal site (important identified risks); Damage to nerves or blood vessels during insertion and/or removal procedure, Implant migration and/or missing implant or partial implant (important potential risks); Patients >65 years old (missing information).

### II.C.2 Other studies in post-authorisation development plan

**Study short name: Prospective descriptive observational study of insertion-, localization-, and removal-related events and their sequelae associated with the use of Probuphine[1] (PRO-816)**

Purpose of the study: The rationale for study PRO-816 is to determine the incidence of and characterize insertion-, localization-, and removal-related serious adverse events and their sequelae associated with the use of Probuphine. The registry will evaluate the safety of the implants under real-world conditions. There will be no investigational interventions; enrolled patients will receive treatment and evaluations for their opioid addiction as determined by their treating healthcare professionals.

The primary objective of this registry is to determine the incidence of clinically significant linked Probuphine implant insertion-removal complications. The secondary objectives are also related to safety.

The study will address the following safety concerns: Protrusion or expulsion of the SC implant, Infection at the insertion or removal site (both important identified risks); Damage to nerves or blood vessels during insertion and/or removal procedure, Implant migration and/or missing implant or partial implant (both important potential risks); Patients >65 years old (missing information).

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[1] US brand name