TRANSPARENCY COMMITTEE OPINION SUMMARY

ZORYON (methadone), opioid

Substantial clinical benefit but no demonstrated clinical added value in the treatment of chronic cancer pain not adequately relieved by other step 3 opioids

Key points

- ZORYON has an MA in the chronic treatment of moderate to severe cancer pain in patients not adequately relieved by other step 3 opioids.
- Methadone has been used off-label for numerous years in the treatment of patients with chronic cancer pain. Treatment with ZORYON (methadone) may be initiated in these patients during a step 3 opioid rotation.
- The pharmacokinetic characteristics and safety data for methadone call for caution when initiating treatment; initiation should be performed in a hospital setting by a pain management or palliative care team experienced in the use of the product.

Care pathway

- When performing a step 3 opioid switch, the factors that need to be considered are pharmacodynamics and pharmacokinetics of the various opioids, patients' comorbidity and concomitant medication and treatment settings. The administration regimen for the new analgesic should take into account the reason for the switch (inefficacy or intolerance), pharmacokinetics of the drug, metabolic condition of the patient and any interactions with other medicinal products.
- Close monitoring of the patient and periodic multidisciplinary reassessment of the relevance of the prescription are necessary during opioid treatment; the patient's clinical situation must be regularly and carefully monitored by joint assessment by the pain or palliative care specialist and the oncologist.
- **Role of the medicinal product in the care pathway**
  Step 3 analgesics besides methadone appear to be easier to manage in the treatment of patients requiring an opioid rotation.
  There is no consensus concerning opioid analgesic treatment to methadone conversion protocols; the choice of protocol to be used during treatment initiation is left to the assessment of the hospital team. In the event of unstable pain, breakthrough doses are used; the total daily dose administered is divided up over 24 hours.
  Only clinicians familiar with the product's safety profile and willing to educate their patients and monitor them closely (assessment of QT prolongation, ECG monitoring) should prescribe methadone as an analgesic.
  If necessary, a switch from methadone to other opioids is possible, taking into account the product's kinetic characteristics.

Clinical data

- Methadone is an opioid analgesic that has been used and recommended for numerous years in the management of patients with cancer pain, particularly in the context of opioid rotation.
  A Cochrane review of the literature in 2017 demonstrated the limited number of controlled, randomised studies having assessed the efficacy of methadone versus an active treatment in cancer pain. Based on low-quality data, the authors concluded that the analgesic benefits observed with methadone were similar to those provided by morphine and that methadone could play a role in the treatment of adult patients with cancer pain.
- Data from studies assessing the different opioid conversion methods in cancer pain and using methadone are in favour of analgesic efficacy of methadone but have demonstrated heterogeneity in terms of opioid ratios and rotation methods.

Although the use of equianalgesic dose ratio (EDR) tables is recommended, practitioners should be aware of the limitations of this approach and may decide on potential alternatives based on the latest data.

- An open-label superiority study assessed two methadone titration protocols in the context of opioid rotation in patients with cancer pain. These two treatment initiation protocols are mentioned, by way of indication, in the Pharmacodynamics section of the SPC; alternative protocols may be used.
- The major risks of ZORYON treatment are respiratory depression and central nervous system disturbances (drowsiness, confusion, etc.). Although these risks may occur with any opioid, the likelihood of onset is high and reaches a maximum a few days after initiation of treatment for methadone. These risks can also be increased by concomitant medications (see interactions with other medicinal products). The treatment must be administered with caution, with clinical, electrolyte and ECG monitoring, given the cases of QT interval prolongation and torsades de pointes reported during treatment.

Specific prescribing conditions

- Medicinal product subject to initial hospital prescription.
- Medicinal product requiring special monitoring during treatment.
- Narcotic. Secure prescription. Prescription limited to 28 days. Prescription dispensing divided into maximum periods of 7 days. The prescriber may nevertheless specify the duration of each fraction dispensed on the prescription, or exclude divided dispensing by indicating on the prescription “dispensing of full prescription”, or specify that the medicinal product should be dispensed daily.
- Prescriptions are dispensed by a retail pharmacy.

Benefit of the medicinal product

- The clinical benefit* of ZORYON is substantial.
- ZORYON provides no clinical added value** (CAV V, no clinical added value) in the care pathway for the treatment of chronic cancer pain not adequately relieved by other step 3 opioids.
- Favourable opinion for retail pharmacy and hospital reimbursement.

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* The clinical benefit (CB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the clinical benefit, which may be substantial, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement"