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(來函請敍明此檔案號碼) DH DO DIMC/7-30/1
(IN REPLY PLEASE QUOTE THIS FILE REF.)

13 Mar 2025

Dear Healthcare Professionals,

Prolonged-release opioids: Removal of indication for relief of post-operative pain

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that the indication for the treatment of post-operative pain has been removed from the licences of all prolonged release opioids due to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI). It is not recommended to use transdermal patches for the treatment of post-operative pain.

Prolonged-release (modified release) opioids are indicated for moderate or severe pain and cancer pain, although NICE guidance recommends that opioids are not used for chronic primary pain where there is no underlying condition accounting for the pain. A small number of prolonged release opioids containing morphine or oxycodone were also authorised for the treatment of post-operative pain, however concerns were raised on the potential for harm and an increased risk of PPOU and OIVI.

PPOU is defined as continued opioid use beyond 90 days from the day of operation. Dependence is a well-known side effect of opioids and we continue to communicate to raise awareness on this issue. Evidence from across the EU including the UK has shown that the incidence of PPOU ranges from 2% - 44% in patients treated with prolonged-release opioids. Also PPOU is more prevalent (incidence up to 60%) in patients taking prolonged-release opioids pre-operatively.

Respiratory depression is also a well-known side effect of opioids, especially if taken in excess or in combination with other sedating medicines (for example benzodiazepines, pregabalin or gabapentin) which can lead to coma and potentially death. OIVI is a serious form of respiratory depression associated with depression of respiratory rate and/or depth of breathing – 'central respiratory depression', depression of consciousness – 'sedation', depression of supraglottic airway muscle tone – 'upper airway obstruction'. The reported incidence of OIVI is difficult to determine, although the

international multidisciplinary consensus statement quotes an incidence of OIVI ranging from 0.4% to 41% depending on the identification measures used.

Following the conclusion of a safety review undertaken by the MHRA, and advice from the Commission on Human Medicines (CHM), the indication for the treatment of post-operative pain will be removed from the licences of prolonged release morphine and prolonged release oxycodone. The remaining prolonged release opioids are not recommended for acute post-operative pain relief and may already not be indicated for acute use or are contraindicated in acute pain relief. The information considered by the CHM and the advice issued is presented in a Public Assessment Report. For details, please refer to the website in MHRA.

Pain following surgery is usually short-lived, lasting between 5 – 7 days and therefore should only require short-term pain management best treated with immediate release opioids. However, many patients are discharged from hospitals with excessive amounts of opioids to meet their needs for acute post-operative pain management. This excess supply of opioids increases the risk of developing PPOU, dependence, addiction, or could lead to opioid diversion, and an increased risk of OIVI with unmanaged use. Therefore, patients should only be provided with a prescription for a sufficient amount of instant release opioids to manage their acute post-operative pain on discharge from hospital.

A Consensus Best Practice Guideline agreed between the Faculty of Pain Medicine, Royal College of Anaesthetists, Royal College of General Practitioners, Royal College of Surgeons of England, Royal College of Nursing, The British Pain Society, the Centre for Perioperative Care and endorsed by the Royal Pharmaceutical Society, recommend that pre-operative use of opioids should be reviewed prior to surgery.

Adjustments in dose or dosing regimen might be necessary in patients at increased risk of experiencing these severe adverse reactions, including patients with compromised respiratory function or respiratory disease, with neurological disease, with renal impairment, with cardiovascular disorders, using concomitant central nervous system (CNS) depressants, older than 65 years, with opioid tolerance, using opioids pre-operatively. Patients and healthcare professionals are encouraged to discuss treatment regimens and agree a post-operative pain management plan prior to the proposed surgical procedure.

Advice for Healthcare Professionals:

- prolonged-release opioids provide relief from chronic severe pain, however, they should not be used for the treatment of acute pain following surgery.
- prolonged-release opioids are associated with an increased risk of PPOU characterised as continued opioid use beyond 90 days following the operation, and an increased risk of OIVI causing serious respiratory depression, sedation, and depression of upper airway muscle tone.

- before surgery, discuss with the patient the following:
  - explain the risks of PPOU, dependence and potential risk of addiction and withdrawal reactions.
  - explain the risk of OIVI especially for patients with underlying respiratory conditions.
  - immediate-release opioids are used for short-term treatment of pain.
  - discuss with the patient pain management strategies involving the use of immediate-release opioids and multimodal analgesia and plan for end of treatment.
- patients whose pain is managed with opioids pre-operatively should have their treatment reviewed before and after surgery in line with Consensus Best Practice Guidelines.
- at discharge from hospital:
  - only prescribe and supply a sufficient amount of immediate-release opioids to treat acute post-operative pain to minimise the risk of PPOU, dependence, stock piling of unused opioids and potential for diversion.
  - communicate the pain management plan with the primary care practice taking over care in the community and document in patient clinical notes.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/prolonged-release-opioids-removal-of-indication-for-relief-of-post-operative-pain

In Hong Kong, there are 14 pharmaceutical products which belong to prolonged-release opioids, including the ingredients codeine, morphine, oxycodone and tramadol. There are 3 registered pharmaceutical products which is transdermal patch containing fentanyl. These products are prescription-only medicines. So far, the Department of Health (DH) has received adverse drug reaction with regard to morphine (11 cases), tramadol (9 cases), fentanyl (6 cases), codeine (4 cases) and oxycodone (2 cases), of which 5 cases were related to ventilatory impairment and none of these cases were related to persistent post-operative opioid use.

Related news on the safe and appropriate use of opioid analgesics including prolonged-release opioids was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 11 Sep 2013, with the latest update posted on 20 Dec 2023. Letters to inform local healthcare professionals were issued by the DH on 11 Sep 2013 and 14 Apr 2023. In Feb 2015, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that pharmaceutical products which are controlled-release, extended-release or long-acting opioid analgesics (containing hydromorphone, morphine, oxycodone, oxymorphone, tapentadol, fentanyl, buprenorphine and methadone) should include safety information about the risks of addiction, abuse, misuse, overdose and death, and limitations of use in patients with severe pain for which alternative treatment options are inadequate.

In light of the above MHRA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Clinical Trials and Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

pp (Vincent CHIANG)
for Assistant Director (Drug)