Medicines & Healthcare products Regulatory Agency

Modified Release Opioids and Treatment of Post-operative Pain

Public Assessment Report

Published 12 March 2025

Contents

Plain Language Summary

Key messages:

Modified release (prolonged release or sustained release) opioid medicines used in the treatment of pain following an operation may increase the risk of breathing difficulties and persistent use or dependence on these medications. The Commission on Human Medicines (CHM) considered that these risks of these medicines when used for the treatment of pain following an operation exceeded the benefits, and therefore the direction for post-operative pain relief has been removed from all modified release opioids. Therefore, the indication for post-operative pain relief has been removed from morphine and oxycodone modified release medicines' product information and they are no longer recommended for use to relieve pain after surgery.

Patients are advised to talk to their doctor(s) before and after an operation to discuss their pain management plan. If there is a need for opioid pain management, then an instant release opioid is preferred. If you are already being treated with modified release opioids for another condition, talk to your healthcare team to review your treatment and plan for recovery after your operation.

Introduction

After an operation it is common for patients to experience some sort of pain. This is normal and likely to be short-lived, between 5 – 7 days, although this is different for everybody.

Modified release opioids (otherwise known as prolonged release opioids or sustained release opioids) provide relief from long lasting moderate to severe pain and are sometimes used for the treatment of pain following surgery. It is known there is an increased risk of persistent post-operative opioid use (PPOU) (the continued use of opioids beyond 90 days following the operation) (in other words opioid dependence), and opioid induced ventilatory impairment (OIVI) (a serious form of breathing difficulties) when modified release opioids are taken following surgery. Dependence and breathing difficulties (respiratory depression) are well-known side effects of all opioids.

The risks of OIVI may be greater depending on other contributing factors, such as age and weight and if you have other health conditions like heart, kidney or lung disease.

The consensus best practice guidelines (expert agreed upon recommendations on surgery and opioids) recommends that instant release opioids are preferrable to manage pain after an operation. Whether you are already taking opioids before surgery or not, it is important to

talk to your healthcare team both before and after surgery to plan for pain relief. A helpful leaflet is available from the British Pain Society:

Managing pain after your surgery

You might be prescribed a larger pack of opioids that may contain more opioids than you need to recover from pain after surgery. Unused medicines should be taken to the pharmacist to be disposed of safely.

More information about this medicine

Modified release (prolonged release, sustained release and transdermal (through the skin)) opioids are recommended for severe pain, prolonged relief of pain, cancer pain and have previously been used for post-operative pain.

Overall, transdermal patches are already either contraindicated (should not be used for) or not recommended for use for short-term pain relief

Modified release tablets do not need to be taken as often as instant release tablets; however, it may be more difficult or take longer to find out what the right dose is to get enough pain relief. Therefore, it may be beneficial to have instant release opioids to obtain enough pain relief quickly.

Reasons for the latest review and information considered

The Medicines and Healthcare products Regulatory Agency (MHRA) was contacted by healthcare professionals as they were concerned about the increased risks of PPOU and OIVI in patients following the use of modified release opioids after surgery. In addition, the healthcare professionals were concerned that too many tablets were being prescribed to treat acute (short-lived) pain, as patients were discharged from hospital with excessive amounts of tablets resulting in large amounts of unused opioids in the community.

Evidence to inform the review by the MHRA was gathered from the literature, clinical guidelines, and regulatory publications from the UK and international governmental sources.

A high proportion of patients suffer post-operative pain; therefore the importance of safe and effective post-operative pain management is paramount. For the majority of patients, post-operative pain would be considered as acute, short-lived and to resolve within a few days after surgery. Chronic (long-term) pain is specified as pain that lasts for 3 months or more.

It was noted that, historically, the definition of PPOU has been inconsistent, although it is now considered to describe post-operative use of opioids beyond 90 days.

In addition, between 11% to 77% of prescribed opioids were identified as unused worldwide and available in the community. Opioids are authorised to be dispensed with or sold with a variety of different pack sizes, however not all sizes are marketed or available on a local drug formulary. Therefore patients may be discharged from hospital with an excessive amount.

How the CHM reached their conclusions

The CHM reviewed evidence of the risks of PPOU and OIVI, the potential links with over-prescribing, the actions taken by other international regulatory authorities, consensus best practice guidelines and position statements. Comments were also obtained from the Neurology, Pain, and Psychiatry Expert Advisory Group (NPPEAG) of the CHM.

The risk of PPOU and OIVI was concluded to be higher with modified release opioids, therefore it was considered that the risk of PPOU and OIVI with modified release opioids exceeded their benefits for the treatment of short-term post-operative pain relief. While the side effects of dependence and breathing difficulties are well-known for opioids, there are no warnings in the product information concerning the risks of PPOU and OIVI following surgery.

NPPEAG considered that product information should contain warnings for PPOU and OIVI. While respiratory depression and dependence are in the Summary of Product Characteristics (document describing a medicine’s properties conditions for its use), NPPEAG considered that it should also be made clear in relation to the post-operative period. The emerging evidence highlights the risks, and therefore the indication of post-operative pain relief should be removed.

The indication for post-operative pain relief has been removed from the licences of modified release morphine tablets and modified release oxycodone, and warnings for PPOU and OIVI should be added to the product information for all modified release opioids.

Advice from the CHM

The CHM recommended that the indication for post-operative pain relief should be removed from the licences of modified release morphine tablets and modified release oxycodone, and warnings for PPOU and OIVI should be added to the product information for all modified release opioids. In addition, the increased availability of smaller pack sizes for all opioids are to be encouraged to give flexibility in prescribing in original packs, so that patients receive all product information, including warnings of dependence.

Next steps

The MHRA requested the licence holders (for example companies that are authorised to market the medicine) for modified release morphine and modified release oxycodone to remove the indication of post-operative pain relief.

The product information for modified release opioids has been updated with warnings of PPOU and OIVI.

Marketing Authorisation Holders (MAHs) and local drug formularies are encouraged to increase availability of smaller pack sizes to enable prescription for shorter duration of treatment for acute post-operative pain.

Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK and inform healthcare professionals and the public of the latest updates.

In our safety Public Assessment Reports, we discuss evidence-based assessments of safety issues associated with a particular medicine or group of medicines.

This report presents the MHRA's review of safety data for modified release opioids and expert advice on management of risks, as advised by the Commission on Human Medicines (CHM). Changes have been made to the ordering and wording used in the original assessment report to aid readability and presentation.

A glossary is provided for an explanation of the terms used in this report.

The information and analyses contained in this report reflect evidence that was available at the time of the review in May 2024. The MHRA and CHM will continue to monitor the safety of modified release opioids closely, however the information in this report will not be actively updated with new data or studies.

Modified release opioids are of a group of opioid medicines described as prolonged release, sustained release and transdermal opioids. Throughout this report, the term modified release opioids is used to reflect all descriptions.

Issue

The Royal College of Anaesthetists (RCoA), the Faculty of Pain Medicine (FPM), the Centre of Perioperative Care (CPOC), the Safe Anaesthesia Liaison Group (SALG), and the Medicines Safety Improvement programme (NHS England) sought the promotion of the safer use of modified release opioids in acute pain.

Background

Modified release (prolonged release, sustained release and transdermal) opioids are indicated for severe pain, modified relief of pain, cancer pain and post-operative pain.

The SALG contacted the MHRA regarding the the use of modified release opioids in enhanced recovery after surgery (ERAS) pathways in the UK. Concerns were highlighted over the lack of evidence to support use in modern surgical practices, and the potential for harm. Although the FPM and the CPOC have issued advice against use of modified release opioids in perioperative care, the SALG considered that their audience is limited.

Secondly, the group noted that pack sizes are large and highlight the action taken in Australia to request manufacturers to produce smaller pack sizes.

Opioids of Concern

In 2019, the Opioid Expert Working Group reviewed the benefits and risks of opioids in the treatment of non-cancer pain. Safety concerns of dependence, the development of tolerance and the loss of benefit with long-term use were discussed, resulting in the addition of warnings in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet. In addition, guidance was added to promote a discussion between the patient and prescriber to agree a treatment plan. A further resource was also made available to patients and carers on the risk of dependence and addiction to opioids. The National Institute for Health and Care Excellence (NICE) also published recommendations in their guidance [NG193] in the assessment of all chronic pain and management of primary chronic pain excluding the use of opioids.

The CPOC position statement recommended modified release opioids should be avoided during the peri-operative period, highlighting that post-operative pain is largely self-limiting. Therefore, if necessary, the use of instant release opioids is preferable.

Risks associated with the use of opioids include opioid-induced ventilatory impairment (OIVI) (respiratory depression) and persistent post-operative opioid use (PPOU). Respiratory depression is a well-established safety concern for all opioids. In 2019, Public Health England undertook a study which highlighted the high number of patients prescribed opioids over the long-term, however they were not able to differentiate between individual opioids or pharmaceutical form. Therefore they did not identify if long-term use was associated with post-operative use and/or cancer pain.

A large number of opioids have modified release formulations. Whilst codeine may be a commonly prescribed post-operative opioid, there are no modified release formulations.

Only 2 opioid medicines with modified release pharmacological forms have indications for post-operative pain:

1) Oxycodone

Twenty-six licences (with 3 Marketing Authorisation Holders (MAHs)) have indications of:

“treatment of moderate to severe pain in patients with cancer and post-operative pain. Treatment of severe pain requiring the use of a strong opioid.”

2) Morphine sulfate

Seven licences with one MAH have either indications and / or posology for post-operative pain. Four have an indication for post-operative use, whilst the remaining 3 have an

indication for “the modified relief of severe and intractable pain”, however contains posology for post-operative pain.

(See annex 1 for full list of licences)

The remaining licences for modified release opioids contain indications for moderate to severe pain. While post-operative use for fentanyl transdermal patches is contraindicated, buprenorphine transdermal medicines, which have indications for pain, are highlighted as “not for acute use”.

Pack sizes

The request highlighted the large pack sizes, noting that the smallest available pack size is 28 tablets for most of these medicines but 60 for morphine sulfate. This applies to both modified release and immediate release formulations.

Many licences are authorised with 28 tablet pack sizes, however, may not be marketed. This has caused problems at the dispensing level, with patients discharged with excessive quantities. The SALG reports that hospital dispensing pharmacies have insufficient time or resources to break packs, to provide proportionate amounts at hospital discharge.

This is also reflected for oral solutions. The smallest pack size is 100ml. For oxycodone, oral solutions are licenced at volumes of 100ml, although again, may not be marketed. A decision to market any authorised pack size is usually a commercial decision taken by the MAH. However, for those products that are marketed, best practice guidance has been compiled to ensure that sufficient stock is put on the UK market to meet patients’ needs. Larger pack sizes are likely to be in excess of patient need and there is the potential that a considerable amount of unused opioids are retained in the community. The NHS (pharmaceutical and local pharmaceutical services) regulations 2013 were recently updated to recommend that patients discharged from hospital under a pandemic treatment protocol should only be prescribed with sufficient medications for a period not exceeding 5 days. However, this is not applied to all conditions.

With any oral solution, there is a risk that patients will take an incorrect or unmeasured dose. For those patients who have difficulty in swallowing, the administration of a solution is preferable if available. For those patients with malignant pain or prolonged pain, the availability of a reasonable size bottle to cover a period of time in the community may be considered acceptable. However there is a risk of overuse, dose escalation, diversion, respiratory depression and fatalities.

Cases of fatalities were highlighted by NHS South West (August 2016), involving the use of morphine sulfate solution 10mg/5ml, highlighting risks associated with repeat prescriptions of 300ml, and recommending 100ml as sufficient for occasional use. Although, the best

practice guidance notes that 100ml of morphine sulfate 10mg/5ml for opioid naïve patients can be fatal.

Australia

The enquiry highlighted regulatory action taken in Australia. In June 2020, the Therapeutic Goods Administration (TGA) made recommendations to introduce the requirement for instant release codeine, hydromorphone, morphine, oxycodone, codeine and paracetamol, and tramadol marketing authorisations to introduce smaller pack sizes of 10 tablets for the treatment of acute pain.

However, the TGA acknowledged that larger pack sizes may still be required for some patients with acute pain. A full pack size is identified in the Australian Commission on Safety and Quality in Healthcare clinical guidance as 20 tablets, although larger pack sizes are registered in the Pharmaceutical Benefits Scheme (PBS) for Australia.

The Australian Commission on Safety and Quality in Healthcare published clinical guidance in terms of opioid treatment in acute pain.

The guidance provided recommendations in terms of prescribing instant relief opioids for acute pain:

- patient must have experienced inadequate management of pain relief with maximum non-opioid analgesics, or
- patient must be unable to use non-opioid or other opioid analgesics due to contraindications, adverse effects, or intolerance

Modified release opioids and transdermal patches are only indicated for chronic severe pain. Restrictions for prescribing are:

- cancer pain requiring continuous, daily, long-term therapy, or
- patient must have experienced inadequate management of pain relief with maximum non-opioid analgesics or other opioid analgesics, or
- patient must be unable to use non-opioid or other opioid analgesics due to contraindications, adverse effects, or intolerance

Although, some restrictions have not changed for a number of opioids, for example an authorised oxycodone suppository, which includes treatment for cancer pain and/or post-operative pain following a major operative procedure.

The aim of the recommendations from the TGA and the Australian clinical guidance is to reduce the circulation of unused opioids in the community and make it easier for healthcare

professionals to prescribe smaller amounts. However, the TGA noted that they can compel the registration of smaller pack sizes, but not the supply.

Other information

A high proportion of patients suffer post-operative pain; therefore the importance of risk averse and effective post-operative pain management is paramount. Guidelines have been developed to recommend multimodal treatment encompassing both non-pharmacological and pharmacological therapies (Chou and colleagues 2016). ERAS protocols have been developed for various surgical procedures. Whilst there is a move to reduce the amount of opioids used during the peri-operative period, concerns are raised in terms of bleeding for NSAIDs. For the majority of patients, post-operative pain would be considered as acute, short-lived and to resolve within a few days after surgery. Chronic pain is specified as pain that lasts for 3 months or more.

In the UK, modified release opioids are all prescription-only medicines. Only 2 modified release opioids (morphine and oxycodone) have an indication for post-operative pain. Each have indications for the treatment of severe and intractable pain or chronic pain. Fentanyl and buprenorphine transdermal products identify that they are not for acute pain, although this is not reproduced in other modified release opioid product information.

In terms of post-operative pain, short-term use of instant release opioids would be preferable, although patients' pre-operative use of opioids may influence considerations of peri-operative use. In these cases, it may be considered as preferable to provide or continue modified release opioid use following surgery, although Levy and colleagues (2021) identified that the incidence of PPOU is higher in patients taking opioids before surgery.

The SALG highlighted evidence of harm associated with post-operative use of modified release opioids, including OIVI and PPOU (Levy 2021). Whilst respiratory depression is well known for all opioids, the risks of OIVI and PPOU was also highlighted by Quinlan (2022) to be greater with modified release opioids. PPOU was also identified to be more prevalent in patients who were treated with opioids pre-surgery (Sitter and Forget 2021).

With over-prescribing there are risks of stockpiling of unused opioids, misuse, dependence and diversion. In October 2023, the US Food and Drug Administration (FDA) issued a safety communication highlighting the risks associated with over-prescribing and unused opioids in the community, also specifying that only a few days use is sufficient to cover any treatment occurring in the outpatient setting, although recognises the individual need of the patient. Wyles (2021) and Ho (2018) each described studies of the prescribing of opioids following orthopaedic surgery in the US and Australia, which indicated a high proportion of unused opioids (50% – 70%) following surgery. In contrast, in Sweden, prescribing in the 7 days following surgery was significantly less than the US and Canada (11.1% vs 76.2% vs 78.6% respectively). However Ladha (2019) identified that although post-surgery prescriptions were lower in Sweden compared with Canada, the mean (SD) morphine milligram equivalent (MME) dispensed in Sweden (197±191) was greater than in Canada (169±93), therefore a

balance needs to be drawn between the duration of treatment and strength of the medicine. The FPM best practice guidelines recommends that pre-operative use of opioids should be reviewed and potentially tapered prior to surgery.

Oxycodone and morphine are both controlled drugs under schedule 2 of the Misuse of Drugs Regulations 2001 (exception for low strength morphine as schedule 5). The NHS Business services authority (NHSBSA) has provided strong recommendations that a prescription for all controlled drugs in schedules 2 to 4 do not exceed 30 days' supply. Similar prescribing restrictions are not in place for those opioids in schedule 5, for example codeine is available without prescription under the supervision of a pharmacist (P) with a pack-size restriction of 32 tablets. Currently, there are no modified release codeine tablets authorised in the UK.

The International Classification of Diseases issue 11 (ICD-11) defines chronic pain as persistent or recurring pain lasting for at least 3 months, therefore anything less would be deemed as acute pain. However, the patient's experience of severity of pain or duration of pain may depend on the type of surgery. Bansal (2023) noted that the definition of PPOU has also been inconsistent, either determined by the number of post-surgery prescriptions or by the numbers of days after surgery. The best practice consensus guideline defined PPOU as the use of opioids 90 days after surgery to align with ICD-11 classification of chronic postsurgical pain. The Australian Anzca FPM position statement on acute pain management identified OIVI as a result of interlinked mechanisms:

- depression of respiratory drive with a reduction in alveolar ventilation (respiratory rate and/or depth of breathing) – 'central respiratory depression'
- depression of consciousness (and therefore arousal) – 'sedation'
- depression of supraglottic airway muscle tone – 'upper airway obstruction'

Therefore, OIVI may be considered a development of respiratory depression with a serious outcome. Risk factors for OIVI are older age, female gender, sleep-disordered breathing, obesity, renal impairment, pulmonary disease (in particular chronic obstructive pulmonary disease), cardiac disease, diabetes, hypertension, neurologic disease, 2 or more comorbidities, genetic variations in opioid metabolism, and opioid-tolerance. Whilst little can be done with respect to comorbidities, the use of opioids can be reviewed prior to surgery.

The introduction of smaller pack-sizes would have little effect on the amount that can be prescribed within the bounds of the Misuse of Drugs Regulations 2001, although would enable easier prescription of smaller amounts. A pack size containing 28 modified release tablets would be sufficient to cover a period of approximately 14 days (assuming one tablet every 12 hours), whilst 28 tablets of instant release opioids would cover approximately 7 days (assuming one tablet every 6 hours). The recommended daily dose of instant release morphine in adults is 10mg-20mg every 4 hours up to a maximum of 120mg per day. Therefore, the smallest authorised 100ml bottle size of morphine 10mg/5ml oral solution

would last for 2 to 25 days. Levy and colleagues (2019) commented that post-operative prescriptions should not exceed 5 days, and for opioid naïve patients, should not go onto automatic repeat. The FPM best practice guidelines recommend prescriptions at discharge from hospital should not exceed 7 days, and a medicine review should be held usually 5 to 7 days post discharge. However, Levy and colleagues (2019) also went on to highlight that instant release morphine 10mg/5ml is a schedule 5 drug and therefore is not subject to the controls of instant release oxycodone which requires dispensing in the presence of a witness and additional staff. Therefore, the FPM recommends that immediate release morphine oral solution 10mg/5ml is preferred in the ward as it is less labour intensive, although do not recommend prescription of a specific opioid at hospital discharge.

It was initially anticipated that modified release opioids would reduce nursing workload, although, the slow onset and offset of action makes it difficult to titrate appropriate analgesia (Quinlan, 2022). The increased risks of OIVI and PPOU also indicate that additional healthcare monitoring would be needed. The SALG noted that modified release opioids continue to be prescribed despite revised guidelines.

In conclusion

- Over prescribing can lead to a significant proportion of unused opioids in the community.
- Risks associated with over-prescribing include dependency, diversion, abuse and misuse.
- There are significant risks associated with the use of modified release opioids during the post-operative period, including OIVI and PPOU. Therefore, the risks indicate that modified release opioids outweigh the benefits in the treatment of post-operative pain.
- Reduced pack sizes would enable prescription of smaller amounts of opioids without the need for pharmacists to break packs, however MAHs need to be encouraged to market the smaller packs.
- A pack size of 28 modified release opioid tablets will cover a longer period than the same pack size of instant release opioids. To meet consensus best practice guidelines to limit discharge prescriptions to less than a week, the minimum pack size for the modified release opioids would need to be reduced.

CHM advice

The CHM discussed the current guidance on the use of opioids for post-operative pain. The CHM noted that post-operative pain was usually of short duration although many patients were being discharged from hospital with significant quantities of opioids. Therefore there is a large amount of unused opioids in the community with the risk of stockpiling, diversion and dependence. Similarly, the risks of a severe form of respiratory depression (OIVI) and dependency following surgery (PPOU) increased with post-operative use of modified release opioids. Given the risks and need for treatment of a short duration of pain relief, in line with current clinical guidance, the CHM recommended that instant release opioids would be sufficient and modified release opioids should not be used.

The CHM recommended that the indication for post-operative pain relief should be removed from the licenses of all modified release opioids and warnings for OIVI and PPOU should be added to the product information.

MAHs and local formularies are encouraged to increase availability of smaller pack sizes of all opioids to give flexibility in prescribing of smaller amounts of opioids in original packs, so that patients receive all product information, including warnings of respiratory depression and dependence. This also enables hospital pharmacies to discharge patients with original packs without the need to split larger packs.

Next steps

- The indication for post-operative pain relief has been removed from modified release morphine tablets and modified release oxycodone tablets (annex 1).

- There are significant risks associated with the use of modified release opioids during the post-operative period, including OIVI and PPOU. Therefore warnings have been added to product information of modified release opioid tablets or healthcare professionals and patients (annex 2)

- Local formularies and MAHs are encouraged to increase availability of smaller pack sizes to enable hospital discharge in original packs

- Production of a Drug Safety Update (DSU) to communicate the CHM's advice to healthcare professionals.

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Glossary of terms

Enhanced recovery after surgery (ERAS)

Enhanced recovery is an evidence-based approach that helps people recover more quickly after having major surgery.

Centre of Perioperative Care (CPOC)

A cross-specialty collaboration dedicated to the promotion, advancement and development of perioperative care for the benefit of patients at all stages of their surgical journey.

Commission on Human Medicines

The Commission on Human Medicines (CHM) advises ministers on the safety, efficacy and quality of medicinal products.

Faculty of Pain Medicine

The Faculty of Pain Medicine (FPM) is the professional body responsible for the training, assessment, practice and continuing professional development of specialist medical practitioners in the management of pain in the UK.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) provides national guidance and advice to improve health and social care. Their role is to improve outcomes for people using the NHS and other public health social care services. They also provide clinical guidance on how to manage specific conditions in England.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of medicines used to relieve pain, reduce inflammation and bring down high temperature.

Marketing Authorisation

A marketing authorisation (MA) grants permission to place a medicine on the market. The MHRA is the regulatory organisation who will review and assess evidence to support the granting of a licence to be sold.

Marketing Authorisation Holder

The company or other legal entity that has the authorisation to market a medicine in the UK.

Morphine Milligram Equivalent (MME)

The MME gives an approximate equivalent potency of an opioid in comparison with morphine. MMEs may also be referred to as morphine equivalent dose.

Opioid-induced ventilatory impairment (OIVI)

A serious form of respiratory depression appearing as breathing difficulties, sedation and a blockage in the airways.

National Health Service Business Authority (NHSBSA)

The government authority providing platforms and delivering services to support the priorities of the NHS, government and local health economies.

Patient Information Leaflet (PIL)

Medicine packs include a Patient Information Leaflet (PIL), which provides information on using the medicine safely. PILs are based on the Summaries of Product Characteristics (SPCs) which are a description of a medicinal product's properties, and the conditions attached to its use.

Persistent Post-operative Opioid Use (PPOU)

The use of opioids beyond 90 days after the day of operation

Pharmaceutical Benefits Scheme (PBS)

The PBS contains a list of medicines which are subsidised by the Australian government.

Royal College of Surgeons (RCS)

The Royal College of Surgeons (RCS) provides education, assessment and development of surgeons, dental professionals and wider surgical and dental health care teams. The RCS set professional standards championing the best outcomes for patients.

Summary of Product Characteristics (SmPC)

Detailed information that accompanies every licensed medicine, listing its composition and characteristics and conditions attached to its use, which is available at: https://www.gov.uk/guidance/find-product-information-about-medicines

Therapeutic Goods Administration (TGA)

Australia's government authority for evaluating, assessing and monitoring products that are defined as therapeutic goods. The TGA regulate medicines, medical devices and biologicals in Australia.

The Safe Anaesthesia Liaison Group (SALG)

A collaborative project between the Association of Anaesthetists, the Royal College of Anaesthetists and NHS England/NHS Improvement to promote patient safety across the perioperative pathway.

Neurology, Pain, and Psychiatry Expert Advisory Group (NPPEAG)

NPPEAG advises the CHM on the safety and efficacy of medicines for use in neurological conditions, pain management and psychiatric conditions..

Annex 1- Licenced modified release opioids with post-operative indication

Morphine sulfate

Licensed Product Name	Authorisation Holder Company Name
MST CONTINUS 5 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
MST CONTINUS 10 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
MST CONTINUS 15 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
MST CONTINUS 30 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
MST CONTINUS 60 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
MST CONTINUS 100 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
MST CONTINUS 200 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED

Oxycodone Hydrochloride

Licensed Product Name	Authorisation Holder Company Name
OXYCONTIN 10 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXYCONTIN 20 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXYCONTIN 40 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXYCONTIN 80 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXYCONTIN 5 MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXYCONTIN 15MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXYCONTIN 30MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXYCONTIN 60MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXYCONTIN 120MG PROLONGED RELEASE TABLETS	NAPP PHARMACEUTICALS LIMITED
OXELTRA 5MG PROLONGED-RELEASE TABLETS	WOCKHARDT UK LIMITED
OXELTRA 10MG PROLONGED-RELEASE TABLETS	WOCKHARDT UK LIMITED
OXELTRA 15MG PROLONGED-RELEASE TABLETS	WOCKHARDT UK LIMITED
OXELTRA 20MG PROLONGED-RELEASE TABLETS	WOCKHARDT UK LIMITED
OXELTRA 30MG PROLONGED-RELEASE TABLETS	WOCKHARDT UK LIMITED
OXELTRA 40MG PROLONGED-RELEASE TABLETS	WOCKHARDT UK LIMITED
OXELTRA 60MG PROLONGED-RELEASE TABLETS	WOCKHARDT UK LIMITED
OXELTRA 80MG PROLONGED-RELEASE TABLETS	WOCKHARDT UK LIMITED

LONGTEC 5 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED
LONGTEC 10 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED
LONGTEC 20 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED
LONGTEC 40 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED
LONGTEC 80 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED
LONGTEC 15 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED
LONGTEC 30 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED
LONGTEC 60 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED
LONGTEC 120 MG PROLONGED RELEASE TABLETS	QDEM PHARMACEUTICALS LIMITED

Annex 2 - warnings to be included in the SmPC and PIL

Warnings to be included in modified release (prolonged release, sustained release) tablets.

Summary of Product Characteristics

Section 4.4: Special warnings and precautions

"Do not use for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI)".

Patient Information Leaflet

The risk of PPOU may be more readily understood by the layperson as 'dependence' and OIVI as 'respiratory depression' or 'breathing problems. For those patients who are already receiving treatment with prolonged-release opioids prior to surgery the following direction will encourage both the patient and healthcare professional to discuss their ongoing pain management treatment:

Section 2

"Do not use <x> for acute post-operative pain because of the increased risk of dependency and developing serious breathing problems"

"If you are going to have an operation, or have just had an operation, please tell the doctor at the hospital if you are taking <x>. Your doctor may adjust your <dose/treatment >."

For Buprenorphine transdermal patches

Summary of Product Characteristics

Section 4.4: Special warnings and precautions

Buprenorphine patches for non-malignant pain currently contain a warning in section 4.4 of the SmPC which should be updated to state:

~~"Buprenorphine is not recommended for analgesia in the immediate post-operative period~~ Do not use for **acute** post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI)".

Buprenorphine patches for cancer pain are also recommended to include the same warning in section 4.4 of the SmPC.

Patient Information Leaflet

Section 2

"Do not use if you have pain which lasts only for a short period or pain after having an operation because of the increased risk of dependence and developing serious breathing problems"

"If you are going to have an operation, or have just had an operation, please tell the doctor at the hospital if you are currently treated with <x> transdermal patch to discuss your pain management"

For Fentanyl Transdermal patches

Summary of Product Characteristics

Section 4.3 Contraindications

Fentanyl transdermal patches are currently contraindicated for the treatment of:

"Acute or postoperative pain because there is no opportunity for dose titration during short-term use and because serious or life threatening hypoventilation could result"

It is recommended that the contraindication is amended to state:

"Acute pain because there is no opportunity for dose titration during short-term use, or postoperative pain because persistent post-operative opioid use or serious or life threatening hypoventilation could result"

Patient Information Leaflet

Section 2

"Do not use if you have pain which lasts only for a short period or pain after having an operation because of the increased risk of dependence and developing serious breathing problems"

"If you are going to have an operation, or have just had an operation, please tell the doctor at the hospital if you are currently treated with <x> transdermal patch to discuss your pain management."