

Re-Submission

Extended release epidural morphine, 10mg/ml (10mg, 15mg and 20mg) (Depodur®) **No. (528/09)**
Flynn Pharma Ltd

05 February 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a re-submission

extended release epidural morphine (Depodur®) is not recommended for use within NHS Scotland for the relief of post-operative pain following major orthopaedic, abdominal or pelvic surgery.

Extended-release epidural morphine has shown some advantages in terms of efficacy versus a single dose of epidural opioid. However, as there are limited comparative data versus epidural analgesia techniques currently used in NHS Scotland it was difficult to assess clinical efficacy in relation to current Scottish practice.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit or request an Independent Review Panel.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Relief of post-operative pain following major orthopaedic, abdominal or pelvic surgery.

Dosing information

For major orthopaedic surgery of the lower extremity, the recommended dose of extended-release epidural morphine (EREM) is 15mg.

For lower abdominal or pelvic surgery, the recommended dose of EREM is 10-15mg.

Some patients may benefit from a 20mg dose of EREM. However the incidence of serious adverse events, including respiratory depression, was dose-related in clinical trials.

For caesarean section, the recommended dose is 10mg (contra-indicated in patients who have received epidural local anaesthetics for analgesia during labour).

For operations associated with less severe pain and/or where freedom from the usual side effects of morphine is a priority or in elderly, frail or debilitated patients, lower doses may suffice. Maximum dose in elderly is 15mg.

EREM should be administered by or under the direction of a physician experienced in epidural administration of opioids, and only where there are immediate facilities for resuscitation, including staff trained in airway management and artificial ventilation.

Product availability date

October 2008

Summary of evidence on comparative efficacy

Extended-release epidural morphine (EREM) is a lipid-encapsulated formulation with a duration of action of about 48 hours following a single epidural injection.

Five pivotal studies that assessed analgesia across the range of surgery covered by the licensed indication are described below. All trials recruited adult patients but excluded patients with life-threatening disease. Efficacy analyses were conducted on intention to treat (ITT) populations. Supplementary analgesia was available to all patients in each trial. Epidural EREM, active comparator or placebo was given either before initiating surgery or at the final stages. Long-acting opioid medication was discouraged but not prohibited pre-operatively, while intra-operative analgesia, and post-operative opioid analgesia over 48 hours were specified by protocol. The post-operative use of anti-inflammatory medications was prohibited in all but one trial and the protocols discouraged the use of sedating medications including sedating antihistamines. All but one trial assessed the consumption of supplemental analgesia as the primary endpoint and all measured pain intensity on visual analogue scales (VAS, 0=no pain to 100=most severe pain possible) and categorical (CAT) scales (none, mild, moderate or severe pain). Pain assessments were conducted at rest and during an activity relevant to the patient's operation (e.g joint flexion for orthopaedic patients).

There were two studies in the orthopaedic setting. In the first, a total of 200 patients scheduled for unilateral hip arthroplasty were randomised to receive 15mg, 20mg or 25mg of EREM or an epidural injection of saline placebo. All patients were set up within 30 minutes of the end of surgery with a patient-controlled analgesia (PCA) device for the delivery of intravenous fentanyl. At the first request for supplementary pain medication, patients received a 25 microgram bolus dose of fentanyl followed by activation of on-demand bolus PCA. The primary endpoint was the mean quantity of fentanyl used in the 48 hours after study drug administration, analysed by analysis of variance (ANOVA) with terms for treatment group and type of anaesthesia. For all EREM groups combined (n=145) this was 510 ± 708 micrograms compared with $2,091 \pm 1,803$ micrograms for the placebo group (n=49). Differences were significant for EREM overall and for all individual doses, and the reductions were greater with increasing doses. The reductions in fentanyl requirements were significant for all EREM doses during 0 to 24 hours and 24 to 48 hours post-dose. There were significant advantages for EREM in VAS scores over 0 to 48 hours and at 24 hours post-dose. CAT pain intensity scores were significantly reduced for the EREM groups over 48 hours.

In the second study in an orthopaedic setting, 168 patients scheduled for unilateral knee arthroplasty were randomised to 20mg or 30mg EREM or a sham epidural injection. For the group receiving sham epidural, post-operative analgesia was an initial bolus dose of morphine at first request for pain medication, followed by morphine delivered by PCA. For the groups assigned to EREM, bolus IV injections of hydromorphone were given on request, and a PCA device was set up but delivered saline placebo. The primary outcome in this trial was a time-weighted pain intensity score in answer to the question, 'how much pain have you had since your last pain assessment?' using a 100mm VAS analysed by analysis of variance (ANOVA) with terms for treatment group and type of anaesthesia. Averaged over the 48-hour study period, this was lower for all EREM groups combined (33mm) than for the group assigned to sham epidural (39mm) but the difference was not significant, therefore significance was not assessed for individual EREM dose groups. There was a significant difference in favour of each of the EREM doses in secondary analyses of pain intensity recall up to 30 hours. There were also significant advantages for EREM over the comparator group for secondary outcomes including end-points relating to opioid consumption (33mg morphine equivalent for all EREM versus 122mg by IV PCA), pain intensity scores, overall rating of pain control and ability to tolerate physical therapy.

Patients scheduled for lower abdominal surgery were randomised to EREM 5, 10, 15, 20 or 25mg or unencapsulated epidural morphine 5mg. The 10, 15 and 20mg EREM groups were compared to the unencapsulated epidural morphine and to the 5mg EREM (dose control) group. Otherwise the study was similar in design to the hip arthroplasty study. There was a dose-related reduction in 48-hour fentanyl use for EREM compared with unencapsulated epidural morphine that was significant for the 10mg, 15mg and 25mg doses. For all EREM doses combined, mean fentanyl usage was 965 micrograms (n=402) compared with 1,218 micrograms for comparator (n=85). Fentanyl usage was significantly reduced on the second day of assessment (24 to 48 hours) for all EREM doses >5mg but only for the 25mg dose over the first 24 hours post-dose. At 48 hours, VAS pain intensity scores were significantly reduced at rest for the 15mg, 20mg and 25mg doses compared with unencapsulated morphine and on activity for the two higher doses only. CAT scores on activity and at rest were significantly lower than with unencapsulated MS at various time periods up to 36 hours but not consistently across doses and not at 48 hours.

Two studies were conducted in patients undergoing elective Caesarean section. In the first, 79 patients were randomised to EREM 5, 10 or 15mg or to unencapsulated MS 5mg following delivery and clamping of the umbilicus. Post-operatively, patients could receive oral paracetamol with codeine, IV morphine as an intermittent bolus or via a PCA pump. Mean opioid consumption over 48 hours (the primary outcome) was 30 mg IV morphine equivalent for the EREM groups combined compared with 47mg for unencapsulated MS representing a significant dose-related decrease overall and for all individual EREM groups except 5mg. Outcomes for 24 to 48 hours followed a similar pattern but there were no significant differences over the first 24 hours.

The second study had a broadly similar design but was more reflective of current obstetric analgesia. Epidural doses were 4mg for conventional MS and 10mg for EREM, and post-operative pain was managed according to a strict study protocol: oral oxycodone 5mg plus paracetamol 325mg was the primary opioid with IV morphine available for severe or unresponsive pain. In this study all patients received 600mg ibuprofen orally every six hours. The median IV morphine equivalent opioid consumption was 10mg in the EREM 10mg group and 17mg in the morphine 4mg group, and the difference was significant over 48 hours and during the second, but not the first day post-dose. EREM was also significantly superior to morphine 4mg for pain intensity at rest and during activity, but there was no significant difference for time to first request for supplemental analgesia. There were no significant differences in ability to breast feed, sleep quality or awakenings due to night pain.

Summary of evidence on comparative safety

Overall EREM was generally well tolerated with an adverse event (AE) profile similar to unencapsulated epidural morphine, though pruritus and urinary retention occurred significantly more frequently with higher doses of EREM. The use of opioid antagonist in the EREM groups was 12.5% in hip arthroplasty, 15% in knee arthroplasty, (compared with no cases with unencapsulated epidural morphine n=18), 12% in lower abdominal surgery (compared with 5% with unencapsulated epidural morphine) and 4% in Caesarean section. Opioid antagonist was most commonly required for pruritus or respiratory depression.

Delayed respiratory depression is a potentially life-threatening complication following epidural administration of opioids, especially hydrophilic agents such as morphine. It may be sudden in onset and occurred up to 48 hours post-dosing in approximately 2% of patients who received EREM. According to the Medicines and Healthcare products Regulatory Agency (MHRA) there were 13 cases of probable delayed respiratory depression associated with higher doses of EREM in the trials submitted for registration, representing an incidence of 2%. No data are given for the rate of delayed respiratory depression with comparators in studies, but the MHRA estimated from the literature that the incidence with epidural morphine is about 1% (although figures of up to 3% are reported).

Summary of clinical effectiveness issues

In three studies the active comparator was a single dose of unencapsulated epidural morphine while in two others it was stated to be placebo or opioid analgesia by the intravenous route. All patients in the clinical studies reviewed had access to supplemental analgesia as an ethical requirement making it difficult to distinguish the contribution of the individual components to the overall level of pain relief. In the orthopaedic study in patients undergoing knee arthroplasty different supplemental analgesia regimens were employed in each of the randomised treatment arms. The licensing authority considered this design flaw to be an important limitation.

Clinical experts have indicated that the use of bolus epidural morphine is not common clinical practice in Scotland. In a web-based survey, a group of Scottish anaesthetists were asked about their post-operative pain management. The results suggest that diamorphine and fentanyl are used more commonly than morphine and are likely to be used in conjunction with levobupivacaine, that an epidural catheter is most commonly used after open abdominal surgery and that for limb surgery, spinal anaesthesia is most common. Existing opioid administration via epidural or spinal routes is established off-label practice.

Two supportive, retrospective studies of EREM compared with continuous epidural infusion of bupivacaine with fentanyl or bupivacaine with morphine in patients who had undergone hip or knee arthroplasty were described. One study of 659 patients (327 patients in the EREM (5 to 15mg) group and 332 patients in the control group [IV PCA opioid or epidural PCA bupivacaine/fentanyl]) measured pain control and found significantly improved pain control in the EREM group at 24 and 48 hours. The second study in 210 patients (109 patients in the EREM group and 101 in the bupivacaine/morphine group) reported better pain control in the EREM group at 72 hours (with the difference emerging after stopping of the epidural infusion) and a better return to function but in the subset of hip arthroplasty patients only. Although these studies more closely reflect current practice than the double-blind single dose pivotal studies, there are a number of limitations: both were retrospective analyses and were undertaken only in the US, and there was non-random assignment of patients. In the first study described pain control was a secondary outcome and in the second study the dose of EREM was not reported.

In most of the clinical studies, the primary endpoint was use of supplementary opioid analgesia as a surrogate for pain relief. While the MHRA accepted this as an end-point, their assessment of efficacy also took account of more direct measures of pain intensity and pain relief. The requirement for supplemental analgesia over 48 hours was consistently reduced with EREM. While this would be expected given the prolonged duration of action of EREM, reductions were also observed over the first 24 hours, and a number of measures of pain intensity and quality of analgesia sufficiently favoured EREM. A benefit in the reduction of hospital stay for patients treated with EREM compared with alternative pain strategies has not been clearly established.

Some doses of EREM used in the studies exceeded the licensed dose and some exceed the recommended dose for the specific surgery and this is relevant when considering pooled efficacy and safety data.

Epidural analgesia with shorter-acting agents may require continuous or repeated intermittent administration and therefore require an epidural catheter to remain in situ. The use of a single-dose epidural agent by needle has the potential to reduce some catheter related complications of epidural administration. However, as the comparators in the studies were single dose injections of either unencapsulated morphine or placebo the advantages compared with an indwelling catheter are not known.

EREM is contra-indicated in patients receiving concurrent epidural anaesthesia as local anaesthetics may disrupt the modified release mechanism, potentially resulting in overdose. Once EREM has been administered, no other medication should be administered into the epidural space for at least 48 hours. In addition, if a test dose (e.g. with lidocaine/adrenaline) is used to confirm placement of the epidural needle, EREM must be administered after an interval of at least ten minutes.

Practice guidelines for the prevention, detection and management of respiratory depression associated with neuraxial opioid administration recently published by the American Society of Anesthesiologists (and endorsed by the UK Chief Medical Officers) state that all patients

receiving neuraxial opioids should be monitored regularly for adequacy of ventilation, oxygenation and level of consciousness. Monitoring during or after continuous infusion with neuraxial lipophilic opioids should be performed during the entire time the infusion is in use, at least once every hour during the first 12 hours, at least once every two hours during the period from 12 to 24 hours, and at least once every four hours in the period after 24 hours. For extended release epidural morphine monitoring should be performed at least once every hour during the first 12 hours, at least once every two hours from 12 to 24 hours, and at least once every four hours during the period from 24 to 48 hours after administration.

Because of the risk of delayed respiratory depression, the summary of product characteristics (SPC) states that EREM should be administered only where there are immediate facilities for resuscitation, including staff trained in airway management.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing EREM with bolus epidural morphine supplemented with IV PCA, continuous epidural analgesia (CEA), and IV PCA alone for the relief of postoperative pain following major orthopaedic, abdominal or pelvic surgery in situations where extended (up to 48 hours) pain relief was required. A decision tree model was used to model the results for hip arthroplasty, knee arthroplasty, caesarean section and lower abdominal surgery over a 2-week time horizon. Clinical data included in the model were based on clinical studies for the different surgeries and supplemented with the results of a meta-analysis of RCT literature where necessary. The clinical outcomes in the model were the rates of sufficient pain relief over 48 hours without the need for additional analgesia, visual analogue scale (VAS) pain scores at 24 and 48 hours, and the rates of adverse events. Utility values were derived using a double mapping approach where VAS pain scores were mapped to the physical and mental components of the SF-12 which in turn were mapped to EQ-5D. Resource use estimates in relation to hospital length of stay were based on data from the literature.

In the base case analysis the manufacturer estimated that EREM would be the dominant treatment with estimated net savings of between £87 and £174 and a QALY gain of 0.0001 to 0.0005 depending on the comparator and surgery type modelled.

Some limitations of the analysis were noted:

- The key weakness was the inclusion of savings from reduced time in a high dependency unit (HDU) and reduced length of hospital stay associated with EREM. This may not be appropriate as the resource use estimates were based on US data sources where practice is likely to be different from Scotland. SMC clinical experts commented that it was unlikely these savings would be realised in Scottish practice. The manufacturer also provided some additional analysis based on numbers needed to treat but this analysis still rests on achieving reductions in hospital resources which there is limited UK data to support.
- The sensitivity analysis showed that the results were sensitive to the estimated savings from reduced length of stay. When the savings were removed EREM was no longer cost-effective with ICERs of between £78k and £102k per QALY. SMC clinical experts suggested that there may actually be increased resource use associated with EREM as monitoring requirements may necessitate admission to a HDU setting for a minimum of 48 hours.
- SMC clinical experts indicated that bolus epidural morphine and IV PCA were not appropriate comparators. CEA appears to be the most relevant comparator, although some experts suggested that none of the comparators were relevant because they did not feel EREM would replace current practice.

- Whilst it may be difficult to obtain robust utility values in this area, there were some weaknesses with the method used to derive the utility values. In addition, no sensitivity analysis was provided using more pessimistic utility values which would have been useful given the uncertainty around the values used in the base case.

Due to the uncertainty associated with the inclusion of savings from reduced length of stay in hospital in the EREM arm of the model and the other weaknesses outlined above, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

A best practice statement on post-operative pain management was issued by National Health Service Quality Improvement Scotland in June 2004. It has sections that discuss advantages, disadvantages and practical aspects of subcutaneous opioids, PCA, and epidural analgesia and the use of regional methods of pain relief using local anaesthetic. It expresses no preference for any individual modality aside from a statement suggesting a possible efficacy advantage for epidural opioids over IV PCA in major lower abdominal surgery.

A statement of good practice in the management of continuous epidural analgesia in the acute hospital setting (including post-operative analgesia) was developed by an interdisciplinary working group with representation from The Royal College of Anaesthetists, The Royal College of Nursing, The Association of Anaesthetists of Great Britain and Ireland, The British Pain Society and The European Society of Regional Anaesthesia and Pain Therapy and published in November 2004. It refers to continuous epidural infusions, intermittent top-up injections and patient-controlled epidural analgesia.

It recommends that patient selection and consent for continuous epidural analgesia should be based on discussion of its risks (which may be serious and potentially life-threatening) and potential benefits, as well as the features of other options for postoperative analgesia.

In February 2009, the American Society of Anaesthetists (ASA) issued practice guidelines for the prevention, detection and management of respiratory depression associated with neuraxial opioid administration. This guidance provides advice on monitoring requirements for respiratory depression. The guidelines state that: The consultants and ASA members are equivocal regarding whether extended-release epidural morphine increases the occurrence of respiratory depression compared with either parenteral opioids or conventional (immediate-release) epidural morphine.

Additional information: comparators

In terms of epidural analgesia the main UK comparators are fentanyl and diamorphine. EREM was compared with epidural morphine in trials, though this is a less relevant comparator in the UK. Post-operative analgesia involves a multimodal approach, and alternative/supplemental options include sub-cutaneous opioids, intravenous opioids by bolus or continuous infusion (which may be patient-controlled), local anaesthetics by neuraxial routes and non-steroidal anti-inflammatory drugs.

Cost of relevant comparators

The costs below are drug acquisition costs for epidural administration. Additional costs associated with epidural administration may include formulation costs and costs of administration devices. Note that EREM is ready-formulated for epidural administration.

Drug	Dose regimen	Cost over 48 hours
Extended release epidural morphine	10 to 20mg by epidural bolus	83.00
Fentanyl epidural Infusion ^{***}	2micrograms/ml at a rate of 5-15 ml/hour [*]	1.05 to 3.15
Unencapsulated morphine	5mg by epidural bolus ^{**}	2.10
Diamorphine ^{***}	3-4mg by epidural bolus [*]	2.75

Doses are for general comparison and do not imply therapeutic equivalence. Costs were from eVadis on 24 November 2009, BNF no 58 and the submitting company for EREM. ^{*} Doses by personal communication as administration via this route is an off-label use. ^{**} Dose used in comparative trials versus EREM. ^{***} These agents are routinely combined with a local anaesthetic e.g. bupivacaine 0.1% to 0.125% infusion at 5 to 15ml per hour at a cost over 48 hours of £21 to £32.

Additional information: budget impact

The manufacturer estimated a gross drug budget impact of £448k per year. This includes the drug acquisition cost of EREM and additional IV PCA as required according to the efficacy estimates used in the economic model. 3,335 patients were estimated to be treated with EREM per year based on an assumption that EREM would be used in 5% of the indicated operations. SMC clinical experts indicated that the only relevant comparator would be CEA. Based on EREM replacing 5% of operations where patients would otherwise receive CEA, the annual gross drug budget impact was estimated to be £326k.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 January 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

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Hartrick CT, Martin G, Kantor G, Koncelik J, Manvelian G. Evaluation of a single-dose, extended-release epidural morphine formulation for pain after knee arthroplasty. *J Bone Joint Surg* 2006;88:273–281.

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