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

09 January 2009

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 full 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. Evidence for clinical efficacy was obtained from studies that do not reflect current practice for epidural analgesia in NHS Scotland. The manufacturer did not present a sufficiently robust clinical or economic analysis to gain acceptance by the SMC.

The licence holder has indicated their intention to resubmit.

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 which assessed analgesia across the range of types of surgery covered by the licensed indication are discussed below. Supplementary analgesia was available to all patients in each trial. All trials recruited adult patients in the American Society of Anaesthetists (ASA) functional classification between P1 (a normal healthy patient) and P3 (a patient with severe systemic disease), thereby excluding patients with life-threatening disease. Efficacy analyses were conducted on intention to treat (ITT) populations. 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 medication was prohibited in all but one trial and the protocols discouraged the use of sedating medicines 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 trials 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 were to receive 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 ±1,803 micrograms for the placebo group. Differences were significant for EREM overall and for all individual doses, and the differences were greater with increasing EREM doses. There were also significant reductions in fentanyl requirements for all EREM doses during the first (0-24 hours) and second (24-48 hours) days post-dose. CAT pain intensity scores were significantly reduced for the EREM groups over 24 hours but not over 48 hours. There were significant advantages for EREM in VAS scores over 0-48 hours and at 24 hours post-dose, and for rating of quality of analgesia by the surgeon and the patient (25mg dose only).

In the second trial 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 consisted of 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 ANOVA with terms for treatment group and type of anaesthesia. Averaged over the 48-hour study period, this was lower for all EREM groups (33.1mm) than for the group assigned to sham epidural (39.1mm) but the difference was not significant over the entire study period for EREM overall, 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 trial was similar in design to the hip arthroplasty trial. There was a dose-related reduction in 48-hour fentanyl use for EREM compared with unencapsulated epidural morphine, which 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 except for the 25mg dose where the reduction was significant only 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 morphine sulphate (MS) at various time periods up to 36 hours but not consistently across doses and not at 48 hours. At day 2, significantly more patients had higher ratings of pain control in the 15 and 25mg groups compared with unencapsulated MS, but there were no significant differences for this measure at day 3 or for the proportion of patients whose surgeon rated control as good or very good at day 2 or day 3 (though surgeon's actual pain ratings were significantly better for EREM).

Two trials 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 were permitted to 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 29.6mg IV morphine equivalent for the EREM groups combined compared with 47.0mg for unencapsulated epidural morphine representing a significant dose-related decrease overall and for all individual EREM groups except 5mg. Findings for the second post-dose day (24 to 48 hours) followed a similar pattern. There were no significant differences over the first 24 hours. There were significant differences in favour of EREM for measures of pain intensity and for functional ability at some doses and some time points.

The second study had a broadly similar design but was designed to be more reflective of current obstetric analgesia. Epidural doses were 4mg for unencapsulated 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%, and this AE was implicated in one death due to cardio-respiratory arrest. No data are given for the rate of delayed respiratory depression with comparators in trials, 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 trials 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. Clinical experts have indicated that the use of bolus epidural morphine is not common clinical practice in Scotland.

As all patients in the clinical trials reviewed had access to supplemental analgesia it is difficult to distinguish the contribution of the individual components to the overall level of pain relief. In the orthopaedic trial 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.

In most clinical trials the primary endpoint was use of supplementary opioid analgesia as a surrogate for pain relief. While the MHRA accepted that 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. The difference between combined EREM groups and comparators for the time between administration and discharge in four studies was in the range 0.1 to 0.5 days and was not significant.

Experience of EREM in clinical trials has been limited to patients assessed as ASA grade I to III. It is therefore not recommended in patients graded ASA IV or V. Some doses of EREM used in trials exceeded the licensed doses 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.

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.

The prolonged action of epidural morphine in the EREM formulation may potentially increase the risk of delayed respiratory depression. The MHRA considered the balance of risk and benefit with EREM to be positive only within the context of high dependency monitoring for 48 hours following administration. 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.

Freezing results in disruption of the extended release mechanism of EREM with the potential for overdosage. The pack has an indicator which changes colour if freezing has occurred, and if this occurs the product should be discarded.

Summary of comparative health economic evidence

The manufacturer presented a cost impact study. A cohort-based model was constructed using a decision-tree process that compared EREM to bolus epidural morphine sulphate (MS 5mg) supplemented with IV PCA and to IV PCA alone. The clinical effectiveness data populating the economic model were based on pooled estimates calculated in a meta-

analysis of the clinical trial reports. Resource use data incorporated in the model was drawn largely from other literature. Key results indicated that treatment with EREM 10mg and 15mg cost £86.79 and £94.47 less (net, on average per patient per 48 hours) than treatment with epidural MS and £65.07 and £72.75 less (net, on average per patient per 48 hours) than treatment with IV PCA respectively, leading the manufacturer to conclude that the cost-offsets obtained by treatment with EREM outweighed the increased cost of drug acquisition. Sensitivity analysis indicated that the key cost drivers in the model were reduction in hospital length of stay and high dependency unit (HDU) time and the acquisition price of the drug. EREM remained cost saving across all sensitivity analyses scenarios. However, reducing the assumed length of stay saving by 30% reduced the savings associated with EREM compared to epidural MS and IV PCA to £56.19 and £34.47 respectively. Removing the length of stay saving completely resulted in EREM becoming more expensive than the comparators.

Weaknesses of the analysis included:

- The economic study did not include final health outcomes and presented cost data only. Consequently, a full economic evaluation was not presented. Some additional sensitivity analysis was provided to show indicative level of QALY gains that would be needed to result in incremental cost per QALY ratios of £20,000 and £30,000. However, the assumptions used to derive these figures used an assumption of a linear relationship between VAS pain scores and utility improvements which did not seem appropriate.
- The validity of the unimodal comparators and their generalisability to multimodal Scottish practice were uncertain. Experts indicated that use of bolus epidural morphine is not common in Scotland and suggested alternative, more relevant, comparators.
- Development of one economic model incorporating pooled clinical effectiveness estimates from a meta-analysis of several heterogeneous trials covering all surgery/patient types and dosage levels was questionable. Further, incidence rates for severe adverse events were drawn from literature other than the meta-analysis of trial data and the incidence of respiratory depression adverse events was not included in the model.
- The 48-hour time horizon of the economic model is a limitation as it encapsulates only part of the care pathway, making it difficult to contextualise the results to the total pain management package.
- Resource utilisation estimates were generally taken from secondary literature and not drawn directly from the trial data. The validity and generalisability to Scotland of some of the assumptions underpinning the economic model were, therefore, uncertain. Incorporation of length of stay savings (estimated across whole episodes of care and drawn from non-trial literature) in a model with a 48-hour time horizon only seemed questionable and of particular note given that this parameter was a driver in the model and when removed resulted in EREM becoming more expensive than comparators. Further, exclusion of additional costs associated with the 48-hour continuous monitoring within an HDU setting is likely to be key, with the inclusion of these costs expected to result in EREM becoming more expensive than comparators. In addition, the extent to which identified savings could be realised in practice was questionable. The sensitivity analyses presented were limited and lacked an underpinning rationale and thus did not help clarify the magnitude of the uncertainty regarding the results.

As a consequence, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by the SMC.

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 which 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 inter-disciplinary working group and published in November 2004. It refers to continuous epidural infusions, intermittent top-up injections and patient-controlled epidural analgesia, but makes no mention of single-dose epidural analgesia as used in the EREM clinical trial programme. 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.

Additional information: previous SMC advice

Following a full submission, SMC issued advice in December 2004: paracetamol 1g/100ml infusion (Perfalgan®) is accepted for use within NHS Scotland for the short-term treatment of moderate pain following surgery and fever, when administration by intravenous route is clinically justified.

Following a full submission, SMC issued advice in March 2008: diclofenac (Dyloject®) is accepted for restricted use within NHS Scotland for the treatment or prevention of post-operative pain by intravenous injection, in supervised healthcare settings. When given as an intravenous bolus, it showed non-inferiority to a comparator non-steroidal anti-inflammatory drug infusion at providing pain relief over an initial 4 hour period and caused less thrombophlebitis. The manufacturer's submission related only to intravenous use of diclofenac (Dyloject®) in the post-operative setting. SMC cannot recommend its use by the intramuscular route.

Following a full submission, SMC issued advice in January 2003: parecoxib is not recommended for use within NHS Scotland. There is no evidence that the parenteral COX-2 selective non-steroidal anti-inflammatory drug (NSAID), parecoxib, is associated with a reduction in clinically significant post-operative haemorrhagic or gastro-intestinal complications compared with the non-selective NSAIDs. Parecoxib is substantially more expensive than non selective NSAIDs and should therefore not replace these drugs.

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. These will vary between cases and are discussed in health economic evidence. 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**
Fentanyl epidural infusion	2micrograms/ml at a rate of 5-15 ml/hour*	1.09 to 3.26
Unencapsulated morphine	5mg by epidural bolus**	2.10
Diamorphine	3-4mg by epidural bolus *	2.69

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 10 November 2008 except for EREM (supplied by submitting company).
* Doses by personal communication. ** Dose used in comparative trials versus EREM

Additional information: budget impact

The manufacturer estimated a net saving of £94 per patient treated with EREM (15mg dose). This translates to net savings of £362k in 2009 (5% market share; 3,831 patients) rising to £1.448 million in 2013 (20% market share; 15,324 patients) for the 15mg dose. However, these savings are based largely on the manufacturer's assumed savings in length of stay that experts indicated may not be realistic or realisable.

Net drug budget impact is difficult to calculate given the multimodal practice typical in this area. Gross drug costs (based on an acquisition cost of £83.25 for EREM and the manufacturer's estimated market share figures) are estimated to be £319k in year 1 rising to £1.276m in year 5.

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 12 December 2008.

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.

Flynn Pharma. Data on file: Study SKY0401-011.

Viscusi ER, Martin G, Hartrick CT et al. Forty-eight hours of postoperative pain relief after total hip arthroplasty with a novel, extended-release epidural morphine formulation. Anesthesiology 2005;102:1014–1022.

Flynn Pharma. Data on file: Study SKY0401-012B.

Gambling D, Hughes T, Martin G et al. A comparison of Depodur, a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. Anesth Analg 2005;100:1065–1074.

Flynn Pharma. Data on file: Study SKY0401-017.

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.

Flynn Pharma. Data on file: Study SKY0401-015.

Carvalho B, Riley E, Cohen SE et al. Single-dose, sustained-release epidural morphine in the management of postoperative pain after elective cesarean delivery: results of a multicenter randomized controlled study. Anesth Analg 2005;100:1150–1158.

Carvalho B, Roland LM, Chu LF et al. Single-dose, extended-release epidural morphine (DepoDur) compared to conventional epidural morphine for post-cesarean pain. Anesth Analg 2007;105:176–183