oxycodone hydrochloride 50mg/ml solution for injection or infusion  
(OxyNorm®) SMC No. (648/10)

Napp Pharmaceuticals Limited

8 October 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 full submission

**oxycodone hydrochloride 50mg/ml injection (OxyNorm®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** treatment of moderate to severe pain in patients with cancer

**SMC restriction:** patients who have difficulty in tolerating morphine or diamorphine therapy and who require a high dose of oxycodone delivered via syringe pump which necessitates the daily preparation of an additional syringe pump if oxycodone 10mg/mL is used.

No new clinical or pharmacokinetic evidence has been presented for this higher strength formulation. Comparative evidence of analgesia achieved with parenteral administration is extrapolated from the lower strength 10mg/mL oxycodone formulation compared with morphine 10mg/mL.

The economic case was made only for patients in a hospice or community setting who require a high dose of oxycodone which necessitates the daily preparation of an additional syringe pump.

Care should be taken to minimise any risk of administration error with the introduction of this increased strength formulation.

Oxycodone 50mg/mL is also licensed for the treatment of moderate to severe post-operative pain and severe pain requiring the use of strong opioid. The manufacturer’s submission related only to use in moderate to severe pain in patients with cancer therefore SMC cannot recommend the use of oxycodone 50mg/mL injection in the treatment of non-cancer pain.

Overleaf is the detailed advice on this product.

**Chairman,**  
Scottish Medicines Consortium
Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord and is similar to morphine in its action.

SMC has previously accepted oxycodone injection for restricted use in the treatment of cancer patients with moderate to severe pain who have difficulty in tolerating morphine or diamorphine therapy. This submission relates to a new higher strength formulation of oxycodone injection. The company has requested that SMC considers the use of oxycodone 50mg/mL injection in patients with moderate to severe cancer related pain who have difficulty in tolerating morphine or diamorphine and who require a daily dose of oxycodone delivered via a syringe pump which would necessitate the preparation of two syringes per day using oxycodone 10mg/mL. This new higher strength formulation would allow the dose to be delivered in one syringe over 24 hours. The regulatory authorities required no new clinical or pharmacokinetic evidence for this new strength. The clinical evidence presented here is therefore for oxycodone 10mg/mL.

Oxycodone 50mg/mL is also indicated for treatment of post-operative pain and for the treatment of severe pain requiring the use of a strong opioid. The current submission does not include these elements of the indication and therefore they have not been considered by SMC.

A double-blind crossover study recruited 20 metastatic cancer patients with severe pain, who required a change from their weaker opioid analgesic (e.g. codeine) to morphine. Patients were randomly assigned for 48 hours to oxycodone 10mg/mL and morphine 10mg/mL via a patient-controlled analgesia (PCA) device, which administered 3mg IV bolus over one minute followed by 2mg over the next hour, with a 15-minute lock-out. If patients were not pain free they could titrate the dose given over the one-hour period by 2mg each time until pain control was achieved. Patients crossed over to the alternative treatment for a further 48 hour treatment period. Median pain intensity was measured on a 0-10 visual analogue scale (VAS). The last 24 hours of each stage of the study were regarded as the steady state and the drug consumptions, and the ratings from the VAS during this period were used for the statistical analysis. The mean VAS score for the analgesic agents used prior to the start of the study was 7.6. This decreased to a mean of 2.4 for IV oxycodone and 1.6 for IV morphine with a median

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment of moderate to severe pain in patients with cancer.</th>
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<tbody>
<tr>
<td>Dosing Information</td>
<td>Initially in opioid naïve patients, 1 to 10mg via intravenous (IV) bolus injection over 1 to 2 minutes no more than every 4 hours, 2mg/hour by IV infusion, 0.03mg/kg via IV patient controlled analgesia with minimum lock-out time of 5 minutes, 5mg via subcutaneous bolus injection every four hours if required or 7.5mg/day via subcutaneous infusion. Doses may be gradually increased if analgesia is inadequate or pain severity increases.</td>
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<tr>
<td>Product availability date</td>
<td>June 2009</td>
</tr>
<tr>
<td>Summary of evidence on comparative efficacy</td>
<td>Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord and is similar to morphine in its action. SMC has previously accepted oxycodone injection for restricted use in the treatment of cancer patients with moderate to severe pain who have difficulty in tolerating morphine or diamorphine therapy. This submission relates to a new higher strength formulation of oxycodone injection. The company has requested that SMC considers the use of oxycodone 50mg/mL injection in patients with moderate to severe cancer related pain who have difficulty in tolerating morphine or diamorphine and who require a daily dose of oxycodone delivered via a syringe pump which would necessitate the preparation of two syringes per day using oxycodone 10mg/mL. This new higher strength formulation would allow the dose to be delivered in one syringe over 24 hours. The regulatory authorities required no new clinical or pharmacokinetic evidence for this new strength. The clinical evidence presented here is therefore for oxycodone 10mg/mL. Oxycodone 50mg/mL is also indicated for treatment of post-operative pain and for the treatment of severe pain requiring the use of a strong opioid. The current submission does not include these elements of the indication and therefore they have not been considered by SMC. A double-blind crossover study recruited 20 metastatic cancer patients with severe pain, who required a change from their weaker opioid analgesic (e.g. codeine) to morphine. Patients were randomly assigned for 48 hours to oxycodone 10mg/mL and morphine 10mg/mL via a patient-controlled analgesia (PCA) device, which administered 3mg IV bolus over one minute followed by 2mg over the next hour, with a 15-minute lock-out. If patients were not pain free they could titrate the dose given over the one-hour period by 2mg each time until pain control was achieved. Patients crossed over to the alternative treatment for a further 48 hour treatment period. Median pain intensity was measured on a 0-10 visual analogue scale (VAS). The last 24 hours of each stage of the study were regarded as the steady state and the drug consumptions, and the ratings from the VAS during this period were used for the statistical analysis. The mean VAS score for the analgesic agents used prior to the start of the study was 7.6. This decreased to a mean of 2.4 for IV oxycodone and 1.6 for IV morphine with a median</td>
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pain intensity of 1.1 for both oxycodone and morphine. The median consumption of oxycodone was 30% higher than with morphine, which was statistically significant (p<0.01).

Summary of evidence on comparative safety

Oxycodone has an adverse event profile similar to other opioids. The most frequent adverse event with morphine and oxycodone was sedation. Excessive perspiration was slightly more common with IV oxycodone than with morphine.

Compatibility studies with other commonly used palliative care medicines were undertaken with the 50mg/mL formulation. The palliative care drugs with which oxycodone hydrochloride 50mg/mL is compatible are listed in the Summary of Product Characteristics.

Summary of clinical effectiveness issues

No new clinical or pharmacokinetic data were presented for the 50mg/mL formulation. The pharmacokinetic data presented for registration was conducted with a 10mg/mL concentration of oxycodone. The results were considered applicable to the 50mg/mL solution.

There is a lack of comparative data with morphine and diamorphine but if previous SMC advice is followed, oxycodone should only be used in patients with moderate to severe cancer pain who have difficulty tolerating morphine or diamorphine. Therefore the comparator in this submission is the lower strength oxycodone formulation (10mg/mL). The company has suggested that for patients requiring a high dose of oxycodone, use of the 10mg/mL formulation limits the ability to combine appropriate medications due to volume constraints, and may lead to the requirement for an additional syringe pump. The company proposes that the treatment pathway for patients eligible for parenteral opioids for cancer pain would initially involve morphine or diamorphine, then if the patient is intolerant to these, oxycodone 10mg/mL, then if the patient requires high dose oxycodone such that the preparation of more than one syringe pump in 24 hours is needed, oxycodone 50mg/mL.

There are possible advantages to the service and the patient with this new higher strength formulation which would allow the use of smaller volumes to deliver equivalent doses of oxycodone thus providing an opportunity to combine with adjuvant therapies, savings on nursing time and lessening the opportunity for calculation/measurement errors. Since oxycodone is a controlled drug (CD), this also eliminates additional checking and recording in the CD register.

A generic formulation of oxycodone 10mg/mL has recently been licensed.

Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing oxycodone 50mg/mL to oxycodone 10mg/mL for the treatment of moderate-to-severe pain in patients with cancer, who are intolerant of morphine or diamorphine and require a daily dose of oxycodone requiring an additional syringe pump if oxycodone 10mg/mL is used. These patients are a subset of the full indication. The manufacturer assumed that the cut-off daily dose of oxycodone 10mg/mL, where an additional syringe pump would be necessary, would be around 100mg, due to the
capacity available in the syringe. This was based on 20mL and 30mL syringes, giving useable volumes for injection of 17mL and 22mL respectively. The manufacturer assumed that an additional syringe pump would only be required in hospices and the community as in the hospital setting, a larger 50mL syringe can be used. The duration of treatment was assumed to be 11 days.

The evidence base to support the clinical equivalence necessary for the cost-minimisation analysis is the licence for the 50mg/mL oxycodone formulation granted by the Medicines and Healthcare products Regulatory Agency (MHRA), which was introduced as a line extension to an existing marketing authorisation for the lower concentration formulation, oxycodone 10mg/mL.

The analysis compared the drug acquisition and administration costs of oxycodone 50mg/mL to oxycodone 10mg/mL. Drug costs were based on a weighted average of daily doses assumed to be used in the range 100mg to 179mg. The administration costs considered in connection with the use of an additional syringe pump related to nursing time and consumables. The base-case assumed 15 minutes of nursing time each day would be required to allow the use of an additional syringe pump. The cost per hour of nursing time was based on an Agenda for Change band 6 community nurse.

The results showed the weighted incremental drug acquisition cost per patient to be £135.39 and the incremental administration cost to be -£221.71, resulting in an overall cost impact per patient of -£86.31 over 11 days. The manufacturer therefore reported the use of oxycodone 50mg/ml to be cost saving at a cut-off daily dose for an additional syringe pump of 100 mg.

The key findings from the sensitivity analysis were that the estimated base case saving per patient is sensitive to the overall nursing time spent attending the additional syringe pump and the hourly rate assumed for this. The source document for the cost per hour of nursing time also quoted lower hourly rates, depending on the assumptions made about on-costs and working hours available. The use of a lower hourly rate for the nursing time released would impact on the savings estimated accordingly.

The main limitations of the analysis were:

- The key parameter that drives the savings associated with oxycodone 50mg/mL is overall nursing time spent attending the additional syringe pump of oxycodone 10mg/mL. While SMC experts indicate that the time estimated by the manufacturer was reasonable it should be noted that it is not a cash-releasing direct saving. If this estimated saving is not realisable in clinical practice then the use of oxycodone 50mg/mL could result in an incremental cost to NHS Scotland, rather than produce a cost-saving. Sensitivity analysis suggested that the cost impact per patient would be neutral if the nursing time associated with the additional syringe pump was at least 8 minutes per day.
- The incremental treatment drug cost per patient increases with the daily dose required, therefore reducing the estimated savings associated with administration costs.
- The comparator strategy of oxycodone 10mg/mL requiring two syringe pumps was viewed appropriate for the subset of patients under consideration however there was no consideration of moving to other opioids as an alternative treatment option.

Despite these limitations, the economic case was considered demonstrated for the positioning proposed by the manufacturer.
A patient interest group submission was not made.

Additional information: guidelines and protocols

Scottish Intercolligate Guidelines Network. (SIGN) no 106. November 2008. The control of pain in adults with cancer. This guideline recommends that:
The oral route should be used for administration of opioids, if practical and feasible. Oral morphine is recommended as first line therapy to treat severe pain in patients with cancer. Diamorphine is ten times more soluble in water than morphine, and is easier to administer at higher doses. For subcutaneous administration, diamorphine is the preferred opioid for the control of severe pain and is recommended as first line to treat severe pain in patients with cancer. Continuous subcutaneous infusion of opioids is simpler to administer and equally as effective as continuous intravenous infusion and should be considered for patients unable to take opioids orally.

The aim of the statement is to offer guidance to health professionals on the best practice in this area, aiming to provide a consistent approach to practice to enable seamless provision of care to be delivered between the hospital and the community.
The statement is divided into four sections covering:
Section 1: Pain management education
Section 2: Pain assessment
Section 3: The pharmacological management of pain
Section 4: The non-pharmacological management of pain

British Pain Society’s Cancer Pain Management. January 2010
It is recognised that the World Health Organisation (WHO) analgesic ladder, whilst providing relief of cancer pain towards the end of life for many sufferers worldwide, may have limitations in the context of long-term survival and increasing disease complexity. In order to address these weaknesses, it is suggested that a more comprehensive model of cancer pain management is needed that is mechanism-based and multimodal, using combination therapies including interventions where appropriate, which is tailored to the needs of an individual, with the aim of optimising pain relief while minimalising adverse effects.

Additional information: comparators

Other parenteral opioids but since oxycodone is only recommended by SMC for patients having difficulty tolerating morphine and diamorphine, the main comparator for this new formulation of oxycodone is the lower strength formulation of oxycodone.
### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost Per Day (£)</th>
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</thead>
<tbody>
<tr>
<td>Oxycodone 50mg/mL</td>
<td>100 to 200mg daily</td>
<td>28 to 56</td>
</tr>
<tr>
<td>Oxycodone 10mg/mL</td>
<td>100 to 200mg daily</td>
<td>16 to 32</td>
</tr>
<tr>
<td>Diamorphine 10mg</td>
<td>50 to 130mg daily</td>
<td>18 to 29</td>
</tr>
<tr>
<td>Diamorphine 30mg</td>
<td>50 to 130mg daily</td>
<td>8 to 19</td>
</tr>
<tr>
<td>Morphine 10mg/mL</td>
<td>100 to 200mg daily</td>
<td>7 to 14</td>
</tr>
<tr>
<td>Morphine 30mg/mL</td>
<td>100 to 200mg daily</td>
<td>4 to 8</td>
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</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Conversion ratios could not be confirmed and therefore an approximate equivalent daily dose is presented. Costs from eVadis on 9.8.10.

### Additional information: budget impact

Approximately 174 patients were estimated by the manufacturer to be eligible for treatment and 80% of those would be prescribed oxycodone 50mg/ml injection in year one, rising to 100% by year five, giving 139 patients treated with oxycodone in year one, rising to 174 by year five.

The manufacturer estimated the net budget impact to be a saving of £12k in year one, increasing to £15k in year five. These estimates took account of estimated savings in nursing time and consumables. The drug budget only impact was estimated as £19k in year one rising to £24k in year five.

SMC clinical experts have suggested that use of this product may be greater in practice than the manufacturer's budget impact analysis suggests.
References

The undernoted references were supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 17 September 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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.