

## prilocaine hydrochloride 2% hyperbaric solution for injection (Prilotekal®) SMC No. (665/10)

### Goldshield Group

17 December 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

**prilocaine hydrochloride 2% hyperbaric solution for injection (Prilotekal®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** spinal anaesthesia

**SMC restriction:** for use in spinal anaesthesia in ambulatory surgery settings such as day surgery units.

Prilocaine 2% hyperbaric solution for injection was associated with faster discharge times than a hyperbaric formulation of another local anaesthetic in one small single-centre, double-blind, randomised study. Use of this preparation may allow service improvement through benefits to individual patients or service delivery.

Overleaf is the detailed advice on this product.

**Chairman  
Scottish Medicines Consortium**

## Indication

Spinal anaesthesia

## Dosing Information

Established on an individual basis taking consideration of the patient's physical condition and other concomitant medicinal products. The duration of action is dose-dependent. The summary of product characteristics (SPC) gives the following guidelines for adults of average height and weight (approximately 70kg) for obtaining an effective block with one single dose. A dose of 40 to 60mg would be expected to provide extension of sensory blockade required T10 for approximately 100 to 130 minutes. As a general guideline, the maximum recommended dose is 80 mg of prilocaine hydrochloride. There are wide individual variations with regard to extent and duration of action.

Administration is restricted to anaesthetists.

## Product availability date

1 July 2010

## Summary of evidence on comparative efficacy

Prilocaine is a local anaesthetic with a similar duration of action to lidocaine. This is a new hyperbaric formulation of prilocaine for use in spinal anaesthesia. Hyperbaric solutions have a greater specific gravity than the cerebrospinal fluid often making the spread of anaesthesia more predictable with greater spread in the direction of gravity.

The submitting company requested that SMC consider the use of prilocaine hyperbaric as spinal anaesthesia only in ambulatory surgery settings such as day surgery units.

Evidence to support the use of this new formulation in spinal anaesthesia comes from a single-centre, double-blind, randomised study in 88 patients. Eligible patients were aged 18 to 75 years and were undergoing day-case surgery, using spinal anaesthesia, of the lower limbs lasting for a maximum of 45 minutes. Patients were randomised to receive prilocaine hyperbaric 2% (60mg) or bupivacaine hyperbaric 0.5% (15mg), administered in a sitting position over 10 to 15 seconds. Patients were then positioned flat on their back for 2 minutes before having the torso elevated to 30°. All patients were pre-medicated with paracetamol and dipotassium clorazepate and could receive additional sedation with midazolam or propofol and supplementary anaesthesia with sufentanil if necessary.

The primary outcome was not clearly defined but the aim of the study was to determine whether using prilocaine hyperbaric 2% rather than bupivacaine hyperbaric 0.5% would optimise day-case surgery. The submission presented the primary outcome as the proportions of patients achieving discharge criteria from the recovery room and discharge home. Discharge from the recovery room required regression of the anaesthetic level to below T12, adequate vigilance, sufficient breathing and haemodynamic stability, absence or containment of pain, nausea and

secondary bleeding. Discharge home required complete regression of the motor and sensory block, tolerance of oral fluid and successful micturition. The patients fulfilled the discharge criteria after spinal anaesthesia with prilocaine hyperbaric 2% significantly faster than with bupivacaine hyperbaric 0.5%. Patients were suitable for discharge from the recovery room significantly sooner in the prilocaine group (median 91 [quartile distance 30] minutes) compared to the bupivacaine group (150 [60] minutes) and also suitable for discharge home significantly sooner: median 308 (52) minutes versus 407 (132) minutes respectively. At 6 hours, 78% of patients in the prilocaine group were eligible for discharge compared to 33% in the bupivacaine group. In the majority of patients, the last criterion achieved to allow discharge home was voluntary micturition.

Secondary outcomes assessed the quality of the block. The success of the block was reported to be comparable in both treatment groups but patients in the bupivacaine 0.5% group achieved a significantly higher level of sensory block than prilocaine (T6 versus T8). Similar analgesic levels of at least T12 were achieved in both groups and block intensity and onset times were also similar. The duration of effect (an analgesic level of T12) was significantly longer in bupivacaine than prilocaine patients (median 120 [69] minutes versus 60 [30] minutes respectively). There were no significant differences between the two groups in pain scores assessed in the operating theatre, recovery ward, surgical ward or after discharge or in the amount of non-steroidal anti-rheumatic drugs or opioids used.

A double-blind, randomised non-inferiority study compared two doses of prilocaine hyperbaric 2% (60mg and 40mg) with prilocaine isobaric 2% (60mg) in 90 adult outpatients undergoing spinal anaesthesia for any surgical procedure of less than 60 minutes duration. The primary endpoint, mean time to sensory block at T10 level, was significantly shorter in both hyperbaric groups compared to the isobaric group ( $7 \pm 4$  minutes and  $9 \pm 5$  minutes versus  $14 \pm 7$  minutes respectively) demonstrating non-inferiority.

Supportive evidence included a review of 231 patients treated with prilocaine hyperbaric 2% for spinal anaesthesia in a Swiss regional hospital. A number of different types of surgery were performed including general, orthopaedic, gynaecological/obstetric and urological surgery with a mean duration of 35 minutes (range 5 to 126 minutes). The mean dose of prilocaine hyperbaric 2% used was 47mg (range 10 to 100mg). Concomitant treatment to reduce hypotension and bradycardia was used in 30% of patients and 33% of patients received analgesia with fentanyl. Treatment for severe hypotension was reported in six (2%) patients, while atropine therapy for the treatment of bradycardia was necessary in two patients. Sedation e.g. propofol was administered to a small percentage of patients. A change to general anaesthesia due to block failure was not required in any patient. There were no reported allergic reactions to prilocaine, no discomfort, pain or burning sensation during injection and no signs of transient neurologic symptoms (TNS) or urinary retention.

## Summary of evidence on comparative safety

In the comparison with bupivacaine hyperbaric 0.5%, there was no significant difference in the incidence of adverse events between treatment groups but the patient numbers may have been too small to confirm relative safety. Headache was numerically more common in the prilocaine group (15% versus 5%) but was not considered typical of those associated with cerebrospinal fluid loss syndrome. Disturbances in micturition were numerically more common in the

bupivacaine group (10% versus 5%) with two patients requiring catheterisation. Systolic blood pressure decreased from baseline by a median of 22% in the bupivacaine and 19% in the prilocaine group and in both groups heart rate reduced by 20%. Hypotension (systolic blood pressure <85mmHg) was reported in 2.5% prilocaine and 5% bupivacaine patients; bradycardia in 10% prilocaine and 2.5% bupivacaine patients; transient incontinence in 2.5% prilocaine and 10% bupivacaine patients; postoperative nausea in 10% prilocaine and 5% bupivacaine patients and backache in 10% prilocaine and 5% bupivacaine patients. Backaches were reported as localised to the region of the puncture site.

Local anaesthetics have been associated with transient neurologic symptoms (TNS), a syndrome characterised by mild to severe pain in the buttocks or legs starting within 24 hours of spinal anaesthesia and lasting for less than 2 days. No cases of TNS were reported in either group of this study. A recent Cochrane review determined that the risk of TNS was significantly lower with prilocaine than with lidocaine. The review included four prilocaine studies only one of which used the hyperbaric 2% formulation.

## **Summary of clinical effectiveness issues**

Prilocaine is not a new drug but this is a new hyperbaric formulation of the local anaesthetic for use in spinal anaesthesia. One comparative study against bupivacaine hyperbaric 0.5% indicated reduced time to discharge from the recovery room and discharge home. Although this study included an active comparator relevant to clinical practice, the patient numbers enrolled were small and the primary outcome was not clearly defined. The aim of the study was described as to determine whether using prilocaine hyperbaric 2% could optimise day-case surgical procedures. The potentially faster discharge from the recovery room and discharge home within a clinical study may not translate to faster discharge times in clinical practice, which are often affected by the type of surgery, the patient's personal circumstances and local discharge criteria. The shorter overall duration of effect of prilocaine in spinal anaesthesia may also require more accurate planning of the surgical procedure. It is unclear whether the availability of a shorter acting local anaesthetic will increase the use of spinal anaesthesia in day-case surgery.

The licensed indication (spinal anaesthesia) is broad compared with the pivotal study population (day-case surgery using spinal anaesthesia of the lower limbs lasting for a maximum of 45 minutes). However in the economic analysis the submitting company has proposed that prilocaine hyperbaric should be considered in a subset of the licensed population, for use in spinal anaesthesia in ambulatory surgery settings such as day surgery units.

SMC clinical experts advised that it is a policy objective in NHS Scotland to increase day case surgery and that the introduction of prilocaine hyperbaric may lead to service improvement through benefits to individual patients or service delivery.

## **Summary of comparative health economic evidence**

The manufacturer presented a cost-minimisation analysis comparing prilocaine 2% hyperbaric solution to 0.5% hyperbaric bupivacaine in patients requiring spinal anaesthesia in an

ambulatory surgical setting such as a day surgery unit. The choice of comparator was appropriate. The timescale for the analysis was one day, as appropriate for day case surgery.

The manufacturer assumed that both drugs were equally efficacious in establishing anaesthesia for the duration of the operation, this was based on the comparative study indicating that both prilocaine and bupivacaine provided adequate block for lower-limb day case surgery. The analysis used estimates on the time spent in the recovery ward and discharge rooms from the same randomised trial designed to assess the optimisation of procedures in a day surgery setting. On the basis of this study and estimates from a Scottish expert on the nurse to patient ratio in recovery wards, the use of prilocaine was associated with 33.8 minutes fewer nursing minutes per patient. The analysis also took account of any costs associated with the management of adverse events. The duration of operations was assumed to be the same for both drugs.

Prilocaine was associated with incremental drug costs of £6.61 but this was offset by savings of £25.36 from less nursing time being required in the recovery ward and discharge room to give an overall saving of £18.75 per patient. As such, the manufacturer stated that prilocaine would be the preferred treatment on cost-minimisation grounds. One way sensitivity analysis results indicated that the results were most sensitive to the assumption of time spent in the recovery ward. Prilocaine remained cost-saving as long as the average extra nurse time spent with a patient in the recovery ward with hyperbaric bupivacaine was 4.8 minutes.

There were a number of limitations of the analysis:

- The clinical paper upon which the analysis is based was a small study designed to assess optimisation of outpatient management rather than the efficacy of the two anaesthetic agents. Efficacy was assessed as secondary outcome measures and this showed that the quality of the block was comparable.
- The analysis shows prilocaine to be cost-saving because the incremental drug acquisition costs are offset by savings in nurse time in the recovery ward. These savings are time-releasing rather than cash-releasing and if there is little value in freeing up nursing time in the recovery ward in clinical practice, prilocaine may not be the preferred treatment on cost-minimisation grounds. Comments from SMC experts have raised some concerns regarding the ability of the service to make use of such savings given the way services are currently organised. This may suggest that the value placed on the savings in the analysis is not reflective of the true opportunity cost of the outcomes that can be realised. However, additional analysis was provided to show the impact of using lower opportunity costs to value the nursing time released. This showed that if a lower published cost per hour was used the savings in the base case saving fell to £8.81 per patient and thus that prilocaine would still be considered cost-effective.
- The calculation of staff time saved was subject to variability depending on the assumptions made regarding the phases of recovery and staffing ratios. Using a different set of assumptions gave a saving in staff time of 21.8 minutes which reduced the overall cost saving with prilocaine to around £11. This saving was reduced to £4.55 if the lower hourly cost for nursing time was used.
- The analysis could possibly miss some costs if in clinical practice the rate of additional analgesia was higher with prilocaine (it was slightly higher in the trial – three patients in the prilocaine group versus one patient in the bupivacaine group).

Despite these issues, the economic case was considered demonstrated.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: comparators

Hyperbaric bupivacaine is the main comparator but other potential comparators include plain bupivacaine, levobupivacaine, and ropivacaine, although these are described as long-acting local anaesthetics.

## Cost of relevant comparators

Drug	Dose Regimen	Cost per ampoule (£)
<b>Prilocaine hydrochloride hyperbaric 2%</b>	<b>Up to a maximum dose of 80mg</b>	<b>7.80</b>
Bupivacaine hyperbaric 0.5%	Up to a maximum dose of 20mg	1.21

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 1 October 2010.

## Additional information: budget impact

The manufacturer assumed that there would be 9,225 spinal anaesthesia procedures in Scotland in year one rising to 13,765 in year five and that 10% of patients would switch to prilocaine in year one rising to 23% by year five to give patient numbers of 922 in year one and 3,166 in year five. On this basis the manufacturer estimated a saving of £4k in year one rising to a saving of £14k in year five arising from the introduction of prilocaine. These figures are the overall net budget impact and take account of estimated savings in staff time associated with less time being spent in the recovery and discharge rooms when using prilocaine. The net impact on the medicines budget, was estimated at £4k in year one rising to £18k in year five.

## References

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Ratsch G, Niebergall H, Hauenstein L, Reber A. Spinal anaesthesia in day-case surgery. Optimisation of procedures. *Anaesthetist* 2007;56:322-327

Camponovo C. Ultrashort local anaesthetics: spinal hyperbaric prilocaine. *Perimed* 2008; 26-32.

Zaric D, Pace NL. Transient neurologic symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. *Cochrane Database of Systematic Reviews* 2009, issue 2 article number CD003006.

Camponovo C, Fanelli A, Ghisi D et al. A prospective, double-blinded, randomized, clinical trial comparing the efficacy of 40mg and 60mg hyperbaric 2% prilocaine versus 60mg plain 2% prilocaine for intrathecal anaesthesia in ambulatory surgery. *Anesth Analg* 2010;111:568-72.

This assessment is based on data submitted by the applicant company up to and including 12 November 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.*