chloroprocaine hydrochloride, 10mg/mL, solution for injection (Ampres®)
SMC No. (885/13)

Mercury Pharmaceuticals Ltd

05 July 2013

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 Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**chloroprocaine hydrochloride (Ampres®)** is not recommended for use within NHS Scotland.

**Indication under review**: spinal anaesthesia in adults where the planned surgical procedure should not exceed 40 minutes.

In a small, single-centre, randomised, double-blind, controlled study spinal anaesthesia with chloroprocaine injection compared with a hyperbaric formulation of an amide-type local anaesthetic agent was associated with a faster resolution of sensory and motor block, resulting in a shorter time to meet eligibility criteria for discharge.

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

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**
**Indication**
Spinal anaesthesia in adults where the planned surgical procedure should not exceed 40 minutes.

**Dosing Information**
Chloroprocaine is administered via intrathecal route into the intervertebral space L2/L3, L3/L4, and L4/L5.

The dose is determined on an individual basis in accordance with the characteristics of the specific case with consideration of: the patient’s physical condition and the concomitant administration of other medicinal products. Duration of action is dose-dependent.

The maximum recommended dose is 50mg (5mL).

**Product availability date**
June 2013

**Summary of evidence on comparative efficacy**

Chloroprocaine is an ester-type local anaesthetic agent with a rapid onset of action and a duration of anaesthesia of up to 100 minutes.

The submitting company has requested that SMC considers the use of chloroprocaine in spinal anaesthesia in ambulatory surgery settings such as day surgery units.

A small, single-centre, double-blinded, randomised, controlled study recruited adult patients who were scheduled for elective ambulatory surgery of expected duration not exceeding 60 minutes.\(^1\) All patients had skin infiltrated with lidocaine 1% followed by spinal anaesthesia, either: 1mL of 0.75% hyperbaric bupivacaine (7.5mg, n=53) or 2mL of 2% chloroprocaine (40mg, n=53). No adjuvant intrathecal medication was permitted, but sedation with intravenous midazolam was given either prior to or immediately after the spinal injection as required at the discretion of the anaesthetist. During the surgical procedure, additional sedation (midazolam or propofol) and analgesia with intravenous fentanyl (25 to 100 micrograms) could be administered if required. Conversion to general anaesthesia was permitted if the patient was still experiencing pain, and resulted in withdrawal of the patient from the study. Post-operative analgesia consisted of intravenous fentanyl (25 micrograms every 5 minutes as required) and, if the pain was intense and difficult to control, additional subcutaneous morphine (2mg every 15 minutes as needed). Once the patients were able to feel a light touch on their legs, they were encouraged to ambulate without assistance and, if that was successful, attempt to void.

The primary outcome was the time to meet all the eligibility criteria for discharge from hospital: complete regression of the block to light touch, ability to walk, ability to tolerate oral fluids, pain controlled with oral analgesia, stable vital signs, no nausea, and ability to void. This was measured from the time the spinal anaesthetic was performed to the time that all criteria were met. Motor block was measured using the modified Bromage scale (0=no motor block, 1=flex knee but unable to lift straight leg, 2=flex ankle but not knee, 3=complete motor block). Height
of sensory block was tested using the loss of cold sensation to ice, with a non-anaesthetised cervical dermatome as a reference point. The mean time to eligibility for discharge from hospital was significantly shorter in the chloroprocaine-anaesthetised group (277 [standard deviation, SD=87] minutes), compared with the bupivacaine group (353 [SD=99] minutes): treatment difference 76 minutes (95% confidence interval: 40 to 112), p<0.001.1

Secondary endpoints concerned the quality of the block and comparison of individual eligibility criterion. The time to onset of adequate block to allow commencement of surgery (at the T10 dermatome) was similar for both treatment groups, a mean of six minutes. The peak block height for both groups was T7. No patient in either group required to convert to general anaesthesia. Duration of sensory and motor block was significantly shorter in chloroprocaine-anaesthetised patients compared with bupivacaine. The time to regression of sensory block to the L1 dermatome was 82 (SD 24) minutes versus 160 (SD 62) minutes and the S2 dermatome (146 [SD 38] minutes versus 329 [82] minutes) for chloroprocaine and bupivacaine respectively, both comparisons p<0.001. Motor block resolved (Bromage scale = 0) after a mean of 76 (SD 25) minutes and 119 (SD93) minutes, respectively, p=0.005. There was no significant difference between the groups in the length of stay in the post-anaesthetic recovery unit, which was around 68 minutes in both groups. A faster time to ambulation (225 [SD 56] minutes versus 265 [SD 65] minutes, p=0.001) and micturition (271 [SD 96] minutes versus 338 [SD 99] minutes, p=0.001) in the chloroprocaine group contributed to the shortened time to meeting discharge from hospital criteria.1

Supportive data come from a single-centre, randomised, double-blind study that compared chloroprocaine with lidocaine spinal anaesthesia in 30 patients undergoing elective outpatient knee arthroscopy.2 Anaesthesia consisted of sedation with midazolam, followed by intrathecal injection of 50mg chloroprocaine 1% (n=15) or 50mg lidocaine 1% (n=15). There were no clinically significant differences between the anaesthetic agents with regard to onset characteristics, perioperative hypotension, or requirement for fentanyl supplementation during the procedure. No patient required general anaesthesia. The median (range) duration of motor block was 60 (45 to 120) and 100 (60 to 140) minutes for the chloroprocaine and lidocaine groups respectively, p=0.0005. The median (range) time to regression of sensory block was 95 (68 to 170) and 120 (80 to 175) minutes, respectively, p=0.019. There was no significant difference between the groups in the time to meet eligibility criteria for discharge, as defined in the first study above.2

Summary of evidence on comparative safety

In the pivotal study, during surgery, the incidence of bradycardia (n=3 versus n=4) and hypotension (n=4 versus n=2) was low in the chloroprocaine and bupivacaine groups respectively. A higher proportion of patients in the chloroprocaine group required analgesia (10/53 versus 5/53), with a mean total fentanyl dose of 13 micrograms versus 8 micrograms, respectively. In the post-anaesthetic recovery unit, a greater proportion of chloroprocaine patients required analgesia (13/53 versus 3/53, respectively) and the mean total dose of fentanyl was 25 micrograms (SD 53) versus 4 micrograms (SD 14). The incidence of postoperative nausea or vomiting was similar between the groups (n=2 in each group). In postdischarge follow-up, there were similar rates of postdural puncture headache (n=1 in each group) and transient neurological symptoms (n=1 in each group). Back pain was reported by 45% of chloroprocaine patients and 38% of bupivacaine patients.1
In the supportive study there were five cases of transient neurological symptoms, all reported in patients anaesthetised with lidocaine.²

**Summary of clinical effectiveness issues**

The submitting company has requested that SMC considers the use of chloroprocaine in spinal anaesthesia in ambulatory surgery settings such as day surgery units. In this setting, general anaesthesia is commonly employed.

The primary outcome measure in the pivotal study was a surrogate outcome measure, time to achievement of eligibility criteria for discharge following surgery. Patients anaesthetised with chloroprocaine were eligible for discharge more quickly than those anaesthetised with hyperbaric bupivacaine, mainly because of reduced time to ambulation and first micturition.¹ Time to discharge from surgery is an outcome of relevance to service providers and patients, but it is recognised that readiness for discharge and the actual time of discharge are not necessarily the same. Other factors affecting the time to discharge include patients’ social circumstances and the type of surgery performed.³ Although patients anaesthetised with chloroprocaine were more likely to meet discharge criteria more rapidly compared with those anaesthetised with hyperbaric bupivacaine, they were more likely to require rescue intravenous opioid in the post-anaesthetic recovery area.¹

A limitation of the study was that observer blinding in the study may not have been maintained because the block in the chloroprocaine group regressed earlier and faster, which may have resulted in bias in assessing outcomes.¹

Neither preparation used in the study is available in the UK. The dose of chloroprocaine used in the study (40mg) is in line with the recommendations in the chloroprocaine (Ampres®) summary of product characteristics (maximum dose 50mg). The bupivacaine (Marcain Heavy®) summary of product characteristics does not provide dosage recommendations for procedures of up to 40 minutes duration.⁴ However, clinical experts consulted by SMC advised that 7.5mg of hyperbaric bupivacaine was an appropriate dose and that dose, rather than concentration or volume injected, is the main influence of the degree and duration of sensory and motor block, and the experts confirmed the different preparations used would not affect generalisability of the study results.

Hyperbaric prilocaine is considered a key comparator. Clinical experts consulted by SMC confirmed that when spinal anaesthesia is employed in day case settings, hyperbaric prilocaine is commonly used. No comparative data with hyperbaric prilocaine were presented.

The speed of the onset and resolution of sensory block may require an alteration in practice, and careful planning, to ensure the surgery is conducted and completed within the relevant timeframe.
The submitting company presented a cost-minimisation analysis comparing chloroprocaine hydrochloride to hyperbaric bupivacaine in patients requiring spinal anaesthesia in an ambulatory surgical setting such as a day surgery unit. The timescale for the analysis was one day, as appropriate for day case surgery.

The submitting company assumed that both medicines were equally efficacious in establishing anaesthesia for the duration of the surgery. This assumption was based on the results of the pivotal study where chloroprocaine was compared to bupivacaine in patients requiring elective ambulatory surgery of expected duration not exceeding 60 minutes.

The primary outcome of the pivotal study, the time to meet all the eligibility criteria for discharge from hospital, was significantly lower in the chloroprocaine-anaesthetised group (277 minutes), compared with the bupivacaine group (353 minutes); a treatment difference of 76 minutes. The potential cost saving associated with the primary outcome was a key component of the economic analysis, which also took into account costs associated with adverse events. Surgery duration was assumed to be the same for both groups.

Chloroprocaine was associated with an increased medicine cost of £8 per patient, but this was offset by savings of £12 per patient since patients in the chloroprocaine group would be eligible for discharge earlier than those in the bupivacaine group. The submitting company also assumed that the use of chloroprocaine would lead to small cost savings from a reduction in adverse events such as urinary retention. Overall, the submitting company stated that chloroprocaine would result in a cost saving of £7 per patient, and would therefore be the preferred treatment on cost-minimisation grounds.

The key uncertainty associated with the analysis is the submitting company’s choice of comparator. SMC clinical expert responses have indicated that bupivacaine may not be the appropriate comparator. Rather, prilocaine is the predominant medicine for spinal anaesthesia in day surgery settings. In December 2010, SMC accepted prilocaine for restricted use in this indication.

There are a number of other uncertainties associated with the analysis, with the key concerns as follows:

- The economic case is reliant on the assumption that the use of chloroprocaine leads to an earlier hospital discharge relative to bupivacaine. The pivotal study demonstrated that the time to meet all the eligibility criteria for discharge from hospital was lower in the chloroprocaine group. However, although SMC clinical experts have confirmed that chloroprocaine would likely offer a faster recovery time than bupivacaine, caution was noted as to whether this would lead to an earlier hospital discharge owing to the multiple factors involved in patient discharge.

- The submitting company has assumed an hourly hospital stay cost of £10. This is a considerable underestimate. Despite this apparently conservative approach, it does not alter the fact that the overall cost saving associated with chloroprocaine is dependent on hospital stay savings.
• The submitting company has assumed that 38% of patients receiving bupivacaine require catheterisation for urinary retention. This assumption is said to be based on the summary of product characteristics (SPC) for bupivacaine. However, the SPC notes that urinary retention as a side effect of bupivacaine has an incidence between 1 and 10% of patients.4

Due to the choice of comparator used and the uncertainties above, the economic case is not demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

General anaesthesia is commonly employed in ambulatory surgery settings. Options for spinal anaesthesia include hyperbaric formulations of prilocaine and bupivacaine.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per treatment (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloroprocaine hydrochloride 1%</td>
<td>Up to a maximum dose of 50mg</td>
<td>9</td>
</tr>
<tr>
<td>prilocaine hydrochloride hyperbaric 2%</td>
<td>Up to a maximum dose of 80mg</td>
<td>8</td>
</tr>
<tr>
<td>bupivacaine hyperbaric 0.5%</td>
<td>Up to a maximum dose of 20mg</td>
<td>1</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from www.mims.co.uk on 16 April 2013, except chloroprocaine (from the company’s submission).

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 26,153 in year 1 rising to 32,975 in year 5.

Based on an estimated uptake of 20% in each year, the gross impact on the medicines budget was estimated to be £40k in year 1 and £51k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact was estimated to be £40k in year 1 and £46k in year 5.
References

The undernoted references were supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 18 June 2013.

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.