IN USE PRODUCT SAFETY ASSESSMENT REPORT FOR BUPIVACAINE

<table>
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<th>SUMMARY OF ASSESSMENT AND ITS FINDINGS</th>
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BACKGROUND

Bupivacaine is used as a local anaesthetic for a range of different anaesthetic techniques including local infiltration, peripheral and sympathetic nerve block, epidural and intrathecal block. Bupivacaine is contra-indicated for intravenous use and severe toxicity usually results from accidental intravascular injection or too rapid injection. There is some evidence to suggest that newer agents such as ropivacaine are less cardiotoxic; however, all local anaesthetics are potentially cardiotoxic.

In 2007, the NPSA issued an alert “Safe practice with epidural injections and infusions”. The alert makes several recommendations as to how Trusts can reduce risks with epidurals. However, National Reporting and Learning Service (NRLS) data continues to indicate patient safety incidences involving epidural and other local anaesthetic administration. Of particular note, cases have been reported in which bupivacaine solution for injection has been prepared in syringes for local anaesthesia but given intravenously and where bupivacaine solutions prepared for epidural infusion have been connected to intravenous cannulas and given intravenously. Prescribing of and administration of local anaesthetics are often undertaken in highly pressurised environments, such as theatres and maternity, and doses may vary dependent on clinician experience. The prescribing of bupivacaine is complex and the required dose is calculated according to the specific indication (i.e. the type of local anaesthetic required), and the patient’s physical status and individual response.

DETAILS OF PRODUCT (S) ASSESSED

See Appendix 1 for UK licensed bupivacaine products. Other unlicensed and specials products exist but for the purposes of this analysis we have focused on licensed products only. Licensed indications for the ampoules include anaesthesia for local infiltration; and epidural (including for Caesarean section), intrathecal, and peripheral nerve block. Bupivacaine ready-to-use infusion bags are licensed only as an analgesic for continuous epidural infusion.

Images were available for the following products and these were assessed using the UKMi validated tool to determine whether presentational issues could have had a bearing on the background described above.

| Manufactured by AstraZeneca UK Ltd | • Marcaín Heavy® (bupivacaine 0.5%, glucose 80mg/mL) solution for injection  
  • Marcaín Polyamp® Steripack (bupivacaine) 0.5% and 0.25% solution for injection |
|------------------------------------|----------------------------------|
| Manufactured by Amdipharm Mercury Group | • Bupivacaine 0.125% solution for infusion  
  • BUFYL® solution for infusion (bupivacaine 0.1%, fentanyl 2mcg/mL)  
  • Bupivacaine 0.25%, 0.5% solution for injection  
  • Bupivacaine and adrenaline solution for injection (bupivacaine 0.5%, adrenaline 1 in 200,000) |

CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL

The following points were raised after consideration of bupivacaine products by 3 pharmacists:

- There are a large range of licensed bupivacaine products on the market, including epidural infusions, solutions for injections and combination products with fentanyl or adrenaline. The broad range of licensed indications for some of the products could lead to unfamiliarity and therefore potentially increase the risk of errors.
- The prescribing information provided by the manufacturer for bupivacaine was deemed to have a number of potential gaps, in particular in relation to the way information was expressed in Summary of Product Characteristics (SPCs). The impact of this is unclear but concerns included:
  - Complexity in relation to dosing is compounded by ambiguity in the product literature, i.e. statements that doses are dependent on the patient’s physical status, size and individual response, but does not guide further on the nature of adjustments necessary.
  - General lack of supportive technical information supplied within the product packaging for use at the point of administration.
- Use of negative language which introduces the potential for misinterpretation of the literature, e.g. “this formulation is not to be used as a bolus”.

In our view, the information provided by the manufacturer would need to be amended or supplemented to support safe administration of these products.

With regards to **product packaging and presentation**, critical information was not always presented in a clear way. The following points were raised:

- The brand name was deemed to be more prominent than the generic name on some product packaging, and this may affect user recognition of the product. The medicine names of combination bupivacaine products were not always expressed in a clear way, which could potentially lead to wrong product selection. For example, on one particular product label, one active ingredient is on the top line and the other on the line underneath.
- Ambiguity and a lack of prominence with reference to the route of administration. The warning on one particular product label reads “for infiltration/peripheral/epidural use” and this is concerning as it could potentially be misinterpreted to mean intravenously via a peripheral line.
- Expression of strength on the products was found to be inconsistent, in some instances product strengths were labelled as % w/v and on others as mg per mL and in some cases both units of expression used on combination products. This could lead to confusion, especially as often the accompanying product literature describes infusion rates as mg per hour, although it is acknowledged that prescribers are likely to be (or should be) following local prescribing guidelines.
- Less than optimal use of colour to differentiate between strengths.
- Legibility of product labelling, in some instances, was found to be poor, with very condensed text and lack of appropriate use of spacing to highlight critical information.

**Product formulation** may also potentially affect safe use of these products. In particular, whilst the infusion bags are presented in ready-to-use presentations, the solutions for injection (which are used for most indications) will require manipulation before administration. The NRLS data indicates incidents in which injections prepared for nerve blocks have been mistakenly injected intravenously due to confusion between them and other prepared syringes, and it is possible that the relative lack of ready-to-use presentations may have contributed to such incidents occurring. The [NPSA](https://www.npsa.nhs.uk) have previously highlighted maximising the use of ready-to-administer epidural infusions reduces the need for complex calculations and enhances patient safety.

**Appropriate storage** of some of the bupivacaine products is a potential patient safety issue. The NPSA alert for epidural injections and infusions recommends separate storage from intravenous products, however the wide range of other indications (infiltration, nerve block, AND epidural use) may complicate putting storage controls in place. In practice, we believe these products may not always be isolated from intravenous preparations, and that the range of indications and product presentation may contribute storage issues.

**Medical device issues** are also present since, as with other local anaesthetics, epidural administration sets can connect with intravenous luer connectors due to the incomplete range of non-luer and infusion devices for epidural and regional procedures in the UK market. See [NHS England Patient Safety Alert](https://www.england.nhs.uk/patient-safety/alerts) for further information.

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**POTENTIAL NEXT STEPS AND MITIGATION ACTIONS**

Human error will play a part in “wrong drug” selection and it very difficult to prospectively assess the risk of this happening and to try and mitigate against this. However our analysis suggested that improvements could be made to the products to promote their use in the safest possible way. Our recommendations fall into two categories. The first are points we feel should be addressed with manufacturers to enhance the safe use of their products. The second relate to steps healthcare providers should also consider.

In our view, **regulators and manufacturers** could prioritise these actions:

- Critical information on packaging should include warnings on the route of administration, which should include “For local anaesthetic use only”. More effective use of blank spacing and colour is required to emphasise critical information.
- As a minimum, the strength on the product packaging and in the product literature should be consistent.
- Bupivacaine product ranges could potentially be rationalised to reflect the range of indications for each product and the strengths required to meet such needs. This action could promote safer product selection and prescribing.

- In addition, improving the availability of commercial medicinal products in ready-to-use presentations could be considered.

- Product literature could be improved significantly so that it accurately reflects practice.

In relation to healthcare providers, bupivacaine is an injectable often used by the epidural route, hence providers should consider its use in the context of previous NPSA work in this area including Safer practice with epidural injections and infusions and Promoting safer use of injectable medicines. In our view, use of bupivacaine should only be within the context of local guidance that restricts use to clinical areas where staff have adequate training in anaesthesia and airway management, and healthcare providers should make appropriate checks to ensure approved local guidance is in place. Such local practice should also enable and ensure appropriate storage of such products. Additionally it should facilitate risk assessment of individual products before local purchasing and procurement decisions are made.

The NPSA has recommended the use of devices with safer connectors that do not connect with intravenous luer connectors for epidural and regional procedures, with a target implementation date of April 2013. However, as it stands the range of infusion devices for epidural and regional procedures is incomplete, and therefore compliance to this is not possible. Suitable safer devices should be introduced in local practice as soon as they are available. See NHS England Patient Safety Alert.

This report was produced in January 2014 using photographic images (not physical products) of licensed bupivacaine products available at the time of assessment. Images were obtained primarily from pharmaceutical companies, but also from the Commercial Medicines’ Unit PharmaQC database (http://cmu.dh.gov.uk/medicines/pharmaqc-database/) and from various sources within the NHS.

This report summarises product assessments undertaken by:
London Medicines Information Service
East Anglia Medicines Information Service
London and South East Medicines Information Service

For comments email nwlh-tr.medinfo@nhs.net
Appendix 1 - Available bupivacaine products and licensed indications:

<table>
<thead>
<tr>
<th>Product</th>
<th>Strength &amp; presentation</th>
<th>Manufacturer</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Bupivacaine solution for injection (non-proprietary)</td>
<td>Bupivacaine 2.5mg/mL (0.25%); 10mL</td>
<td>Amdipharm Mercury Group</td>
<td>Local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural)</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine 5mg/mL (0.5%); 10mL</td>
<td>Amdipharm Mercury Group</td>
<td>Local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural)</td>
</tr>
<tr>
<td>Marcin® Polyamp Steripack solution for injection</td>
<td>Bupivacaine 2.5mg/ml (0.25%); 10mL</td>
<td>AstraZeneca UK Ltd</td>
<td>Local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural)</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine 5.0mg/ml (0.5%); 10mL</td>
<td>AstraZeneca UK Ltd</td>
<td>Local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural)</td>
</tr>
<tr>
<td>Marcin Heavy® solution for injection</td>
<td>Bupivacaine 5mg/ml (0.5%), glucose 80mg/ml; 4mL</td>
<td>AstraZeneca UK Ltd</td>
<td>Intrathecal (subarachnoid) spinal anaesthesia for surgery</td>
</tr>
<tr>
<td>Bupivacaine solution for infusion (non-proprietary)</td>
<td>Bupivacaine 1mg/mL (0.1%); 250mL</td>
<td>Amdipharm Mercury Group</td>
<td>Continuous epidural analgesia</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine 1.25mg/mL (0.125%); 250mL</td>
<td>Amdipharm Mercury Group</td>
<td>Continuous epidural analgesia</td>
</tr>
<tr>
<td>Bupivacaine and adrenaline solution for injection B.P (non-proprietary)</td>
<td>Bupivacaine 2.5mg/ml (0.25%), adrenaline 1 in 200,000; 10mL</td>
<td>Amdipharm Mercury Group</td>
<td>Local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural)</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine 5mg/ml (0.5%), adrenaline 1 in 200,000; 10mL</td>
<td>Amdipharm Mercury Group</td>
<td>Local anaesthesia by percutaneous infiltration, peripheral nerve block(s) and central neural block (caudal or epidural)</td>
</tr>
<tr>
<td>BUFYL® solution for infusion</td>
<td>Bupivacaine 1mg/mL (0.1%), fentanyl 2mcg/mL; 250mL or 500mL</td>
<td>Amdipharm Mercury Group</td>
<td>Continuous epidural analgesia</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine 1.25mg/mL (0.125%), fentanyl 2mcg/mL; 250mL or 500mL</td>
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