# IN USE PRODUCT SAFETY ASSESSMENT REPORT FOR LEVOBUPIVACAINE

## SUMMARY OF ASSESSMENT AND ITS FINDINGS

### BACKGROUND

Levobupivacaine 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. Levobupivacaine 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 potentially 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, NRLS data continues to indicate patient safety incidences involving epidural and other local anaesthetic administration. Of particular note, cases have been reported in which levobupivacaine solution for injection has been prepared in syringes for local anaesthesia but given intravenously. In addition, concern has been raised in relation to confusion between levobupivacaine injections and other products presented in what have been reported to be very similar plastic ampoules e.g. water for injections and sodium chloride 0.9%.

### DETAILS OF PRODUCT(S) ASSESSED

The following products were assessed using the UKMi validated tool to determine whether presentational issues could have had a bearing on the background described above:

- **Chirocaine® (levobupivacaine) 2.5 mg/ml, 5 mg/ml, 7.5 mg/ml solution for injection.**
  Manufactured by Abbvie Limited.
- **Chirocaine® (levobupivacaine) 1.25 mg/ml solution for infusion.**
  Manufacturer by Abbvie Limited.
- **Water for Injection BP.**
  Manufactured by Fresenius Kabi; and B Braun.
- **Sodium chloride 0.9% solution for injection.**
  Manufactured by Fresenius Kabi; Fannin; and B Braun.

### CONCLUSION FOLLOWING APPLICATION OF VALIDATED ASSESSMENT TOOL

The prescribing information provided by the manufacturer for Chirocaine® was deemed to have a number of potential gaps, in particular in relation to the way information was expressed on SPCs. The impact of this is unclear; the specific concerns are covered in the full report. With regards to product packaging and presentation, clarity of critical information was not always presented in the clearest way. 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. Appropriate storage of some of the Chirocaine® products is a potential patient safety issue as the wide range of other indications (infiltration, nerve block, AND epidural use) may complicate putting storage controls in place. 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-leur and infusion devices for epidural and regional procedures in the UK market.

In relation to confusion between Chirocaine® plastic ampoules and diluents in plastic ampoules...
we believe this is possible; however, it is also entirely possible, in our view, that there are risks with “wrong drug” selection which are completely unrelated to product presentation, and for which alternative mitigation strategies should be pursued locally. The wide range of manufacturers and non-standardisation of presentation for diluent plastic ampoules is of particular note here. This could make it more likely that confusion with Chirocaine® may occur, but equally it complicates a prospective assessment of the likelihood of such instances occurring.

**POTENTIAL NEXT STEPS AND MITIGATION ACTIONS**

Our analysis suggested that improvements could be made to the products to promote their use in the safest possible way. As discussed, 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. Notwithstanding this, for the range of diluent products we were able to identify and assess the quality of product packaging and accompanying literature could be improved significantly, and in particular be made more consistent.

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 actions that included:

Warnings on the route of administration should appear on both the primary and outer packaging of Chirocaine® ampoules and also include “For local anaesthetic use only”. Chirocaine® 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. There is significant scope for rationalising the design and labelling of the diluent products available, with a view to improving consistency across the product range and thereby reducing risks of user unfamiliarity. Chirocaine® product literature could be improved significantly so that it accurately reflects practice.

In relation to healthcare providers, levobupivacaine 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 levobupivacaine 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. Such local practice should also enable and ensure appropriate storage of such products. And it should facilitate risk assessment of individual products before local purchasing and procurement decisions are made. To help address the "wrong drug" problem identified (i.e. the confusion between levobupivacaine and diluents) education of staff will be important in relation to the nature of the problem, and the use of standardised drug storage, layout and selection protocols. 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 Link and NHS England Draft Patient Safety Alert
FULL ASSESSMENT REPORT

1 BACKGROUND

Levobupivacaine 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. Levobupivacaine is contra-indicated for intravenous use and severe toxicity usually results from accidental intravascular injection or too rapid injection. Serious systemic adverse effects mainly involve the central nervous system (convulsions, drowsiness, respiratory failure) and the cardiovascular system (hypotension and bradycardia, arrhythmias, cardiac arrest).

The prescribing of levobupivacaine is complex. 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. Prescribing and administration is often undertaken in highly pressurised environments such as theatres and maternity, and doses may also vary dependent on clinician experience.

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. Suggestions include:

- Ensuring infusion bags and syringes are labelled “For Epidural Use Only”
- Rationalising ranges held, and particularly using ready-to-administer injections
- Using commercial epidural administration sets that have specific labelling and design (usually including yellow colour identification) that differentiates the route
- Using discrete storage areas for epidurals in clinical areas

Despite the alert, NRLS data continues to indicate patient safety incidences involving epidural and other local anaesthetic administration. Of particular note, cases have been reported in which levobupivacaine solution for injection has been prepared in syringes for local anaesthesia but given intravenously. In addition, concern has been raised in relation to confusion between levobupivacaine injections and other products presented in what have been reported to be very similar plastic ampoules e.g. water for injections and sodium chloride 0.9%.

Using the validated product safety assessment tool, UKMi have analysed whether the presentation of a range of levobupivacaine products is appropriate. We have compared the presentation of a range of levobupivacaine products against themselves, and we have also compared products against water for injections and sodium chloride 0.9% ampoules. This report gives a brief summary of the findings of the analysis.

2 THE PRODUCT (S)

Levobupivacaine products with UK marketing authorisation are manufactured by a single company: AbbVie. Products are all marketed using the trade name Chirocaine®. Preparations of Chirocaine® include various solutions for injection presented in ampoules, and solutions for infusion presented in ready-to-use infusion bags. Chirocaine® Injection solutions are available in strengths 2.5 mg/mL, 5 mg/mL, and 7.5 mg/mL in 10mL ampoules; Chirocaine® infusion solutions are available in strengths 0.625 mg/mL, 1.25 mg/mL solution for infusion in 100mL infusion bags. Licensed indications for the ampoules include anaesthesia for local infiltration; peribulbar block in ophthalmic surgery; and epidural (including for caesarean section), intrathecal, and peripheral nerve block. Levobupivacaine ready-to-use infusion bags are licensed only as an analgesic for continuous epidural infusion.

A wide range of suppliers for water for injection and sodium chloride 0.9% exist. For the purposes of the analysis, we restricted consideration to products manufactured by B Braun, Fresenius Kabi, and Fannin. However, this list is not exhaustive and other suppliers of diluents in plastic ampoules may be available in the UK.
3 ASSESSMENT FINDINGS

Images and product literature for the Chirocaine® products and diluents described above were obtained and products were assessed using the full version of the UKMi tool. The risk assessment focused on whether product factors may have contributed to the incidences reported. At this stage, the process sought mainly to identify potential contributory factors and make some limited recommendations only as to potential mitigation measures.

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

- **As specified, three strengths of Chirocaine® ampoules exist with a broad range of licensed indications.** This broad range of licensed indications across different strengths could lead to unfamiliarity and therefore potentially increase the risk of errors. The prescribing of these products is complex and specific for each individual indication and the prescribing information, supplied with the products (as detailed in the Summary of Product Characteristics (SPCs)) was found to be unclear especially with regards to dosing. Particular concerns included:
  - The SPCs indicate that all three strengths of ampoules are licensed for intrathecal administration; however, the same prescribing information includes dosing for the 5 mg/mL strength only via this route. So an element of ambiguity is introduced.
  - Complexities in relation to dosing are compounded rather than addressed in the product literature. In particular, this states 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.
  - The 5 mg/mL product is presented in a 10 mL ampoule (i.e. 50 mg). In the prescribing information provided with the product, the maximum dose via the intrathecal route is 15 mg (3mL); however, the larger than required ampoule size introduces a risk that 50mg (the whole ampoule) could be administered in error.
  - The package insert for the product contains information aimed at both patients and professionals. The insert is divided into sections aimed at either audience. However, there is some use of negative language in both inserts which introduces the potential for misinterpretation.

Overall the prescribing information provided by the manufacturer was deemed to have a number of potential gaps that in our view introduced the potential for adverse effects on safety. 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, clarity of critical information was not always presented in the clearest way.** The following points were raised:
  - The brand name was deemed more prominent than the generic name on Chirocaine® packaging, and this may affect user recognition of the product.
  - The plastic ampoules do not make any reference to the route of administration; this is only highlighted on the outer boxed packaging which is unlikely to be present at the point of administration. This point is particularly concerning since critical information is missing from the primary packaging and could increase the risk of wrong route administration.
  - Some terms referred to on the product packaging e.g. “peribulbar block” could be ambiguous to the user.
  - The packaging uses colour to distinguish between the three available strengths of Chirocaine®. However, whilst the manufacturers of some epidural solutions have adopted yellow for labelling and for differentiating products from other solutions for infusion, Chirocaine® infusions do not use colour as a means for such differentiation.

- **Product formulation** may 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. With particular reference to epidural use,
Chirocaine® ampoules will require significant manipulation before administration. This may affect safety of administration, since as highlighted by the NPSA previously, maximising the use of ready-to-administer epidural infusions reduces the need for complex calculations and enhances patient safety.

- **Appropriate storage** of these products is a potential patient safety issue. The NPSA alert for epidural injections and infusions recommends separate storage from intravenous products. However, although Chirocaine® should obviously not be used intravenously, 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 issues may contribute to this.

- **Medical device issues** are also integral to these wrong route scenarios, as currently epidural administration sets can connect with intravenous luer connectors and there is therefore a risk of inadvertent intravenous administration of levobupivacaine. The range of non-leur and infusion devices for epidural and regional procedures in the UK market remains incomplete. See NHS England Draft Patient Safety Alert for further information.

The following points were raised after consideration of water for injection and sodium chloride 0.9% 10mL plastic ampoules by 3 pharmacists. The consideration was performed with particular reference to potential confusion between these products and Chirocaine® ampoules:

- **Product packaging and presentation** varies significantly for water for injection and sodium chloride 0.9% in 10mL plastic ampoules; the design, shape and quality of labelling are different for products manufactured by a broad range of manufacturers. In addition, in some instances a single manufacturer might supply preparations of a single diluent in two or more designs, with presentation and luer lock connectivity of the designs varying. This significant variation makes consistent assessment of risks and implementation of solutions particularly problematic.

- The **clarity of critical information** varied both between products from different manufacturers and for preparations and designs from the same manufacturer. Product names were displayed on the packaging in different ways, with sometimes only the chemical abbreviation and not the full name present (e.g. NaCl in place of sodium chloride). Product labels were also sometimes found to contain non-standardised and ambiguous terms such as “Mini Plasco”; unnecessary information was also found on some primary labelling. The route of administration was also expressed in many different ways for the various products assessed; again abbreviation was a particular concern here. Other examples of potentially concerning variations in presentation and clarity here included:
  - Water for injection - “Not be used alone as an intravenous injection. For use as a diluent, and thereafter by any parenteral route”; “For the preparation of parenterals”
  - Sodium chloride 0.9% - “iv, im or sc use”; “For parenteral use”; “For I.V or S.C use”

- Accompanying **product literature** was in some instances considered to be of poor quality. For example, a patient information leaflet was present for a water for injection product with instructions on "How to take water for injection"; this was felt to be potentially misleading given that such language normally refers to oral administration. Some use of negative language was also found in information leaflets accompanying these products.

### 4 CONCLUSIONS, RECOMMENDATIONS, AND THEIR BASIS

The patient safety incidents involving Chirocaine® that have been reported through the NRLS data will, in our view, have involved an element of human error. However, our analysis suggested that improvements could be made to the products to promote their use in the safest possible way.
To summarise our findings and recommendations:

i. We believe there is some (although potentially quite limited) potential for confusion between Chirocaine® plastic ampoules and diluents in plastic ampoules. The wide range of manufacturers and non-standardisation of presentation for diluent plastic ampoules is of particular note here since it could make it more likely that confusion with Chirocaine® may occur. However, the huge range of diluent products available on the market makes it very difficult to definitively assess the risk of this happening in every scenario, and there will undoubtedly be an element of human error that will affect the possibility of "wrong drug" selection too. Notwithstanding this, for the range of diluent products we were able to identify and assess the quality of product packaging and accompanying literature could be improved significantly and in particular made more consistent.

ii. We believe our analysis has identified a number of issues with Chirocaine® products that could and should be addressed. In particular:

- Warnings on the route of administration should appear on both the primary and outer packaging of Chirocaine® ampoules and should include positive language i.e. "For local anaesthetic use only".
- Rationalisation of the current range of Chirocaine® products should be considered, both in relation to the range of indications for each product and the strengths available. Consideration should also be given to improving the availability of commercial medicinal products in ready-to-use presentations. Such actions could promote safer product selection and prescribing. However, further actions in this area will require discussion with clinicians in the first instance.
- There is significant scope for pharmaceutical companies to rationalise the design and labelling of diluent products available, with a view to improving consistency and thereby reducing risk of user unfamiliarity and the potential for confusion.
- For all products there are also actions that could be taken to improve product literature and to ensure it accurately reflects best practice as much as is possible.

iii. To enable safe use of Chirocaine® products, we also believe that healthcare 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 levobupivacaine 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. Such local practice should also enable and ensure appropriate storage of such products. And it should facilitate risk assessment of individual products before local purchasing and procurement decisions are made. To help address any "wrong drug" problems identified (e.g. confusion between levobupivacaine and diluents) education of staff will be important in relation to the nature of the problem, and the use of standardised drug storage, layout and selection protocols. 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 with this is not possible. Suitable safer devices should be introduced in local practice as soon as they are available. See Link and NHS England Draft Patient Safety Alert.

This report was produced in December 2013 using photographic images (not physical products) of licensed levobupivacaine 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
London & South East Medicines Information Centre
Newcastle Regional Drug and Therapeutics Centre

For comments email nwlh-tr.medinfo@nhs.net