

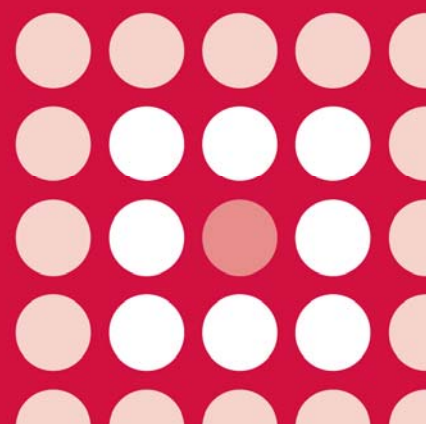
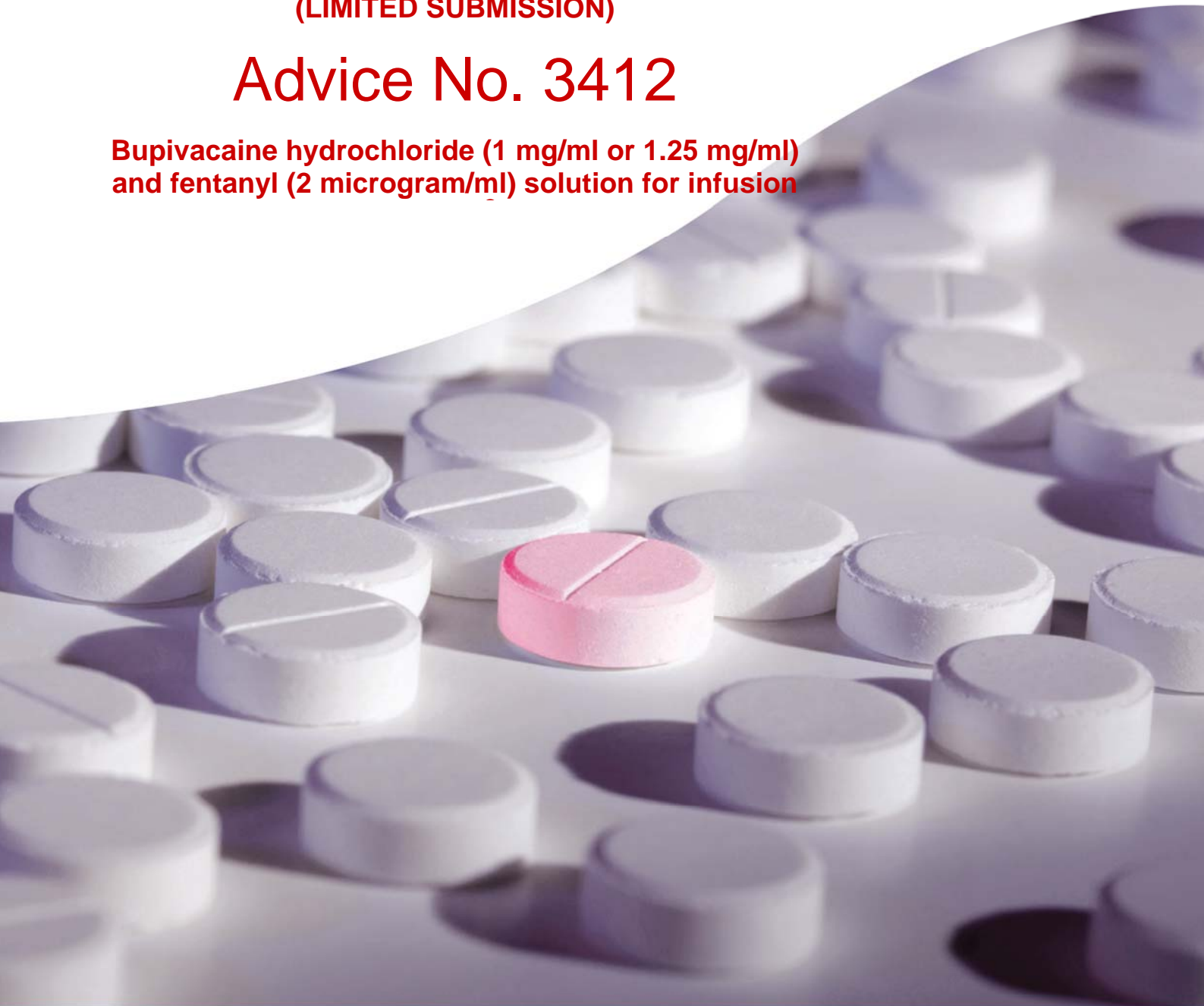


All Wales Therapeutics
and Toxicology Centre
Canolfan Therapiwteg a
Thocsicoleg Cymru Gyfan

**AWMSG SECRETARIAT ASSESSMENT REPORT
(LIMITED SUBMISSION)**

Advice No. 3412

**Bupivacaine hydrochloride (1 mg/ml or 1.25 mg/ml)
and fentanyl (2 microgram/ml) solution for infusion**



AWMSG Secretariat Assessment Report – Advice No. 3412
Bupivacaine hydrochloride (1 mg/ml or 1.25 mg/ml) and fentanyl
(2 microgram/ml) solution for infusion (Bufyl®)

This assessment report is based on evidence from a limited submission by Mercury Pharmaceuticals Ltd on 23 April 2012¹.

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Bupivacaine hydrochloride/fentanyl (Bufyl®) is indicated for maintaining analgesia post-operatively and for maintaining epidural analgesia during labour ^{2,3} .
Marketing authorisation date	14 September 2011 ^{2,3} .
Comparators	Bupivacaine hydrochloride/fentanyl pre-mixed bags (unlicensed use).
Limited submission details	Bupivacaine hydrochloride/fentanyl (Bufyl®) for the above indication met the following criteria for eligibility for a limited submission: <ul style="list-style-type: none">• Anticipated minimal budgetary impact in NHS Wales.• Estimated small difference in cost compared to comparator(s).

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Overview of company submission

The company submission includes a review of available literature evaluating the safety and efficacy of the use of bupivacaine hydrochloride (administered as a dose of 0.0625%–0.125%) in combination with fentanyl (2 micrograms/ml) for maintaining analgesia post-operatively and during labour¹. This literature review was also included as part of the marketing authorisation application, and at the time of licensing, the Medicines and Healthcare products Regulatory Agency (MHRA) concluded that this literature supports the efficacy of the bupivacaine hydrochloride/fentanyl combination and identifies no new safety signals⁴. The MHRA also noticed that the combination of bupivacaine hydrochloride and fentanyl is already widely used in the UK and has been endorsed by the National Institute for Health and Clinical Excellence (NICE)⁴.

2.2 Points to note

- As previously noted, the company submission does not include new efficacy, safety or bioequivalence studies¹, as this was not required at time of licensing⁴.
- Bufyl[®] is the first and only licensed bupivacaine hydrochloride/fentanyl combination product available in the UK, although unlicensed pre-mixed products are available¹. Prior to the marketing authorisation of Bufyl[®] being granted, bupivacaine hydrochloride was licensed for use post-operatively and during labour, while fentanyl was licensed for analgesia during surgical procedures⁵. The company submission notes that the availability of a licensed, ready-to-use solution should improve patient safety, as risks associated with extemporaneous preparations, such as inappropriate dosing, stability and contamination issues, will be much reduced¹.
- NICE Clinical Guideline 55 recommends that epidural analgesia is established during labour with a low concentration local anaesthetic and opioid solution, and suggests the use of 10–15 ml of 0.0625%–0.1% bupivacaine in combination with a fentanyl dose of 1–2 micrograms/ml⁶.

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company estimates that approximately 6,462 obstetric epidural and 3,917 perioperative epidural procedures per annum take place in Wales¹, reportedly based on UK observational data from 2006⁷. The company estimates that 15% of these procedures are performed using licensed, single-agent, local anaesthetic infusion bags, with the remaining 85% using a range of pre-mixed, unlicensed infusion bags containing local anaesthetics and an opioid. The company reports the acquisition costs of the unlicensed pre-mixed infusion bags to be in the range £5.90 to £12.00 each, and assumes an average cost of £8.00. Acquisition costs of Bufyl[®] infusion bags range from £8.50 to £9.20, depending on the bupivacaine concentration (0.1% or 0.125%) and volume (250 ml or 500 ml). The company presents budget impact scenarios assuming use of one infusion bag per procedure, and assuming Bufyl[®] uptake will displace use of 12–15% of unlicensed pre-mixed infusion bags.

At an assumed average cost of £8.00 per unlicensed infusion bag, Bufyl[®] is estimated to increase total annual acquisition costs by a maximum of £1,588 (range £573 to £1,588). At an assumed cost of £5.90 per unlicensed infusion bag, Bufyl[®] (0.125% bupivacaine) 250 ml infusion bag is estimated to increase total annual acquisition costs by a maximum of £4,168 (range £3,613 to £4,168). However, at an assumed cost of £12.00 per unlicensed infusion bag, Bufyl[®] (0.125% bupivacaine) 250 ml infusion bag is estimated to be cost saving, reducing annual acquisition costs by a maximum of £3,904 (range –£3,383 to –£3,904). The company therefore considers the use of Bufyl[®] will be broadly cost neutral.

3.2 AWTTTC critique of the budget impact analysis

The budget impact associated with the use of Bufyl[®] is primarily dependent on the assumed costs of comparator pre-mixed, unlicensed infusion bags (i.e. specials). The company has reported a range of prices that could not be verified, and it is unclear from the information provided whether or not these unlicensed infusion bags provide comparable volumes to Bufyl[®]. The company has assumed one infusion bag will be sufficient on the basis of the volume of ropivacaine (plus fentanyl) used in a small study of its use as an analgesic in labour pain⁸. Wastage has not been

explicitly discussed. It should be noted that the reported cost of the Bufyl[®] 500 ml infusion bag is similar to that of the 250 ml infusion bag, and each infusion bag may only be in use for a maximum of 24 hours. The company estimates of eligible patient numbers are dated and are assumed to be constant over the next five years. The source for estimates of use of unlicensed and licensed infusion bags is not stated and would determine estimates of eligible patient numbers and uptake. Actual uptake of Bufyl[®] is therefore subject to uncertainty, as are the resultant budget impact estimates. However, the company reported worst case scenario may result in increased costs of around £4,000 per year.

3.3 Comparative unit costs

Table 1. Examples of acquisition costs for local anaesthetics and opioids.

Drug	Recommended dose*	Example of average treatment cost per patient**
Bupivacaine 0.1% with fentanyl 2 microgram/ml (Bufyl [®]) solution for infusion bags (250 ml and 500 ml)	Analgesia in labour: 10–15 ml/hour Post operative pain: 4–15 ml/hour	£8.50 – £9.20
Bupivacaine 0.125% with fentanyl 2 microgram/ml (Bufyl [®]) solution for infusion bags (250 ml and 500 ml)	Analgesia in labour: 8–15 ml/hour Post operative pain: 6–15 ml/hour	
Pre-mixed unlicensed specials (e.g. levobupivacaine + fentanyl, bupivacaine + diamorphine, ropivacaine + fentanyl)	Based on the individual components	£5.90 – £12.00
Bupivacaine hydrochloride 0.125% solution for infusion (250 ml)	Analgesia in labour: 8–12 ml/hour Post operative pain: 4–12 ml/hour	£10.59 – £10.80 [†]
Ropivacaine hydrochloride 2 mg/ml solution for infusion (200 ml)	Analgesia in labour: 6–10 ml/hour Post operative pain: 6–14 ml/hour	£14.45 [†]
Levobupivacaine hydrochloride (Chirocaine [®]) 0.625 mg/ml and 1.25 mg/ml solution for infusion (200 ml)	Analgesia in labour: 5–12.5 mg/hour Post operative pain: 12.5–18.75 mg/hour	£10.37 – £12.20 [†]
<p>* Recommended doses for the licensed products based on British National Formulary (BNF)/Summaries of Product Characteristics (SPCs). See SPCs for licensed indications and full dosing details^{2,3,5,9–11}.</p> <p>** Costs for licensed products are based on BNF list prices as of 30/05/2012⁵. Costs for specials as reported by the company¹ - not verified by AWTTTC.</p> <p>[†] Additional cost of up to £3 if fentanyl is to be used in combination with local anaesthetic.</p>		

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTTC is of the opinion that, if recommended, bupivacaine hydrochloride/fentanyl (Bufyl[®]) solution for infusion is appropriate for specialist only prescribing within NHS Wales for the above indication.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 3 May 2012.

Date range of evidence search: No date limits were applied to database searches.

REFERENCES

- 1 Mercury Pharmaceuticals Ltd. Form C: Limited appraisal submission. Bupivacaine hydrochloride/fentanyl (Bufyl[®]). Apr 2012.
- 2 Mercury Pharmaceuticals Ltd. Bufyl[®] 1 mg/ml and 2 microgram/ml solution for infusion. Summary of Product Characteristics. Feb 2012. Available at: <http://www.medicines.org.uk/EMC/medicine/25998/SPC/BUFYL++1mg+ml+and+2microgram+ml+Solution+for+Infusion/>. Accessed May 2012.
- 3 Mercury Pharmaceuticals Ltd. Bufyl[®] 1.25 mg/ml and 2 microgram/ml solution for infusion. Summary of Product Characteristics. Feb 2012. Available at: <http://www.medicines.org.uk/EMC/medicine/25997/SPC/BUFYL+1.25mg+ml+and+2microgram+ml+Solution+for+Infusion/>. Accessed May 2012.
- 4 Medicines and Healthcare products Regulatory Agency. Public Assessment Report. Bupivacaine hydrochloride/fentanyl (Bufyl[®]) solution for infusion. PL 02848/036-7. 2011. Available at: <http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con134885.pdf>. Accessed May 2012.
- 5 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary*. No. 63. Mar 2012.
- 6 National Institute for Health and Clinical Excellence. Clinical Guideline 55. Intrapartum care: care of healthy women and their babies during childbirth. Sep 2007. Available at: <http://publications.nice.org.uk/intrapartum-care-cg55>. Accessed May 2012.
- 7 Cook TM., Mihai R, Wildsmith JA. A national census of central neuraxial block in the UK: results of the snapshot phase of the Third National Audit Project of the Royal College of Anaesthetists. *Anaesthesia* 2008; 63 (2): 143-6.
- 8 Fettes PD, Moore CS, Whiteside JB et al. Intermittent vs continuous administration of epidural ropivacaine with fentanyl for analgesia during labour. *Br J Anaesth* 2006; 97 (3): 359-64.
- 9 Abbott Laboratories Ltd. Chirocaine[®]. Summary of Product Characteristics. Jan 2012. Available at: <http://www.medicines.org.uk/EMC/medicine/19678/SPC/Chirocaine+0.625mg+ml+%26+1.25mg+ml+solution+for+infusion/>. Accessed Jun 2012.
- 10 AstraZeneca UK Ltd. Marcain[®]. Summary of Product Characteristics. May 2012. Available at: <http://www.medicines.org.uk/EMC/medicine/9367/SPC/Marcain+Polyamp+Steri+pack+0.25++and+0.5/>. Accessed Jun 2012.
- 11 AstraZeneca UK Ltd. Naropin[®]. Summary of Product Characteristics. May 2012. Available at: <http://www.medicines.org.uk/EMC/medicine/7151/SPC/Naropin+2+mg+ml+solution+for+infusion/>. Accessed Jun 2012.