NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
MARCH 2021

Liposomal bupivacaine for post-operative pain in children

NIHRIO ID	26932	**NICE ID**	10552
Developer/Company	Pacira BioSciences Inc.	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

Liposomal bupivacaine is in clinical development for the treatment of post-operative pain in paediatric patients. Post-operative pain is a common occurrence in patients who have undergone surgery. Managing post-operative pain is important in order for patients to have a positive post-operative experience and to enhance their recovery, and for the prevention of chronic post-surgical pain in the long-term.

Liposomal bupivacaine is an anaesthetic (numbing agent) administered via local infiltration after surgery. It works by blocking nerve impulses in the body. It is used as a local analgesic to alleviate pain in a particular location of the body. When combined with liposomes, the local anaesthetic remains at the injection site for longer and is released gradually over several days. The benefits of this include the control of post-surgical pain at a minimal level, and lesser need for the use of opioids as a pain relief which further promotes earlier patient mobilisation. Liposomal bupivacaine is given as a prolonged-release dispersion for injection and if licensed, will offer a longer-acting local anaesthetic that can be administered as a single dose for paediatric patients with post-operative pain.

PROPOSED INDICATION

For the treatment of paediatric patients aged 6 to 18 years with somatic post-operative pain from small- to medium-sized surgical wounds.[1]

TECHNOLOGY

DESCRIPTION

Liposomal bupivacaine (Exparel) is a novel formulation which has been developed to address the need for longer-acting local anaesthetics that can be administered as a single dose.[2] Liposomal bupivacaine is a non-pyrogenic sterile preservative-free white to off-white aqueous suspension of (DepoFoam-drug delivery system) multivesicular liposomes containing bupivacaine.[3] On its own, the duration of the local analgesic action of bupivacaine is limited.[4] One approach to prolong analgesia is to complex local anaesthetics with larger carrier molecules that remain at the injection site for a prolonged time, gradually releasing anaesthetic.[5] Multivesicular liposomes constitute an ideal vehicle, because following administration there is a reorganisation of the triglycerides in the external lipid layer which leads to a release of the bupivacaine from within the vesicle. This leads to further reorganisation of the vesicles and continued release of bupivacaine for up to 72 hours.[6,7]

Liposomal bupivacaine is currently in phase III clinical development for the management of post-operative pain in paediatric patients. In phase III clinical trial (PLAY; NCT03682302), participants will receive 4mg/kg (maximum 266 mg) administered intraoperatively at the end of surgery via local infiltration.[1]

INNOVATION AND/OR ADVANTAGES

The preparation of liposomal bupivacaine loaded in multivesicular liposomes increases the duration of local anaesthetic action by slow release from the liposome and delays the peak plasma concentration when compared to plain bupivacaine administration.[5] The benefits of liposomal bupivacaine include that when given to patients following surgery, the duration of analgesia is prolongued and lasts for up to 72 hours.[7] Such extended pain relief would minimize postsurgical pain and reduce the consumption of supplemental opioid medications post-surgery, which could lead to earlier patient mobilisation and bowel function.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently liposomal bupivacaine is licensed in the EU/UK as a treatment for post-operative pain in adults. Liposomal bupivacaine is indicated as a brachial plexus block or femoral nerve block for treatment of post-operative pain in adults, and as a field block for treatment of somatic post-operative pain from small- to medium-sized surgical wounds in adults.[9]

The safety of liposomal bupivacaine was investigated in 10 randomised trials and the most common adverse events (≥ 10%) among patients were constipation, nausea, and pyrexia.[10]

Liposomal bupivacaine is currently in phase II and III clinical development for a range of surgeries (including lumbar fusion, hip and femur fracture repair, open gynaecologic surgery,

breast reconstruction, thoracic surgery, thoracotomy, knee arthroplasty, rotator cuff repair, shoulder arthroplasty, liver surgery).[11]

PATIENT GROUP

DISEASE BACKGROUND

Post-operative pain is a form of acute pain caused by surgical trauma with the initiation of an afferent neuronal barrage and an inflammatory reaction. It is a combination of multiple unpleasant emotional, sensory and mental experiences associated with endocrine-metabolic, autonomic, behavioral and physiological responses triggered by the surgical trauma.[12] The fear of pain is deeply rooted in patients who are scheduled to undergo surgery. All surgical procedures are associated with a level of post-operative pain.[13] A patient's recovery post surgery, can be affected by their experience of postsurgical pain through a variety of mechanisms including harmful changes in pulmonary (e.g. impaired ventilation), cardiovascular (e.g. peripheral vascular resistance), haematologic (e.g. thromboembolism), gastrointestinal (e.g. reduced intestinal motility), renal (e.g. urinary retention), immunologic (e.g. infection), and psychological (e.g. anxiety) function.[14] Post-operative pain increases the utilisation of health services whilst patients are in the hospital as the occurrence of post-operative pain may lead to prolonged post-anaesthesia care unit stays, delayed hospital discharge, and unanticipated admission following ambulatory surgery or subsequent readmissions.[15] Experiencing severe acute postsurgical pain has also been identified as a risk factor for developing chronic postsurgical pain, with the risk being proportional to the amount of time spent in severe pain on the first day after surgery.[16]

CLINICAL NEED AND BURDEN OF DISEASE

Pain is often poorly relieved, with up to 20% of all inpatients suffering moderate to severe pain at any given time. According to Core Standards for Pain Management Service in the UK, two-thirds of hospital patients experience pain during their admission. Even within the surgical population, where the noxious stimulus (the surgery) is well defined and systems are in place to manage acute pain, almost 60% of patients experience severe pain in the post-operative period, with a marked negative impact on health-related quality of life.[17]

In England, in 2019-20 there were 501,623 finished consultant episodes (FCE) for surgical procedures and interventions in children aged 5 to 18 years.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The involvement of the patient on the decisions made with regards to their pain control is important because pain is relative and can be experienced differently by each individual. This discussion should include the likely impact of the procedure on the pain, the patients pain history, the person's preferences and expectations, plans for discharge and the potential benefits and risks, including long-term risks, of different types of pain relief.[19]

Following a surgery, patients should have their pain levels assessed by their healthcare provider on a scale of 0-10. This pain score should be assessed three times a day and after analgesia administration to inform doctors and nurses on the efficacy of the patients current treatment.[20,21] The prescription of analgesia should be individualised and adjusted based on regular assessments. This will help to maintain pain score below 4 in relation to the 10 point scale used to measure pain.[21]

CURRENT TREATMENT OPTIONS

For patients who experience post-operative pain, NICE recommends:[19]

- A multimodal approach where multiple analgesics from different classes are combined to manage post-operative pain.

For paediatric patients who experience post-operative pain, the European Society for Paediatric Anaesthesiology (ESPA) Pain Committee recommends:[21]

- At basic level, offer an oral paracetamol after surgery. For individuals who cannot take oral paracetamol offer rectal paracetamol. For patients in the PACU an intravenous dose of fentanyl or other suitable agent (if available) to treat breakthrough pain is recommended.
- At intermediate level, intravenous nalbuphine or other suitable agent (if available) is recommended to treat serious breakthrough pain in the PACU. Oral or rectal paracetamol and/or NSAIDs (e.g. ibuprofen) in adequate dosing should be offered during the entire postoperative period.
- At advanced level, intravenous dosing of nalbuphine or other suitable agent (if available) is recommended to treat breakthrough pain in the PACU. Oral or rectal paracetamol and/or NSAIDs (e.g. ibuprofen) in adequate dosing should be offered during the entire postoperative period.
- As a rescue option in the ward, intravenous nalbuphine or oral tramadol is recommended.

In patients with obstructive sleep apnea special care must be taken when prescribing opioids. These recommendations are based on a pyloromyotomy procedure.[21]

PLACE OF TECHNOLOGY

If licensed, liposomal bupivacaine will offer an additional therapy for paediatric patients aged 6 to 18 years who have undergone surgery and experience post-operative pain.

CLINICAL TRIAL INFORMATION

Trial	**PLAY; NCT03682302;** A Multicenter Study to Evaluate the Pharmacokinetics and Safety of EXPAREL for Postsurgical Analgesia in Pediatric Subjects Aged 6 to Less Than 17 Years **Phase III** - Completed **Location(s):** USA **Primary completion date:** August 2019
Trial design	Randomized, open-label, sequential assignment
Population	- N= 98 (actual); 6 to 17 years on the day of surgery whose parent(s) or guardian(s) has/have signed and dated the ICF for the subject to participate in the study, and subjects

	who have provided written assent to participate in the study (if capable). - Participants with American Society of Anesthesiologists (ASA) Class 1-3. - Participants with a body mass index (BMI) at screening within the 5th to 95th percentile for age and sex. A negative pregnancy test for female subjects of childbearing potential must be available prior to the start of surgery. The pregnancy test must be conducted in the preoperative holding area according to the study site's standard of care. - Participants must be able to adhere to the study visit schedule and complete all study assessments.
Intervention(s)	- Group 1: Participants aged 12 to less than 17 years will receive single dose of liposomal bupivacaine 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of spine surgery. - Group 2: Participants aged 6 to less than 12 years will receive single dose of liposomal bupivacaine 4 mg/kg (not to exceed a maximum total dose of 266 mg) via local infiltration at the end of cardiac and spine surgery.
Comparator(s)	- Group 1: Participants aged 12 to less than 17 years will receive a single dose of bupivacaine hydrochloride (HCl) 2 mg/kg (not to exceed a maximum total dose of 175 mg) via local infiltration at the end of spine surgery.
Outcome(s)	- Area Under the Plasma Concentration-versus-time Curve (AUC) 0 to Infinity - Maximum Plasma Concentration(Cmax) - The Apparent Terminal Elimination Half-life (t1/2el) - Apparent Clearance (CL/F) - Apparent Volume of Distribution (Vd/F) - Area Under the Plasma Concentration-versus-time Curve (AUC) 0 to Tlast
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of liposomal bupivacaine is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Perioperative care in adults (NG180). August 2020.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- Trust Clinical Guidelines Group. Paediatric Acute Pain Management Guidelines. 2018.[22]
- Chou R. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. 2016.[23]
- European Association of Urology. Guidelines of Pain Management. 2012.[24]

ADDITIONAL INFORMATION

Pacira BioSciences Inc. did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 ClinicalTrials.gov. *Multicenter Study for Pediatric Subjects Evaluating Pharmacokinetics and Safety of EXPAREL (PLAY)*. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03682302 [Accessed 23 February 2021].

2 Bergese, S. D., Ramamoorthy S., Patou G., Bramlett K., Gorfine S. R., Candiotti K. A. *Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia*. Journal of pain research. 2012;5:107. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3346068/ [Accessed 23 February 2021].

3 FDA.gov. *EXPAREL (bupivacaine liposome injectable suspension)*. 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022496s9lbl.pdf [Accessed 23 February 2021].

4 Bramlett, K., Onel E., Viscusi E. R., Jones K. *A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty*. The Knee. 2012;19(5):530-6. Available from: https://www.sciencedirect.com/science/article/pii/S0968016011002262 [Accessed 23 February 2021].

5 Chahar, P., Cummings III K. C. *Liposomal bupivacaine: a review of a new bupivacaine formulation*. Journal of pain research. 2012;5:257. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3442744/ [Accessed 22 February 2021].

6 Hutchins, J., Delaney D., Vogel R. I., Ghebre R. G., Downs Jr L. S., Carson L., et al. *Ultrasound guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine for patients undergoing robotic assisted hysterectomy: A prospective randomized controlled study*. Gynecologic oncology. 2015;138(3):609-13. Available from:

https://doi.org/10.1016/j.ygyno.2015.06.008 https://www.sciencedirect.com/science/article/pii/S0090825815300299 [Accessed 22 February 2021].

7 Liu, Y., Zeng Y., Zeng J., Li M., Wei W., Shen B. *The efficacy of liposomal bupivacaine compared with traditional peri-articular injection for pain control following total knee arthroplasty: an updated meta-analysis of randomized controlled trials*. BMC musculoskeletal disorders. 2019;20(1):1-12. Available from: https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/s12891-019-2660-7 [Accessed 22 February 2021].

8 Müller-Lissner, S., Bassotti G., Coffin B., Drewes A. M., Breivik H., Eisenberg E., et al. *Opioid-induced constipation and bowel dysfunction: a clinical guideline*. Pain Medicine. 2017;18(10):1837-63. Available from: https://academic.oup.com/painmedicine/article/18/10/1837/2649200?login=true [Accessed 23 February 2021].

9 European Medicines Agency. *Exparel liposomal*. 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/exparel-liposomal [Accessed 22 February 2021].

10 RxList. *EXPAREL*. 2021. Available from: https://www.rxlist.com/exparel-drug.htm#description [Accessed 22 February 2021].

11 ClinicalTrials.gov. *Search results-Liposomal bupivacaine*. 2021. Available from: https://clinicaltrials.gov/ct2/results?term=Liposomal+bupivacaine&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 22 February 2021].

12 Gupta, A., Kaur K., Sharma S., Goyal S., Arora S., Murthy R. *Clinical aspects of acute post-operative pain management & its assessment*. Journal of advanced pharmaceutical technology & research. 2010;1(2):97. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3255434/#:~:text=Postoperative%20pain%20is%20considered%20a,of%20an%20afferent%20neuronal%20barrage. [Accessed 23 February 2021].

13 Shafer, A., Fish M. P., Gregg K. M., Seavello J., Kosek P. *Preoperative anxiety and fear: a comparison of assessments by patients and anesthesia and surgery residents*. Anesthesia & Analgesia. 1996;83(6):1285-91. Available from: https://pubmed.ncbi.nlm.nih.gov/8942601/ [Accessed 23 February 2021].

14 Joshi, G. P., Ogunnaike B. O. *Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain*. Anesthesiology Clinics of North America. 2005;23(1):21-36. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0889853704001270?via%3Dihub [Accessed 23 February 2021].

15 Baratta, J. L., Schwenk E. S., Viscusi E. R. *Clinical consequences of inadequate pain relief: barriers to optimal pain management*. Plastic and reconstructive surgery. 2014;134(4S-2):15S-21S. Available from: https://oce.ovid.com/article/00006534-201410002-00005/HTML [Accessed 22 February 2021].

16 Fletcher, D., Stamer U. M., Pogatzki-Zahn E., Zaslansky R., Tanase N. V., Perruchoud C., et al. *Chronic postsurgical pain in Europe: an observational study*. European Journal of Anaesthesiology| EJA. 2015;32(10):725-34. Available from: https://journals.lww.com/ejanaesthesiology/fulltext/2015/10000/Chronic_postsurgical_pain_in_Europe__An.10.aspx [Accessed 23 February 2021].

17 Faculty of Pain Medicine of the Royal College of Anaesthetists. *Core Standards for Pain Management Services in the UK.*: 2015. Available from: https://fpm.ac.uk/sites/fpm/files/documents/2019-07/Core%20Standards%20for%20Pain%20Management%20Services.pdf [Accessed 24 February 2021].

18 National Health Service. *Hospital Admitted Patient Care Activity 2019-20*. 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 22 February 2021].

19 NICE Guidance. *Perioperative care in adults*. 2020. Available from: https://www.nice.org.uk/guidance/ng180 [Accessed 23 February 2021].

20 The Royal Marsden. *Pain control following surgery*. 2020. Available from: https://www.royalmarsden.nhs.uk/your-care/treatments/surgery/pain-control-following-surgery [Accessed 24 February 2021].

21 Vittinghoff, M., Lönnqvist P. A., Mossetti V., Heschl S., Simic D., Colovic V., et al. *Postoperative pain management in children: Guidance from the pain committee of the European Society for Paediatric Anaesthesiology (ESPA Pain Management Ladder Initiative)*. Pediatric Anesthesia. 2018;28(6):493-506. Available from: https://www.euroespa.com/wp-content/uploads/2018/04/Vittinghoff_et_al-2018-Pediatric_Anesthesia-1.pdf [Accessed 1 March 2021].

22 Trust Clinical Guidelines Group. *Paediatric Acute Pain Management Guidelines*. 2018. Available from: http://www.lhp.leedsth.nhs.uk/detail.aspx?id=58 [Accessed 24 February 2021].

23 Chou, R., Gordon D. B., de Leon-Casasola O. A., Rosenberg J. M., Bickler S., Brennan T., et al. *Management of Postoperative Pain: a clinical practice guideline from the American pain society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' committee on regional anesthesia, executive committee, and administrative council*. The journal of pain. 2016;17(2):131-57. Available from: https://pubmed.ncbi.nlm.nih.gov/26827847/ [Accessed 24 February 2021].

24 Bader P, D. M. G., Echtle D, Fonteyne V, Livadas K, Paez Borda A, Papaioannou E.G., Vranken J.H.,. *Guidelines on Pain Management*. 2020. Available from: https://uroweb.org/wp-content/uploads/EAU-Guidelines-Pain_Management-2012.pdf [Accessed 24 February 2021].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.