

HEALTH TECHNOLOGY BRIEFING APRIL 2020

Liposomal bupivacaine for post-operative pain

NIHRIO ID	18325	NICE ID	10358
Developer/Company	Pacira Ireland Ltd	UKPS ID	Not available

Licensing and market availability plans	Currently in phase II/III/IV clinical trials.
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SUMMARY

Liposomal bupivacaine is in late-stage clinical development for the treatment of post-operative pain in adults. Post-operative pain is a common occurrence for those patients who have surgery. Controlling post-operative pain is important for ensuring a good patient experience, optimising post-operative outcomes and enhancing recovering, and the prevention of chronic postsurgical pain in the longer term.

Bupivacaine is an anaesthetic (numbing agent) that blocks nerve impulses in the body. It is used as a local analgesic to alleviate pain in a particular location of the body. Ordinarily, the numbing effects of bupivacaine are short lived, as the molecules are small and rapidly redistributed from the site of injection. However, when combined with larger carriers such as liposomes, which remain at the injection site for longer, the local anaesthetic is released gradually over several days. This has a number of benefits - postsurgical pain is kept to a minimum, and opioid consumption is reduced 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 patients with post-operative pain.

PROPOSED INDICATION

Liposomal bupivacaine is indicated in adults for single-dose infiltration to produce post-surgical local analgesia and as a nerve block to produce post-surgical regional analgesia for acute pain management.^a

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.¹ On its own, the duration of the local analgesic action of bupivacaine is limited.² One approach to prolong analgesia is to complex local anaesthetics with larger carriers that remain at the injection site for a prolonged time, gradually releasing anaesthetic. Multivesicular liposomes (i.e., DepoFoam)³ constitute an ideal vehicle, because following administration there is a reorganisation of the triglycerides in the external lipid layer which leads to 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.^{4,5}

Liposomal bupivacaine is currently in late stage clinical development for management of post-operative pain.⁶⁻¹¹ In these trials, participants were assigned to receive liposomal bupivacaine prolonged-release dispersion for injection with dosing varying between 67 mg and 266 mg.⁶⁻¹¹

INNOVATION AND/OR ADVANTAGES

The benefits of liposomal bupivacaine which when given to patients following surgery centre on the prolonged duration of analgesia for up to 72 hours.¹² 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.^{2,13}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Liposomal bupivacaine does not currently have Marketing Authorization in the EU for any indication.

Liposomal bupivacaine is currently in late stage development, with clinical trials completed 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).¹⁴

PATIENT GROUP

DISEASE BACKGROUND

Post-operative pain is a typical example of acute pain.¹⁵ All surgical procedures are associated with a certain level of post-operative pain. Fear of pain is deeply rooted among patients who are about to have surgery.¹⁶ Experiencing postsurgical pain can interfere with patient recovery after surgery through a variety of mechanisms, including harmful changes in cardiovascular (e.g. peripheral vascular resistance), pulmonary (e.g. impaired ventilation), gastrointestinal (e.g. reduced intestinal

^a Information provided by Pacira Ireland Ltd.

motility), renal (e.g. urinary retention), hematologic (e.g. thromboembolism), immunologic (e.g. infection), muscular (e.g. weakness), and psychological (e.g. anxiety) function.¹⁷ These changes can increase the utilisation of health services while in the hospital, as uncontrolled postoperative pain may lead to prolonged post-anaesthesia care unit stays, delayed hospital discharge, and unanticipated admission following ambulatory surgery or subsequent readmissions.¹⁸ 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.¹⁹

CLINICAL NEED AND BURDEN OF DISEASE

According to Core Standards for Pain Management Service in the UK, two-thirds of hospital patients experience pain during their admission. Pain is often poorly relieved, with up to 20% of all inpatients suffering moderate to severe pain at any given time. 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.²⁰

The number of surgical procedures and interventions performed in England 2018-19 was 12,164,264. If 60% of patients experience severe pain in the postoperative period, this would equate to approximately 7,298,558 of persons who were operated on in 2018-19.²¹

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The involvement of patients in pain control is important because pain is such a personal experience. Following the operation, patients should have their pain level assessed using a 0-10 scale. The pain score should be recorded which will help the doctors and nurses know whether pain treatments are working.²²

Both drug and non-drug treatments can be successful in helping to control pain. In most cases drugs are given to control pain for a few days after surgery. However, non-drug treatments can be just as important in helping to control pain.²²

Drug treatment to control pain

Pain should be treated early rather than allowing it to become worse. The type of drugs should be selected according to the extent of surgery and the amount of pain the patient has, as well as individual patient factors. Opioids should be minimised to avoid opioid related adverse events.²²

Non-drug treatment to control pain

Non-drug treatments include some complementary therapies that can be effective for mild to moderate pain and boost the pain-relief effects of drugs. They include:²²

- simple relaxation techniques such as abdominal breathing, visualisation exercises, and listening to relaxing music
- supporting the wound when coughing, deep breathing and moving after surgery
- massage, which works on the muscles to release excess tension and can help with relaxation.

CURRENT TREATMENT OPTIONS

Recommendations for treating postsurgical pain include surgical site-specific peripheral regional anesthetic techniques with local anesthetics (e.g. bupivacaine), as well as a multimodal regimen of

scheduled systemic non-opioid analgesics (e.g. NSAIDs), with opioids given as needed for moderate to severe pain.²³

PLACE OF TECHNOLOGY

If licensed, liposomal bupivacaine will offer an additional treatment option for the management of post-operative pain when given prior to or during surgery. Target patients and treatment line are surgical procedures in adults which incur moderate to severe somatic postoperative pain for more than 24 hrs.^b

CLINICAL TRIAL INFORMATION

Trial	NCT00890721 , SKY0402-C-316; A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy Phase III, completed Location(s): Republic of Georgia, Poland and Serbia
Trial design	Randomised, double-blind, parallel-group, placebo-controlled study.
Population	n=189; adults 18 yrs and older; scheduled to undergo 2- or 3-column excisional hemorrhoidectomy for internal or internal/external haemorrhoids, under general anesthesia, using the Milligan-Morgan technique.
Intervention(s)	A single administration by intraoperative local infiltration of 266 mg of LB, diluted to a 30 mL injection volume. ^b
Comparator(s)	A single administration by intraoperative local infiltration of preservative-free 0.9% sodium chloride for injection (30 mL injection volume).
Outcome(s)	Primary outcome measure: The area under the curve of NRS-R pain intensity scores through 72 hours (NRS-R AUC0-72). See trial record for full list of other outcomes.
Results (efficacy)^b	The primary endpoint, the area under the curve of NRS-R pain intensity scores through 72 hours (NRS-R AUC0-72) was met. EXPAREL demonstrated a statistically significant reduction in pain through 72 hours compared with placebo (p<0.0001). Multiple secondary endpoint results also demonstrated a statistically significant advantage for EXPAREL, confirming the robustness and clinical significance of the primary endpoint.
Results (safety)^b	The adverse event incidence for EXPAREL was similar to placebo. There were no deaths or withdrawals due to adverse events. There was one SAE of mild thrombophlebitis in the placebo group, which resolved the next day after treatment. Mean scores for overall satisfaction with the subject's wound healing were not statistically significantly different between treatment groups.

Trial	NCT00890682 , SKY0402-C-317; A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Unilateral First Metatarsal Osteotomy (Bunionectomy)
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^b Information provided by Pacira Ireland Ltd.

	Phase III, completed Location: USA
Trial design	Randomised, double-blind, parallel-group, placebo-controlled study.
Population^c	n= 193 (enrolled); adults aged ≥ 18 years at the screening visit; scheduled to undergo primary unilateral first metatarsal osteotomy without hammertoe; able to receive Mayo block for intraoperative local analgesia.
Intervention(s)	106 mg of LB in a volume of 8 mL (mode of administration: Intraoperative local infiltration). ^c
Comparator(s)	A single administration of preservative-free 0.9% sodium chloride for injection. 8 mL injection volume (mode of administration: Intraoperative local infiltration).
Outcome(s)	Primary outcome measure: Area under the curve (AUC) of the Numeric Rating Scale at Rest (NRS-R) Pain Intensity Scores [time frame: 0-24 hours]. See trial record for full list of other outcomes.
Results (efficacy)^{c,24}	<ul style="list-style-type: none"> • The primary efficacy endpoint, AUC of pain intensity scores through 24 hours using the wWOCF+LOCF imputation for NRS scores, was met as shown by the statistically significant difference between EXPAREL and placebo ($p=0.0005$). • The secondary endpoint results support the robustness of the primary endpoint finding that EXPAREL demonstrated analgesic activity in the bunionectomy setting. The AUC of pain intensity continued to be statistically significant through 36 hours ($p=0.0229$).
Results (safety)^{c,24}	<ul style="list-style-type: none"> • EXPAREL was well tolerated in subjects who received postsurgical treatment for pain following bunionectomy. • The incidence of systemic TEAEs was lower in the EXPAREL group (57.7%) compared with the placebo group (65.6%). This difference was largely accounted for by the higher incidence of dizziness in the placebo group (26.0%) compared with the EXPAREL group (11.3%). The incidence of vomiting was higher in the EXPAREL group (27.8%) compared with the placebo group (17.7%). • Most TEAEs were reported as not related to study medication and were mild or moderate in severity. The incidence of related systemic TEAEs was higher in the EXPAREL group (9.3%) compared with the placebo group (5.2%). The incidence of severe TEAEs was higher in the EXPAREL group (11.3%) compared with the placebo group (5.2%); the incidence of moderate TEAEs was higher in the placebo group (20.8%) compared with the EXPAREL group (12.4%). Of note, severe vomiting was observed in 9.3% of subjects in the EXPAREL group compared with 2.1% of subjects in the placebo group. The subgroup analysis did not lead to meaningful conclusions as some of the subgroups had small numbers of subjects and no statistical analysis was planned or performed.

Trial	NCT01683071 ; 402-C-323; A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose Ranging Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Single Injection Femoral Nerve Block With Liposome Bupivacaine for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty Phase II/III, completed Location(s): USA
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^c Information provided by Pacira Ireland Ltd.

Trial design	Randomised, parallel assignment (triple masking), multicentre, placebo-controlled study
Population	n=278; adults aged 18 yrs and older; scheduled to undergo primary unilateral TKA under general or spinal anaesthesia; American Society of Anaesthesiology (ASA) Physical Status 1, 2, or 3; able to demonstrate motor function by performing a 20-meter walk, unassisted, and sensory function by exhibiting sensitivity to cold.
Intervention(s)	Active comparative - Group 1: Bupivacaine liposome injectable suspension 67 mg. Active comparative - Group 2: Bupivacaine liposome injectable suspension 133 mg. Active comparative - Group 3: Bupivacaine liposome injectable suspension 266 mg.
Comparator(s)	Placebo comparative - Group 4: Preservative-free normal saline (20 ml)
Outcome(s)	Postoperative pain [time frame: up to 72 hrs post-surgery]
Results (efficacy)	Femoral nerve block with liposome bupivacaine (266 mg) resulted in modestly lower pain scores and reduced opioid requirements after surgery. ²⁵
Results (safety)	Incidence of adverse events was similar between the groups (part 1: 90 vs. 96%; part 2: 96 vs. 96%, respectively). ²⁵

Trial	NCT02713230 , 402-C-327; A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Brachial Plexus Block (BPB) With EXPAREL for Postsurgical Analgesia in Subjects Undergoing Total Shoulder Arthroplasty or Rotator Cuff Repair Phase III, completed Location(s): Europe (not UK) and the USA
Trial design	Randomised, parallel assignment (triple masking), multicentre, placebo-controlled study
Population	n=156; adults aged 18 yrs and older; females must be surgically sterile, post-menopausal or be using contraception/practicing abstinence; patients should be scheduled to undergo primary unilateral total shoulder arthroplasty or rotator cuff repair; subjects scheduled for rotator cuff repair must have a magnetic resonance imaging (MRI) with a reading confirming a tear of at least 1 cm; American Society of Anaesthesiologists (ASA) physical status 1, 2, or 3; subjects should be able to demonstrate normal motor function and sensory function in the location where sensory function will be measured throughout the study.
Intervention(s)	Active comparator: Liposomal bupivacaine 133 mg in 10 mL expanded with 10 mL of normal saline for a total volume of 20 mL.
Comparator(s)	Placebo comparator: Normal saline in 20 ml
Outcome(s)	Primary outcome measure: Area under the curve (AUC) of the VAS pain intensity scores [time frame: through 48 hrs]. See trial record for full list of other outcomes.
Results (efficacy)^{d,26}	<ul style="list-style-type: none"> • Single-injection BPB with liposomal bupivacaine 133 mg provided analgesia through 48 hours post-surgery with reduced opioid use compared with placebo after shoulder surgery. • The LS mean AUC of VAS pain intensity scores through 48 hours was highly statistically significantly lower in the EXPAREL 133 mg group (136.431) compared to the placebo group (254.119; p<0.0001).

^d Information provided by Pacira Ireland Ltd.

	<ul style="list-style-type: none"> • A supportive analysis examining AUC of VAS pain intensity scores through 48 hours in the Per-Protocol Analysis Set was consistent with these results (LS mean difference -116.267; p<0.0001). • Total postsurgical opioid consumption through 48 hours was highly statistically significantly lower in the EXPAREL 133 mg group (LS mean 25.007) compared to the placebo group (LS mean 109.739; p<0.0001). • A statistically significantly higher (p=0.008) percentage of subjects in the EXPAREL 133 mg group (13.0%) compared to the placebo group (1.4%) were opioid-free through 48 hours and the time to the first use of opioid rescue medication was statistically significantly longer in the EXPAREL 133 mg group compared to the placebo group (p<0.0001).
Results (safety)^{e,26}	<ul style="list-style-type: none"> • The liposomal bupivacaine 133 mg given as a single-injection BPB added to a standardised pain management protocol demonstrated a comparable safety profile with the standardised protocol alone. • The percentage of subjects who experienced a TEAE or study drug-related TEAE was similar in the EXPAREL and placebo groups with no evidence of dose dependence for the 133 mg and 266 mg EXPAREL doses. Most TEAEs were mild or moderate in severity. Severe TEAEs were reported for a similar percentage of subjects in the All EXPAREL (2.4%) and placebo groups (2.8%). • SAEs were reported for four subjects (two in the EXPAREL 133 mg group, one in the EXPAREL 266 mg group, and one in the placebo group); none of the SAEs was assessed by the investigator as being drug related. No subjects died or had a TEAE leading to study discontinuation. Nausea was the most frequently reported TEAE in the All EXPAREL and placebo groups, with no evidence of dose dependence for the EXPAREL 133 mg and 266 mg doses. Headache and hypoaesthesia were the only TEAEs that occurred at a ≥5% higher incidence in the All EXPAREL group than in the placebo group. Nausea, pruritus, and dizziness occurred at a ≥5% higher incidence in the placebo group compared with the All EXPAREL group. • Treatment-emergent AESI were reported in a similar percentage of subjects in the All EXPAREL and placebo groups and all were mild in intensity. No subject reported a fall during the study.

Trial	NCT02713490 , 402-C-331; Multicenter, Randomized, Double-Blind, Controlled Trial Comparing Local Infiltration Analgesia With EXPAREL to Local Infiltration Analgesia Without EXPAREL to Manage Postsurgical Pain Following Total Knee Arthroplasty Phase IV, completed Location(s): USA
Trial design	Randomised, double-blind, active-controlled study.
Population	n = 140; adults aged 18 yrs and older with an American Society of Anesthesiologists physical status 1, 2, or 3, who were scheduled undergo primary, unilateral, tricompartmental TKA under spinal anesthesia for degenerative osteoarthritis of the knee; subjects were not eligible to participate if they had a planned concurrent surgical procedure (e.g., bilateral TKA) or were undergoing unicompartmental TKA or revision TKA.
Intervention(s)	Single dose of EXPAREL 266 mg in 20 mL admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 80 mL normal saline (total volume of 120 mL). Mode of administration: Intraoperative local infiltration.

^e Information provided by Pacira Ireland Ltd.

Comparator(s)	Single dose of bupivacaine HCl 0.5% in 20 mL expanded in volume with 100 mL normal saline (total volume of 120 mL). Mode of administration: Intraoperative local infiltration.
Outcome(s)	Primary outcome measures: <ul style="list-style-type: none"> The area under the curve (AUC) of the VAS pain intensity [time frame: from 12-48 hours]. Total opioid consumption (in IV morphine equivalents) [time frame: from 0-48 hours]. See trial record for full list of other outcomes.
Results (efficacy)^{f,27}	<ul style="list-style-type: none"> Treatment with EXPAREL+bupivacaine was associated with a significant improvement in pain scores compared with bupivacaine alone. Mean (SD) AUC (12-48) of the VAS pain intensity scores, the co-primary efficacy endpoint, was 180.8 (94.8) with EXPAREL+bupivacaine and 209.3 (78.97) with bupivacaine alone, with a significant least squares mean treatment difference of -26.88 (p=0.0381). EXPAREL+bupivacaine was also associated with a significant reduction in total opioid consumption. The LS mean total opioid consumption from 0 to 48 hours after surgery was 16.321 mg with EXPAREL+bupivacaine and 80.328 mg with bupivacaine alone, with a significant LS ratio of 0.203 (p=0.0029). EXPAREL+bupivacaine was associated with a significant increase in the proportion of opioid-free subjects and a significant delay in the time to first opioid rescue compared with bupivacaine alone. There was no significant difference between groups in the OBAS total score.
Results (safety)^{f,27}	<ul style="list-style-type: none"> The percentage of subjects reporting at least 1 TEAE was 64.3% with EXPAREL+bupivacaine and 56.5% with bupivacaine alone. The most common TEAEs were nausea (EXPAREL+bupivacaine: 30.0%, bupivacaine alone: 31.9%), dizziness (EXPAREL+bupivacaine: 4.3%, bupivacaine alone: 11.6%), and vomiting (EXPAREL+bupivacaine: 7.1%, bupivacaine alone: 7.2%). Most TEAEs were mild or moderate in severity and not considered to be related to study treatment. Events considered to be related to study treatment included nausea, vomiting, arthralgia, joint stiffness, joint swelling, and pruritus in the EXPAREL+bupivacaine group and arrhythmia, arthralgia, and mental status changes in the bupivacaine group. Adverse events of special interest were reported more often with bupivacaine alone (7.2%) than with EXPAREL+bupivacaine (2.9%). No subject discontinued the study because of a TEAE and there were no deaths. One subject in each treatment group experienced an SAE (incision site cellulitis in an EXPAREL+bupivacaine subject and influenza in a bupivacaine subject); neither SAE was considered to be related to study treatment and both resolved with appropriate medical attention.

Trial	NCT03176459 , 402-C-411; A Multicenter, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Safety and Efficacy of EXPAREL When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Bupivacaine Alone in Subjects Undergoing Elective Cesarean Section Phase IV, completed Location(s): USA
Trial design	Randomised, double-blind, active controlled study.

^f Information provided by Pacira Ireland Ltd.

Population	n = 186, female, \geq 18 years of age, scheduled to undergo elective C-section with a term pregnancy of 37 to 42 weeks' gestation, and had an American Society of Anesthesiologists physical status 1, 2, or 3. Subjects were not eligible to participate if they had a high-risk pregnancy (e.g., multiple gestations, pregnancy resulting from in vitro fertilization, gestational diabetes), pregnancy-induced medical condition or complication (e.g., hypertension, pre-eclampsia, chorioamnionitis), or 3 or more prior C-sections.
Intervention(s)[§]	Single infiltration of EXPAREL 133 mg in 10 mL combined with bupivacaine HCl 0.25% in 10 mL (25 mg) and 10 mL normal saline (total mixture 30 mL) into each side of the abdomen (total of 266 mg EXPAREL and total volume 60 mL). Mode of administration: TAP block under ultrasound guidance.
Comparator(s)[§]	Single infiltration of bupivacaine HCl 0.25% in 10 mL (25 mg bupivacaine HCl or 22 mg bupivacaine free base equivalents, calculated as 0.886 mg bupivacaine free base = 1.0 mg bupivacaine HCl equivalents) and 20 mL normal saline (total volume 30 mL) into each side of the abdomen (total of 44 mg bupivacaine HCl and total volume 60 mL). This conversion for bupivacaine HCl is provided in order to report the dose in free base equivalents since the EXPAREL dose is already reported in free base equivalents. Mode of administration: TAP block under ultrasound guidance
Outcome(s)	Primary outcome measure: Total postsurgical opioid consumption (the frame: through 72 hrs). See trial record for full list of other outcomes.
Results (efficacy)[§]	Overall, in the context of non-inferior pain intensity scores, the use of EXPAREL 266 mg+bupivacaine HCl was associated with statistically and clinically significant reductions in opioid use over the 72 hours after surgery compared with bupivacaine HCl alone in subjects undergoing C-section.
Results (safety)[§]	<ul style="list-style-type: none"> The percentage of subjects reporting at least 1 TEAE was 63.9% in the EXPAREL group and 56.2% in the bupivacaine HCl group. Overall, the most common TEAEs were pruritus (EXPAREL: 27.8%, bupivacaine HCl:31.5%), nausea (EXPAREL: 24.7%, bupivacaine HCl: 12.4%), vomiting (EXPAREL: 12.4%, bupivacaine HCl:6.7%), and headache (EXPAREL: 6.2%, bupivacaine HCl: 11.2%). Most TEAEs were mild or moderate in severity and considered not related to study drug. Events considered related to study drug included nausea, vomiting, pruritus, and dizziness in the EXPAREL group and pruritus, back pain, dysuria, and erythema in the bupivacaine HCl group. No subject discontinued the study because of a TEAE and there were no deaths. Three subjects in each treatment group experienced treatment-emergent SAEs; none of the treatment-emergent SAEs was considered related to study drug and all but one (gestational hypertension) resolved with appropriate medical attention.

ESTIMATED COST

The cost of liposomal bupivacaine is not yet known.

[§] Information provided by Pacira Ireland Ltd.

RELEVANT GUIDANCE

NICE GUIDANCE

NICE clinical guidance in development. Perioperative care in adults (GID-NG10072). Expected May 2020.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- 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. 2012.²⁸
- American Society of Anesthesiologists. Practice Guidelines for Acute Pain Management in the Perioperative Setting: An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management. 2012.

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 Bergese S, Ramamoorthy P, Bramlett G, Candiotti K. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. *Journal of Pain Research*. 2012;5:107-16. Available from: <https://doi.org/10.2147/JPR.S30861>.
- 2 Bramlett K, Onel E, Viscusi ER, 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://doi.org/10.1016/j.knee.2011.12.004>.
- 3 Chahar P, Cummings KC, 3rd. Liposomal bupivacaine: a review of a new bupivacaine formulation. *Journal of Pain Research*. 2012;5:257-64. Available from: <http://doi.org/10.2147/JPR.S27894>.
- 4 Hutchins J, Delaney D, Vogel RI, Ghebre RG, Downs LS, 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>.
- 5 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):306. Available from: <http://doi.org/10.1186/s12891-019-2660-7>.
- 6 ClinicalTrials.gov. *A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Efficacy of a Single Administration of SKY0402 for Prolonged Postoperative Analgesia in Subjects Undergoing Hemorrhoidectomy*. Trial ID: NCT00890721. 2009. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT00890721> [Accessed 25th April 2020].
- 7 ClinicalTrials.gov. *Study of Postoperative Analgesia in Bunionectomy*. Trial ID: NCT00890682. 2009. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT00890682> [Accessed 25th April 2020].
- 8 ClinicalTrials.gov. *Femoral Nerve Block With Liposome Bupivacaine for Postsurgical Analgesia Following Total Knee Arthroplasty*. Trial ID: NCT01683071. 2012. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT01683071> [Accessed 16th March 2020].
- 9 ClinicalTrials.gov. *Efficacy, Safety, and Pharmacokinetics of Brachial Plexus Block With EXPAREL in Shoulder Surgery*. Trial ID: NCT02713230. 2016. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT02713230> [Accessed 16th March 2020].
- 10 ClinicalTrials.gov. *Local Infiltration Analgesia With and Without EXPAREL Following Total Knee Arthroplasty*. Trial ID: NCT02713490. 2016. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT02713490> [Accessed 25th April 2020].
- 11 ClinicalTrials.gov. *Evaluate the Safety and Efficacy of EXPAREL When Administered Via Infiltration Into the TAP vs. Bupivacaine Alone in Subjects Undergoing Elective C-Sections (C-Section)*. Trial ID: NCT03176459. 5th June 2017. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT03176459> [Accessed 25th April 2020].
- 12 Malik O, Kaye AD, Kaye A, Belani K, Urman RD. Emerging roles of liposomal bupivacaine in anesthesia practice. *Journal of anaesthesiology, clinical pharmacology*. 2017 Apr-Jun;33(2):151-6. Available from: http://doi.org/10.4103/joacp.JOACP_375_15.
- 13 Müller-Lissner S, Bassotti G, Coffin B, Drewes AM, Breivik H, Eisenberg E, et al. Opioid-induced constipation and bowel dysfunction: a clinical guideline. *Pain Medicine*. 2016;18(10):1837-63. Available from: <https://doi.org/10.1093/pm/pnw255> <https://doi.org/10.1093/pm/pnw255>.
- 14 ClinicalTrials.gov. *Search results - Liposomal bupivacaine*. 2020. 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
- 15 Málek J, Ševčík P, D. B, Gabrhelík T, Hnilicová M, Křikava I, et al. *Postoperative Pain Management*. Prague, Czech Republic: Mladá front; 2017. Available from: https://www.wfsahq.org/components/com_virtual_library/media/125136f77e1b7daf7565bd6653026c35-Postoperative-Pain-Management-170518.pdf.
- 16 Shafer A, Fish MP, Gregg KM, 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://journals.lww.com/anesthesia-analgesia/Fulltext/1996/12000/Preoperative_Anxiety_and_Fear_A_Comparison_of.27.aspx.
- 17 Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. *Anesthesiology Clinics of North America*. 2005;23(1):21-36. Available from: <https://doi.org/10.1016/j.atc.2004.11.013>.
- 18 Baratta JL, Schwenk ES, Viscusi ER. Clinical consequences of inadequate pain relief: Barriers to optimal pain management. *Plastic and Reconstructive Surgery*. 2014;134(4S-2). Available from: https://journals.lww.com/plasreconsurg/Fulltext/2014/10002/Clinical_Consequences_of_Inadequate_Pain_Relief.5.aspx.
- 19 Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, et al. Chronic postsurgical pain in Europe: An observational study. *European Journal of Anaesthesiology (EJA)*. 2015;32(10). Available from:

https://journals.lww.com/ejanaesthesiology/fulltext/2015/10000/Chronic_postsurgical_pain_in_Europe_An.10.aspx.

- 20 Faculty of Pain Medicine of the Royal College of Anaesthetists. *Core Standards for Pain Management Services in the UK*. London: Faculty of Pain Medicine of the Royal College of Anaesthetists; 2015. Available from: <https://fpm.ac.uk/sites/fpm/files/documents/2019-07/Core%20Standards%20for%20Pain%20Management%20Services.pdf>.
- 21 National Health Service. *Hospital Admitted Patient Care Activity 2018-19*. 2019. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19>.
- 22 The Royal Marsden. *Pain control following surgery*. 2020. Available from: <https://www.royalmarsden.nhs.uk/your-care/treatments/surgery/pain-control-following-surgery>.
- 23 Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, 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://doi.org/10.1016/j.jpain.2015.12.008>.
- 24 Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam® bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. *Advances in Therapy*. 2011;28(9):776. Available from: <https://doi.org/10.1007/s12325-011-0052-y>.
- 25 Hadzic A, Minkowitz HS, Melson TI, Berkowitz R, Uskova A, Ringold F, et al. Liposome Bupivacaine Femoral Nerve Block for Postsurgical Analgesia after Total Knee Arthroplasty. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 2016;124(6):1372-83. Available from: <https://doi.org/10.1097/ALN.0000000000001117>.
- 26 Patel MA, Gadsden JC, Nedeljkovic SS, Bao X, Zeballos JL, Yu V, et al. Brachial Plexus Block with Liposomal Bupivacaine for Shoulder Surgery Improves Analgesia and Reduces Opioid Consumption: Results from a Multicenter, Randomized, Double-Blind, Controlled Trial. *Pain Medicine*. 2019;21(2):387-400. Available from: <https://doi.org/10.1093/pm/pnz103>.
- 27 Mont MA, Beaver WB, Dysart SH, Barrington JW, Del Gaizo DJ. Local Infiltration Analgesia With Liposomal Bupivacaine Improves Pain Scores and Reduces Opioid Use After Total Knee Arthroplasty: Results of a Randomized Controlled Trial. *Journal of Arthroplasty*. 2018;33(1):90-6. Available from: <http://doi.org/10.1016/j.arth.2017.07.024>.
- 28 Bader P, De Meerleer G, Echte D, Fonteyne V, Livadas K, Paez Borda A, et al. *Guidelines on Pain Management*. 2020. Available from: https://uroweb.org/wp-content/uploads/EAU-Guidelines-Pain_Management-2012.pdf.

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