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Xaracoll® for Post-Surgical Analgesia in Open Inguinal Hernia Repair

By: Alexa Plutt, Pharm.D.

Background: Inadequate pain control in the post-surgical period can increase morbidity, mortality, and healthcare costs, as well as, decrease the quality of post-surgical recovery.[1,2] Opioid medications have historically been a mainstay for post-surgical pain management; however their use is associated with various side effects (e.g., nausea, vomiting, constipation, respiratory depression) and can lead to dependence and addiction.[1-3] Intraoperative bupivacaine has become a component of the multimodal post-surgical pain control regimen, however its major limitation is a short duration of action of about 2 to 8 hours when administered via local infiltration.[4,5] Methods to extend the duration of analgesia include the use of continuous catheter pumps, which may be limited due to various complications and the use of liposomal bupivacaine (Exparel®) as a local infiltration, which can provide analgesia for up to 72 hours.[4,6] In August 2020, the Food and Drug Administration approved a resorbable and biodegradable collagen implant containing bupivacaine (Xaracoll®; Innocoll Pharmaceuticals) with the potential to deliver analgesia directly into the surgical site over a prolonged time period.[7,8] Xaracoll® is currently only approved for use in open inguinal hernia surgery.

Mechanism of Action: Bupivacaine blocks the generation and conduction of nerve impulses, by increasing the threshold for electrical excitation in the nerve.[8] This occurs by slowing the propagation of the nerve impulse and reducing the rate at which the action potential rises via a decrease in the neuronal membrane permeability to sodium ions.

Key Clinical Trials: The efficacy and safety of Xaracoll® have been evaluated in two similar randomized, multicenter, double-blind, placebo-controlled, phase 3 trials, MATRIX-1 and MATRIX-2,

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Belbuca® for Chronic Pain Management

By: Emily Wings, Pharm.D.

Background: Chronic pain is defined as persistent pain lasting for >3 months or extending beyond the time of normal tissue healing.[1] In 2019, a Task Force established by the US Department of Health and Human Services developed a series of best practices for managing acute and chronic pain; one recommendation was to use buprenorphine as first-line treatment after failure of mu-opioid agonist therapy.[2] On October 23, 2015, buccal buprenorphine (Belbuca®; BioDelivery Sciences International, Inc.) received approval from the Food and Drug Administration for the management of pain requiring daily, around-the-clock, long-term opioid treatment in those for whom alternative treatment options are either ineffective or not tolerated.[3]

Mechanism of Action: Belbuca® acts as a partial agonist at the mu-opioid receptor and as a weak antagonist at the kappa-opioid receptor.[3] Activation of the mu-opioid receptor by buprenorphine promotes G-protein signaling re-

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which included patients undergoing open inguinal hernia repair under general anesthesia.[1] The active group received three Xaracoll® implants containing 100 mg of bupivacaine HCl placed into the hernia repair site. Each implant was cut in half; three halves were placed into the hernia site below the mesh placement site and three halves were placed between the fascia/muscle and skin closures. The placebo group received implants without the active drug in the same manner. Post-surgical medications included scheduled acetaminophen and as needed immediate-release morphine. MATRIX-1 included 298 patients with a median age of 53.2 years and MATRIX-2 had 312 patients with a median age of 49.7 years; over 96% were male in both studies. Pain intensity (PI) was evaluated using an 11-point numerical rating scale and assessed by patients via an electronic diary at predetermined time points (1-, 2-, 3- 5-, 8-, 12-, 24-, 48-, and 72- hours after implantation of the study medication). Total use of opioid analgesia in milligrams of intravenous morphine equivalents was documented from time 0 through 72 hours post-implantation. Safety assessments were done throughout the 30-day trial period. The primary outcome in both trials was the time-weighted sum of PI from time 0 through 24 hours (SPI24). Secondary outcomes included total use of opioid analgesia from time 0 through 24 hours (TOpA24), from time 0 through 48 hours (TOpA48), from time 0 through 72 hours (TOpA72) and the time-weighted sum of PI from time 0 through 48 hours (SPI48) and from time 0 through 72 hours (SPI72). Patients in the Xaracoll® arm experienced a significantly lower mean SPI24 than those receiving placebo in both MATRIX-1 and MATRIX-2 ($p=0.0004$ and $p<0.0001$, respectively). Median TOpA24 was significantly lower for patients receiving Xaracoll® compared to placebo (MATRIX-1: 5 mg vs. 10 mg, respectively; $p<0.0001$; and MATRIX-2: 5 mg vs. 14 mg, respectively; $p<0.0001$). Median TOpA48 and TOpA72 were numerically lower for patients receiving Xaracoll® than placebo in MATRIX-1, but this difference was not significant. Median TOpA48 was significantly lower in patients receiving Xaracoll® than in those receiving placebo in MATRIX-2 (10 mg vs. 20 mg, respectively; $p<0.0003$); however there was no significant difference in median TOpA72 between groups in MATRIX-2. Patients who received Xaracoll® reported lower SPI48 and SPI72 than those receiving placebo in both MATRIX-1 and MATRIX-2 trials, but this difference was only significant for mean SPI48 in MATRIX-2. In MATRIX-1, 36% of patients receiving Xaracoll® and 22% receiving placebo did not use opioids through 72 hours, and in MATRIX-2, 28% of patients receiving Xaracoll® and 12% receiving placebo did not use opioids through 72 hours. The median time to first opioid rescue was 10.7 hours (range, 5.2 to 17.8) in the Xaracoll® group compared to 1 hour (range, 0.9 to 1.1) for the placebo group in MATRIX-1. In MATRIX-2, the median time to first opioid rescue was 6.2 hours (range, 2.0 to 12.0) for patients receiving Xaracoll® versus 0.9 hours (range 0.8 to 1.0) for patients receiving placebo. The authors concluded that Xaracoll® provided sufficient analgesia to cover periods of maximal postsurgical pain associated with post-inguinal hernia repair and may have reduced the need for opioids.

Safety: The most common adverse reactions occurring in ≥2% of the Xaracoll® group compared to placebo in the phase 3 studies included incision site swelling, post-procedural discharge, seroma, dysgeusia, headache, tremor, scrotal swelling, pyrexia, and blurred vision.[1,8] Incision site adverse effects included swelling, pain, post-procedural discharge, erythema, dehiscence, and inflammation.

Dosing and Administration: The recommended dose of Xaracoll® in adults undergoing open inguinal hernia repair is 300 mg (three implants containing 100 mg of bupivacaine each) placed into the surgical site as a single dose.[8] Implants should be cut in half using aseptic technique.[8,9] Three halves should be placed below the mesh placement site and three halves should be just below the skin closure.

Availability and Cost: Xaracoll® is supplied as four or ten single-use cartons containing a tray of three individually sealed sterile blister pouches.[8] Each blister contains 100 mg of bupivacaine HCl and 75 mg purified Type I collagen (approximately 5 cm x 5 cm x 0.5 cm in size). The cost of a single dose of three implants is about $280.[5]

Formulary Status: Xaracoll® is currently being evaluated for addition to the CCHS Adult Formulary.

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sulting in cell membrane hyperpolarization and a reduction in neurotransmitter release, ultimately leading to analgesia.[2]

Clinical Trial: Gimbel and colleagues evaluated the safety and efficacy of Belbuca® in a double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal trial.[4] Eligible adults who were opioid-experienced (on 30 to ≤160 mg/day morphine sulfate equivalent [MSE]) and had moderate to severe chronic low back pain (CLBP) were included. The trial consisted of a screening phase (2 weeks); an opioid taper phase (up to 4 weeks); an open-label buccal buprenorphine titration phase (up to 8 weeks); a double-blind, placebo-controlled, randomized, withdrawal treatment phase (12 weeks); and a follow-up phase (2 weeks). Patients' opioid doses were tapered to ≤30 mg/day MSE before the open titration phase with Belbuca® at doses ranging from 150 mcg to 900 mcg every 12 hours. Those who achieved adequate analgesia for 14 days were then randomized to receive Belbuca® (n=254) or placebo (n=257) buccal film for 12 weeks. The primary outcome was the change in the mean numerical rating scale (NRS) pain intensity score from baseline to week 12 of the double-blind treatment period. A total of 810 patients entered the open-label titration phase, and 511 patients were subsequently randomized in a 1:1 ratio to treatment with either Belbuca® or placebo as part of the 12-week withdrawal treatment phase. The average NRS pain intensity scores increased significantly less from baseline to week 12 in the Belbuca® group (change from baseline, 0.88 ± 1.79) than in the placebo group (change from baseline, 1.92 ± 1.87), with a between group difference of -0.98 (95% CI, -1.32 to -0.64; p<0.001) favoring treatment with Belbuca®. Adverse events reported more frequently with Belbuca® compared to placebo were constipation (2.8% vs. 0.8%, respectively), vomiting (5.5% vs. 2.3%, respectively), and urinary tract infection (3.1% vs. 0.8%, respectively). The authors concluded that the use of Belbuca®, at doses up to 900 mcg every 12 hours, was efficacious for treating moderate-to-severe CLBP in opioid-experienced patients and produced superior analgesia compared to placebo.

Safety: The most common adverse reactions, reported in ≥5% of patients taking Belbuca® in clinical trials, included nausea, constipation, vomiting, headache, fatigue, dizziness, and somnolence.[3] The most common adverse reactions, reported in ≥2% of patients, which led to discontinuation of Belbuca®, were nausea, vomiting, and liver function test abnormality.

Black Box Warnings/REMS Requirements: Belbuca® carries the following Black Box Warnings: Addiction, abuse and misuse, life-threatening respiratory depression, accidental exposure that can result in a fatal buprenorphine overdose, neonatal opioid withdrawal syndrome, and increased risks for sedation, respiratory depression, coma, and death with concomitant benzodiazepine or central nervous system depressant use.[3] Belbuca® is included in the opioid analgesic Risk Evaluation Mitigation Strategy (REMS) program.

Dosing and Administration: In opioid non-tolerant patients, the recommended starting dose of Belbuca® is 75 mcg once daily or, if tolerated, every 12 hours for at least 4 days, followed by 150 mcg every 12 hours.[3] In opioid-experienced patients, it is recommended to taper patients to ≤30 mg/day MSE before initiating Belbuca® and discontinue all around-the-clock opioid analgesics upon initiation. The starting dose of Belbuca® should be based on the patient's daily opioid dose before the taper, as outlined in the package insert. Belbuca® should be titrated in increments of 150 mcg every 12 hours, no more than every 4 days. The maximum dose should not exceed 900 mcg every 12 hours due to potential QTc interval prolongation. Belbuca® is applied to the buccal mucosa every 12 hours with the yellow side of the film placed against the inside of the cheek. When applying the buccal film, areas of the mouth with open sores or lesions should be avoided. The film should be held for 5 seconds and then left in place until fully dissolved; it should not be further manipulated by the tongue or finger(s). Patients should avoid eating or drinking until the buccal film is dissolved, and the film should not be chewed or swallowed. The product should not be used if the pouch seal is broken or the buccal film is cut or damaged.

Cost and Availability: Belbuca® is a Schedule III Controlled Substance.[3] Belbuca® films are available in the following strengths: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg. All packages include 60 individual pouches each containing one buccal film. The average wholesale prices per 150 mcg buccal film and 300 mcg buccal film are $7.32 and $11.51, respectively.[5] The estimated annual cost for a patient receiving Belbuca® 300 mcg every 12 hours is approximately $8,400.

Formulary Status: Belbuca® was added to the CCHS Adult Formulary restricted to the Department of Palliative Medicine for initiation of therapy after failure of two other long-acting opioids; there is no restriction for continuation of home therapy.

References:

1. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2016;65(1)1-49.
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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Afamelanotide (Scenesse®)	Alpha-melanocyte Stimulating Hormone Analog	EPP	Restricted to the Department of Dermatology at Main Campus and to specific physicians (Drs. Arbesman, Matyin, and Vidimos)
Artemether/ lumefantrine (Coartem®)	Antimalarial Agent	Malaria	No restrictions
Bamlanivimab/ etesevimab	Monoclonal Antibody	COVID-19 Infection	For use in adult outpatients ≥ 18 years of age meeting the approved restriction criteria. Specific restriction criteria are included in Lexicomp.
Buprenorphine Buccal Film (Belbuca®)	Analgesic	Pain	Restricted to the Department of Palliative Medicine for initiation of therapy after failure of two other long-acting opioids; there is no restriction for continuation of home therapy.
Cabotegravir (Vocabria™) Cabotegravir/ rilpivirine (Cabenuva™)	Antiretroviral	HIV-infection	No restrictions
Levalbuterol (Xopenex®)	$Beta_2$ Agonist	Asthma	Restricted to PFT lab in patients meeting these criteria: 1) Patients prescribed levalbuterol as home bronchodilator and instructed to avoid albuterol 2) Patients who refuse albuterol in the pulmonary function lab, reporting as severe intolerance (e.g., palpitations, chest pressure, or repeated cough) 3) Resting tachycardia of >110 BPM 4) Patients with a diagnosis of tachyarrhythmias
Lisocabtagene maraleucel (Breyanzi®)	CAR-T Immunotherapy	B Cell Lymphoma	Restricted to the Department of Hematology/Oncology and Bone Marrow Transplantation
Mitomycin gel (Jelmyto®)	Antineoplastic Agent	Urothelial Cancer	Restricted to the Department of Urology for outpatient use only
Moxifloxacin (Avelox®)	Antibiotic	Various infections	Restricted to the Department of Infectious Diseases for indications including infections caused by *Mycobacteria spp, Nocardia spp, and M. genitalium*
Pertuzumab/ trastuzumab/ hyaluronidase-zzxf (Phesgo®)	Monoclonal Antibody	Breast Cancer	Restricted to the Department of Hematology/Oncology for outpatient use only

EPP=Erythropoietic protoporphyria COVID-19= Coronavirus disease 2019 HIV=Human immunodeficiency virus
PFT=Pulmonary function test BPM=Beats per minute CAR-T=Chimeric antigen receptor-T cell

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Ropivacaine-Epinephrine-Clonidine-Ketorolac Periarticular Injection (R.E.C.K.)	Analgesic	Knee surgery	Restricted to the Department of Orthopedics for periarticular use in orthopedic knee surgery
Tolvaptan (Samsca®)	Vasopressin Antagonist	Hyponatremia	Restricted for use in managing hyponatremia in patients with advanced heart failure awaiting LVAD or transplant. Specific restriction criteria are included in Lexicomp.

LVAD=Left ventricular assist device

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Belimumab (Benlysta®)	Monoclonal Antibody	Lupus Nephritis	Modified restriction to include: 1) Restricted to the Departments of Rheumatology and Nephrology for treatment of lupus nephritis for outpatient use only 2) Restricted to the Departments of Rheumatology and Nephrology for treatment of lupus nephritis in patients who have failed previous therapy for inpatient use
Bivalirudin (Angiomax®)	Anticoagulant	HIT	Modified restriction to include the Department of Hematology for patients with HIT
Conivaptan (Vaprisol®)	Vasopressin Antagonist	Hyponatremia	Modified restriction to include for managing hyponatremia in patients with advanced heart failure awaiting LVAD or transplant. Specific restriction criteria are included in Lexicomp.
Fosaprepitant (IV) (Emend®)	Substance P/ Neurokinin 1 Receptor Antagonist	Antiemetic	Modified restriction to include use by Staff Physicians from the Department of Anesthesiology for treatment of severe PONV non-responsive to multiple pre-emptive and rescue anti-emetics and in patients with severe QT prolongation
Isavuconazole (Cresemba®)	Antifungal	Fungal Infections	Modified restriction to include use by the Department of Hematology/Oncology for antifungal prophylaxis when a preferred antifungal therapy cannot be utilized due to drug-drug interactions or for continuation from home therapy prior to admission
Tocilizumab (Actemra®)	Monoclonal Antibody	COVID-19 associated CRS	Modified restriction to include the Department of Infectious Diseases in COVID-19 positive patients who meet restriction criteria. Specific restriction criteria are included in Lexicomp.

HIT=Heparin-induced thrombocytopenia LVAD= Left ventricular assist device IV=Intravenous PONV=Post-operative nausea and vomiting
COVID-19=Coronavirus disease 2019 CRS=Cytokine release syndrome

Product Standardizations of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Standardization**
Monoclonal Antibody Therapy for COVID-19	Monoclonal Antibody	COVID-19 Infection	Monoclonal Antibody Therapy for COVID-19 will be selected in the following order: 1) Preferred: B/E 2) Secondary: If B/E is not available use C/I
Risedronate/ Ibandronate (Oral)	Bisphosphonate	Osteoporosis	Orders for oral risedronate and oral ibandronate will be converted to alendronate via a therapeutic interchange. Details are in Lexicomp.
Paliperidone (Invega®) (Oral)	Second Generation Antipsychotic	Schizophrenia Schizoaffective Disorder	Oral paliperidone orders will be converted to oral risperidone via a therapeutic interchange. Details are in Lexicomp.
Phenylephrine Nasal Spray	Alpha Adrenergic Agonist	Nasal Congestion	Phenylephrine 0.25%, 0.5%, and 1% nasal sprays will be converted to oxymetazoline 0.05% nasal spray*
Statins	HMG-CoA Reductase Inhibitors	Hypercholesterolemia	All statin therapeutic interchanges will be eliminated in the health-system.
Tetracycline (Oral)	Antibiotic	Various Infections	Orders for oral tetracycline will be converted to oral doxycycline via a therapeutic interchange. Details are in Lexicomp.

*The oxymetazoline 0.05% nasal spray dose will be changed from twice daily to twice daily as needed with a default stop date of 3 days.
COVID-19=Coronavirus disease 2019 B/E=Bamlanivimab/etesevimab C/I=Casirivimab/imdevimab

Removal from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bamlanivimab	Monoclonal Antibody	COVID-19 Infection	Bamlanivimab monotherapy has been removed from the Formulary*
Tetracycline (Oral)	Antibiotic	Various Infections	Therapeutic interchange to doxycycline Please see Product Standardization section

*On April 16, 2021, the FDA revoked EUA approval for bamlanivimab monotherapy due to a sustained increase in SARS-CoV-2 viral variants that are resistant to bamlanivimab alone.
COVID-19= Coronavirus disease 2019

Denial to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Modification for Use**
Tenecteplase (TNKase®)	Thrombolytic Agent	Acute Ischemic Stroke	May NOT be used for the treatment of PE*

*Alteplase is the preferred thrombolytic agent for treatment of pulmonary embolism.
PE=Pulmonary embolism

Process Changes of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Process Change**
Ketamine	General Anesthetic	Severe agitation or analgesia	Dose rounding policy: Doses will be rounded to the nearest 20 mg in the severe agitation protocol and doses will be rounded to the nearest 1 mg in the sub-dissociative dose ketamine protocol

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Artemether/ lumefantrine (Coartem®)	Antimalarial Agent	Malaria	No restrictions
Bortezomib (Velcade®)	Antineoplastic Agent	Antibody-mediated Rejection with Allograft Dysfunction	Restricted to Staff Physicians from the Department of Transplant for the treatment of antibody-mediated rejection with allograft dysfunction
Dexmedetomidine Intranasal (Precedex™)	Alpha$_2$-Adrenergic Agent	Sedative	Restricted to the Department of Pediatric Anesthesiology for pre-operative or pre-procedure use only at Main Campus*
Golimumab (Simponi Aria®)	Monoclonal Antibody	Juvenile Idiopathic and Psoriatic Arthritis	Restricted to the Department of Pediatric Rheumatology for outpatient use only in pediatric patients 2 years and older for polyarticular juvenile idiopathic and psoriatic arthritis
N-acetylcysteine (NAC) Irrigation	Mucolytic	Distal Colonic Irrigation	Modified restrictions to include restricted to Pediatric Surgery for distal colonic irrigation
Onasemnogene abeparvovec-xioi (Zolgensma®)	Gene Therapy	SMA	Restricted to Staff Physicians from the Department of Pediatric Neurology in patients who meet the following criteria: 1) Outpatients < 2 years of age with SMA Type I 2) Only after prior authorization has been obtained from patient's insurance company

*Use will be assessed in 6 months to determine if it can be extended to other sites or outside of the OR (e.g., MRI).
SMA=Spinal muscular atrophy

Removal and Product Standardization of the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Tetracycline (Oral)	Antibiotic	Various Infections	Oral tetracycline was removed from the Formulary. Orders for oral tetracycline will be converted to oral doxycycline via a therapeutic interchange. Details are in Lexicomp.

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bivalirudin (Angiomax®)	Direct Thrombin Inhibitor	HIT	Modified restrictions to include restricted to pediatric patients with a ventricular assist device on ECMO or with HIT All other indications are restricted to the Departments of Pediatric Cardiology or Pediatric Hematology
Budesonide (Entocort® EC)	Corticosteroid	CD UC	Modified restrictions to include restricted to the Department of Pediatric Gastroenterology and Pediatric BMT for initiation of therapy
Ethacrynic Acid (Edecrin®)	Loop Diuretic	Edema	Restricted to patients with a documented severe or anaphylactic allergic reaction to bumetanide, torsemide, or furosemide not currently taking one of those agents prior to admission. In all non-emergency cases, an Allergy Consult should be ordered (at available sites).
Factor VIIa (NovoSeven® RT)	Blood Factor	Bleeding Disorders	Modified restrictions to include restricted to the Department of Pediatric Intensive Care
Moxifloxacin (Avelox®)	Antibiotic	Various Infections	Restricted to the Department of Infectious Diseases for indications including infections caused by *Mycobacteria spp, Nocardia spp, and M. genitalium*
N-acetylcysteine IV (Acetadote®)	Antidote	Hepatotoxicity	Modified restrictions to include restricted to consultation with the Regional Poison Control Center and Staff Physicians from Pediatric Gastroenterology or Pediatric Hepatology for non-acetaminophen-induced related liver failure
Tocilizumab (Actemra®)	Monoclonal Antibody	COVID-19 associated CRS	Modified restriction to include the Department of Infectious Diseases in COVID-19 positive patients who meet criteria. Specific criteria are included in Lexicomp.

HIT=Heparin-induced thrombocytopenia ECMO=Extracorporeal membrane oxygenation CD=Crohn's disease
UC=Ulcerative colitis BMT=Bone marrow transplant IV=Intravenous COVID-19=Coronavirus disease 2019
CRS=Cytokine release syndrome