From hospital to home…

REDEFINE YOUR POSTSURGICAL PAIN MANAGEMENT APPROACH

XARACOLL

The **FIRST** and **ONLY** implant to deliver immediate and long-lasting pain control following open inguinal hernia repair, assisting hospital discharge and recovery at home[1]

INDICATIONS AND USAGE

XARACOLL is indicated in adults for placement into the surgical site to produce postsurgical local analgesia for up to 24 hours following open inguinal hernia repair.

Limitations of Use: Safety and effectiveness have not been established in other surgical procedures, including orthopedic and boney procedures.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Most common adverse reactions in clinical trials (incidence ≥2% and higher than placebo) included incision site swelling, dysgeusia, headache, tremor, blurred vision, seroma, scrotal swelling, pyrexia, oral hypoaesthesia, and post procedural discharge.

Please see complete Important Safety Information on last page and accompanying full Prescribing Information.

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(bupivacaine HCl) implant

ASSESS YOUR KEY CONCERNS IN POSTSURGICAL PAIN MANAGEMENT[2]

INTRAOPERATIVE

OR Time and Resources

- Medication preparation
- Medication application
- Additional personnel/resources needed for nerve blocks

Safety

- Multiple needle exchanges between OR personnel
- Multiple injections & injection sites
- Inadvertent vein/nerve injection

PACU

Patient Outcomes and Experience

- Pain management
- Opioid utilization
- Patient mobility
- Length of stay

POST DISCHARGE

Patient Outcomes and Experience

- Pain management
- Opioid utilization
- Physician callbacks
- Hospital readmissions
- Patient quality of life

A COMMON-SENSE APPROACH TO POSTSURGICAL PAIN RELIEF

Combining proven surgical ingredients of collagen and bupivacaine into the first and only drug/device implant for postsurgical pain management

Type 1 Bovine Collagen

- Proven benefits in wound healing: biodegradable, biocompatible, and forms fibers with high tensile strength and stability[3]

Bupivacaine HCl

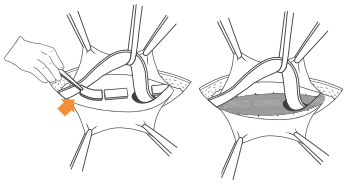
- Commonly used local analgesic with proven efficacy and safety profile[4]

Engineered for OR efficiency with a seamless and safe process from preparation to patient close

Minimal Preparation

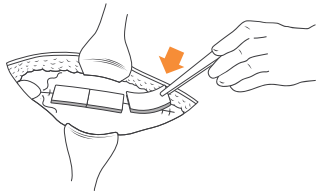
- Package to procedure with no special preparation required
- Provides standardized and consistent dosing[1]

Easy Application



- Minimal time to place implants
- Collapses, conforms, and stays in place in the surgical site[1]
- No additional personnel or resources needed

Additional Implant Benefits



- Needle-free application
- Provides targeted placement of analgesia
- Allows for visual confirmation of where the patient will receive the anesthetic

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Known hypersensitivity to bupivacaine or to any local anesthetic agent of the amide-type or to other components of XARACOLL
- Obstetrical paracervical block anesthesia. The use of bupivacaine in this technique has resulted in fetal bradycardia and death

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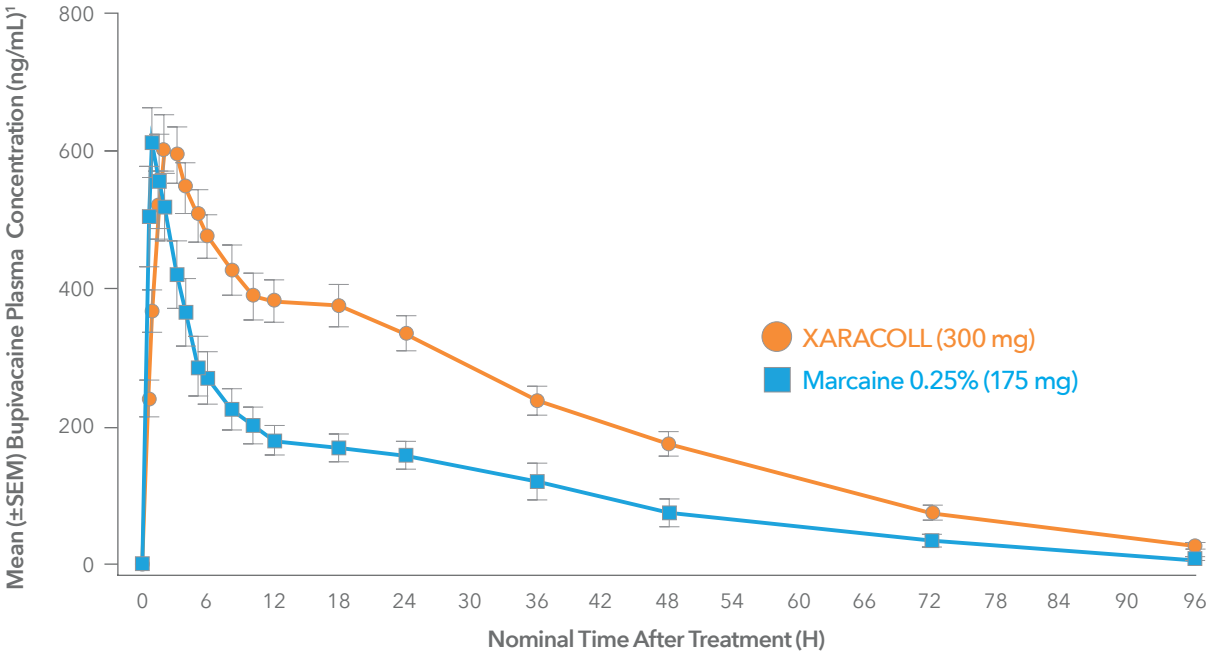
AS FAST ACTING AS MARCAINE®, BUT WITH TWICE THE HALF-LIFE



- XARACOLL bupivacaine plasma levels were detected at the first time point measured (0.5 hours) and through the entire observational period (up to 96 hours)[5]*
- Maximum bupivacaine plasma concentrations seen while patients still in the PACU,† when pain is most severe[5]
- XARACOLL provides an extended release of bupivacaine while the patient is recovering at home[5]

XARACOLL achieves C_{max} in the PACU† and has the longest half-life in hernia repair[5]

Pharmacokinetic Parameter (units)	XARACOLL 300 mg	Marcaine 0.25% 175 mg
T_{max} (h) (Median: minimum, maximum)	3.0 (1.5, 24.0)	1.0 (0.5, 4.0)
$t_{1/2}$ (h) (Mean: SD)	19.0 (5.9)	9.1 (3.8)
C_{max} (ng/mL) (Mean: SD, range)	663.4 (263.8: 274-1230)	641.0 (262.7: 275-1140)

*A multicenter, randomized, single-blind, active comparator-controlled pharmacokinetics study. 52 patients were randomized prior to open inguinal hernioplasty in a 2:1 ratio to receive either 3 x 100 mg XARACOLL bupivacaine HCl collagen implants (total bupivacaine HCl dose 300 mg) or Marcaine® 0.25% (bupivacaine HCl) 175-mg infiltration. The most common treatment-related adverse events reported, experienced by patients across treatments, were tremors (8.8% vs 6.3%), dysgeusia (5.9% vs 6.3%), and somnolence (5.9% vs 6.3%), for patients receiving XARACOLL vs control, respectively.[5] Systemic plasma levels do not correlate with local efficacy.

†In the two pivotal clinical trials for XARACOLL, mean time in the PACU was 3 hours.[1]

C_{max}=maximum (peak) plasma concentration; PACU=post-anesthesia care unit; PK=pharmacokinetics; T_{max}=time to C_{max}; $t_{1/2}$=terminal elimination half-life.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Dose-Related Toxicity:** Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after placement of XARACOLL

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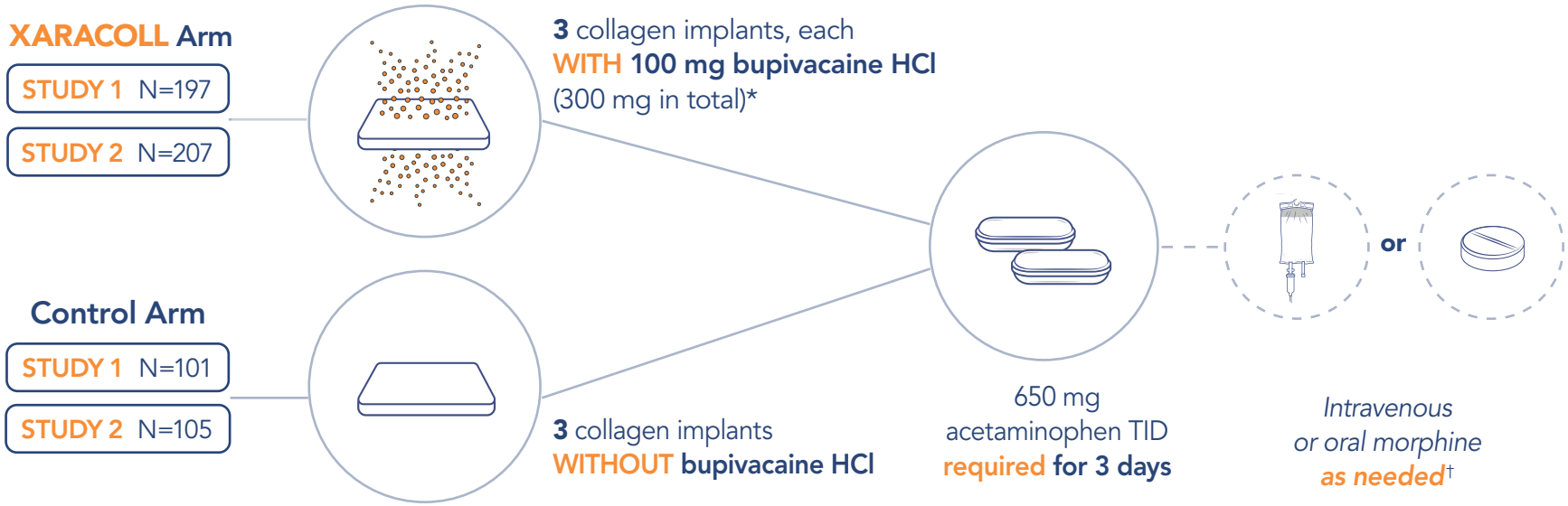
TWO PHASE III STUDIES IN OPEN INGUINAL HERNIOPLASTY

Two Phase III studies of identical design were performed as outpatient surgeries in adults across 39 sites in the US[6]

PATIENT RANDOMIZATION ACROSS BOTH STUDIES (N=610)



PRIMARY ENDPOINT: Time-weighted sum of pain intensity from 0 through 24 hours‡

SECONDARY ENDPOINT: Total use of opioid analgesia (TOpA)

Average discharge time was 3.1 hours post-surgery in both arms of the studies. Patients were required to stay under facility care until 3.0 hours post-surgery.[1]

*Doses above 300 mg per patient have not been studied in clinical trials. †Intravenous morphine provided until patients were able to tolerate oral morphine. ‡Sum of Pain Intensity is an FDA-accepted measurement of pain, calculated by using patient ratings of pain intensity on a 0-10 scale reported at multiple points from baseline over a time period.[6]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Dose-Related Toxicity:** Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after placement of XARACOLL
- **Methemoglobinemia:** Cases of methemoglobinemia have been reported in association with local anesthetic use. See full Prescribing Information for more detail on managing these risks

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PROVEN EFFICACY WHILE UNDER HOSPITAL CARE

In Study 1 and Study 2, XARACOLL patients averaged mild pain intensity in the PACU[1]

Study 1: Mean Pain Intensity
(based on Numerical Rating Scale [NRS])

Time (hours)	1	2	3
XARACOLL	4.0	3.5	3.1
Control	6.0	5.1	4.5

Study 2: Mean Pain Intensity
(based on Numerical Rating Scale [NRS])

Time (hours)	1	2	3
XARACOLL	4.2	3.7	3.1
Control	6.8	5.9	5.1

Study 1: Total Use of Opioid Analgesia
(median IV morphine mg equivalent)

Time (hours)	1	2	3
XARACOLL	0	0	0
Control	1	3	4

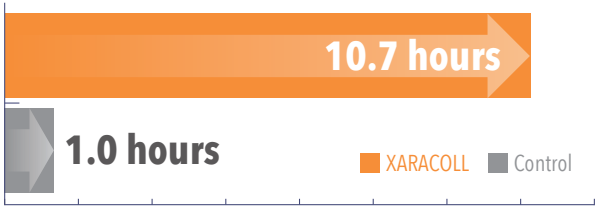
Study 2: Total Use of Opioid Analgesia
(median IV morphine mg equivalent)

Time (hours)	1	2	3
XARACOLL	0	0	0
Control	2	5	6

REDUCED NEED FOR OPIOIDS IN THE PACU

In Study 1 and Study 2, the median time to first opioid use was after discharge for XARACOLL patients[1,6]

Study 1: Median Time to First Opioid Use



Study 2: Median Time to First Opioid Use

IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS

Local Anesthetics: The toxic effects of local anesthetics are additive. Avoid additional local anesthetic administration within 96 hours following XARACOLL implantation. If additional local anesthetic administration with XARACOLL cannot be avoided, monitor patients for neurologic and cardiovascular effects related to local anesthetic systemic toxicity.

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SIGNIFICANT PAIN RELIEF THROUGH 24 HOURS

STUDY 1: XARACOLL patients had a 20% reduction in pain despite using 50% fewer opioids vs control[6]

20%
MEAN REDUCTION IN PAIN INTENSITY*

XARACOLL	Control	*P* Value
85.9	106.8	0.0004

50%
LESS OPIOID USE†

XARACOLL	Control	*P* Value
5 mg	10 mg	<0.0001

STUDY 2: XARACOLL patients had a 24% reduction in pain despite using 64% fewer opioids vs control[6]

24%
MEAN REDUCTION IN PAIN INTENSITY*

XARACOLL	Control	*P* Value
88.3	116.2	<0.0001

64%
LESS OPIOID USE†

XARACOLL	Control	*P* Value
5 mg	14 mg	<0.0001

DATA THROUGH 48 HOURS

STUDY 1: Although not statistically significant, XARACOLL patients had an 11% reduction in pain despite using 64% fewer opioids vs control[6]

11%
MEAN REDUCTION IN PAIN INTENSITY

XARACOLL	Control	*P* Value
179.3	201.3	0.0568

64%
LESS OPIOID USE†

XARACOLL	Control	*P* Value
5 mg	14 mg	—‡

STUDY 2: XARACOLL patients had an 11% reduction in pain despite using 50% fewer opioids vs control[6]

11%
MEAN REDUCTION IN PAIN INTENSITY

XARACOLL	Control	*P* Value
192.6	216.8	0.0270

50%
LESS OPIOID USE†

XARACOLL	Control	*P* Value
10 mg	20 mg	0.0003

*Primary endpoint. †Median IV morphine mg equivalent. ‡Statistical significance not tested based on statistical sequential testing algorithm.[6]

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Known hypersensitivity to bupivacaine or to any local anesthetic agent of the amide-type or to other components of XARACOLL
- Obstetrical paracervical block anesthesia. The use of bupivacaine in this technique has resulted in fetal bradycardia and death

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PATIENTS REQUIRING NO OPIOIDS FROM 0 TO 72 HOURS

In two clinical studies, up to 36% of XARACOLL patients did not need opioids through 72 hours[6]

STUDY 1

Patients NOT USING Opioids (%)

36% XARACOLL

22% Control

STUDY 2

Patients NOT USING Opioids (%)

28% XARACOLL

12% Control

WARNINGS AND PRECAUTIONS

- **Dose-Related Toxicity:** Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after placement of XARACOLL
- **Methemoglobinemia:** Cases of methemoglobinemia have been reported in association with local anesthetic use. See full Prescribing Information for more detail on managing these risks

IMPORTANT SAFETY INFORMATION

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal data, may cause fetal harm
- **Moderate to Severe Hepatic Impairment:** Consider increased monitoring for bupivacaine systemic toxicity

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SAFETY PROFILE IN PHASE III STUDIES

Adverse reactions with incidence ≥2% and greater than control

- All adverse reactions were deemed mild to moderate, with no significant differences seen between treatments

	XARACOLL (N=411) n (%)	Control* (N=208) n (%)
Subjects Reporting Treatment Emergent Adverse Events	**256 (62.3)**	**143 (68.8)**
Injury, Poisoning, and Procedural Complications		
Incision site swelling	60 (14.6)	30 (14.4)
Post procedural discharge	20 (4.9)	10 (4.8)
Seroma	12 (2.9)	5 (2.4)
Nervous System Disorders		
Dysgeusia	31 (7.5)	13 (6.3)
Headache	17 (4.1)	1 (0.5)
Tremor	15 (3.6)	6 (2.9)
Gastrointestinal Disorders		
Hypoaesthesia oral	9 (2.2)	4 (1.9)
Reproductive System and Breast Disorders		
Scrotal swelling	12 (2.9)	2 (1.0)
General Disorders and Administration Site Conditions		
Pyrexia	10 (2.4)	1 (0.5)
Eye Disorders		
Vision blurred	15 (3.6)	6 (2.9)

Adverse events frequently associated with opioid use[1]

ORADE	XARACOLL (N=411) n (%)	Control* (N=208) n (%)	*P* value
Nausea	39 (10)	34 (16)	0.017
Constipation	35 (9)	31 (15)	0.019
Vomiting	9 (2)	10 (5)	0.086

*Control consisted of three collagen implants.
ORADE=opioid-related adverse drug event.

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ADVERSE REACTIONS

Most common adverse reactions in clinical trials (incidence ≥2% and higher than placebo) included incision site swelling, dysgeusia, headache, tremor, blurred vision, seroma, scrotal swelling, pyrexia, oral hypoaesthesia, and post procedural discharge.

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XARACOLL

The **FIRST** and **ONLY** implant to deliver immediate and long-lasting pain control following open inguinal hernia repair, assisting hospital discharge and recovery at home[1]

Minimal preparation and standardized dosing to optimize time in the operating room[1]

Proven rapid-acting pain relief in the PACU, when pain is most severe[1]

Proven long-acting pain relief after discharge, helping patients recover and get back to everyday activities[6]

INDICATIONS AND USAGE

XARACOLL is indicated in adults for placement into the surgical site to produce postsurgical local analgesia for up to 24 hours following open inguinal hernia repair.

Limitations of Use

Safety and effectiveness have not been established in other surgical procedures, including orthopedic and boney procedures.

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PRICING, REIMBURSEMENT, AND ORDERING

ASC REIMBURSEMENT

Certified Medicare ASCs are eligible to receive separate payment for XARACOLL under the ASC payment system as a non-opioid pain management drug that functions as a surgical supply for the 2022 calendar year.

The reimbursement amount for XARACOLL will be the Average Selling Price (ASP) plus 6%, subject to any CMS adjustments, when utilizing the product-specific billing code of C9089.

Wholesale Acquisition Cost

$234 per procedure

XARACOLL can be ordered using standard ordering procedures through your wholesaler for next-day delivery.

- **AmerisourceBergen Corporation: (844) 222-2273**
- **Cardinal Health: (800) 926-3161**
- **Cardinal Health Specialty Distribution: (866) 677-4844**
- **McKesson Customer Support for Hospitals: (855) 625-7385**
- **McKesson Med-Surge: (855) 571-2100**

NDC NUMBERS

4 units: 51715-100-04

10 units: 51715-100-10

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To report SUSPECTED ADVERSE REACTIONS, contact Innocoll at 1-833-606-1421 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

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REFERENCES: 1. Data on File. Innocoll Pharmaceuticals Limited. **2.** Innocoll Hospital Pharmacist Advisory Board; December 2021. **3.** Chattopadhyay S, Raines RT. Collagen-based biomaterials for wound healing. *Biopolymers*. 2014;101(8):821-833. **4.** LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Amide Local Anesthetics. [Updated 2017 Jul 5]. **5.** Leiman D, Niebler G, Minkowitz H. Pharmacokinetics and safety of the bupivacaine collagen-matrix implant (INL-001) compared to liquid bupivacaine infiltration after open inguinal hernia repair. Poster presented at: World Congress on Regional Anesthesia & Pain Medicine; April 19-21, 2018; New York, NY. Accessed July 30, 2020. https://epostersonline.com/ASRAWORLD18/node/1154 **6.** Velanovich V, Rider P, Deck K, et al. Safety and efficacy of bupivacaine HCl collagen-matrix implant (INL-001) in open inguinal hernia repair: results from two randomized controlled trials. *Adv Ther.* 2019;36(1):200-216.

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