SPRIX®
(ketorolac tromethamine)
Nasal Spray
15.75 mg per spray

The non-narcotic intranasal NSAID that provides opioid-level pain relief[1]

Ketorolac strength in the speed of a spray[2]

Efficacy within 20–30 minutes[2,3]

NSAID = nonsteroidal anti-inflammatory drug.

Indications and Usage

SPRIX® (ketorolac tromethamine) is indicated in adult patients for the short term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level.

Limitations of Use

- SPRIX is not for use in pediatric patients less than 2 years of age.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDS) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.**
- **SPRIX® is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDS cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.**

Use SPRIX at the lowest effective dosage for shortest duration consistent with individual patient treatment goals.

Please see Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

Powerful pain relief where it's needed[1]

Address your patients' moderate to moderately severe acute pain treatment needs (up to 5 days) by putting SPRIX® (ketorolac tromethamine) in their hands, allowing them to self-administer at home.[2,4]

Non-Narcotic NSAID Providing Opioid-Level Analgesia[1]

- **Monotherapy or Combination Therapy[1,2]**
  May be used on its own or concomitantly with current opioid treatment plan
- **Opioid Sparing[1]**
  Patients using SPRIX use significantly less opioid (morphine)
- **Acute Injuries[5]**
  Pain relief for multiple areas
- **Postprocedure Acute Pain[1,2]**
  Part of treatment plan

SPRIX may provide relief from acute pain across multiple pain areas.*

NEUROLOGY	PODIATRY	ORTHOPEDICS
PAIN MANAGEMENT	UROLOGY	GYNECOLOGY

*See a complete list of therapeutic areas in which SPRIX may help patients on attached insert.

Prescribe SPRIX—ketorolac strength in the speed of a spray[2]

Efficacy within 20–30 minutes[2,3]

IMPORTANT SAFETY INFORMATION

Contraindications

SPRIX is contraindicated in the following patients:

- Known hypersensitivity to ketorolac or any components of the drug product.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
- In the setting of coronary artery bypass graft (CABG) surgery.
- Use in patients with active peptic ulcer disease or with recent gastrointestinal bleeding or perforation.
- Use as a prophylactic analgesic before any major surgery.

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Rapid absorption similar to IM ketorolac[4]

SPRIX®
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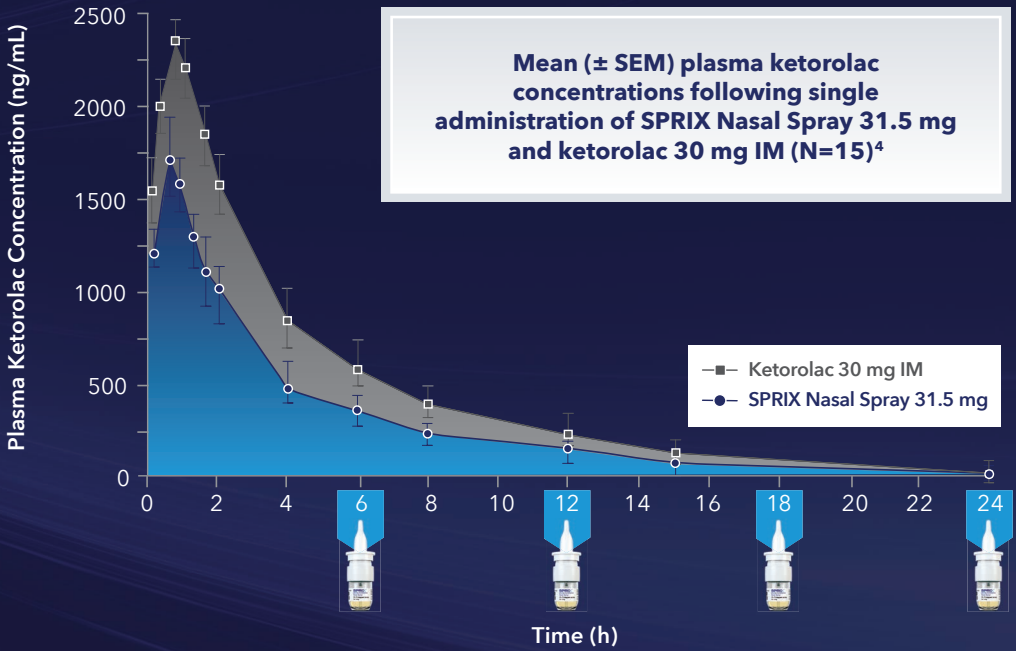
SPRIX achieved time to maximum plasma concentration (T_{max}) in 45 minutes, similar to IM ketorolac[1,4]



Clinical relevance of the pharmacokinetic (PK) data is unknown

- SPRIX is rapidly absorbed through the nasal mucosa[4]
- Intranasal dosing demonstrated that most of the ketorolac was deposited into the nasal cavity and pharynx[1]
- <20% is deposited into the esophagus and stomach[1]

Study design: A phase 1, single-dose, 5-way crossover, randomized study (N=15) of healthy volunteers consisting of 5 periods of identical design, differing only in the allocated treatment and examination of the nares. In all periods, serial blood samples were taken up to 24 hours postdose. SPRIX has been studied in patients with allergic rhinitis before and after administration of fluticasone and oxymetazoline. Neither medicine had any clinically significant effect on the PK characteristics of SPRIX.[1,4]

Graphic adapted with permission from McAleer et al.[4]

IM = intramuscular; SEM = standard error of the mean.

IMPORTANT SAFETY INFORMATION

Contraindications (cont'd)

- Use in patients with advanced renal disease or patients at risk for renal failure due to volume depletion.
- Use in labor and delivery. May adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.
- Use in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, or those for whom hemostasis is critical.
- Concomitant use with probenecid or pentoxifylline.

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Help manage moderate to moderately severe pain across multiple pain areas

NEUROLOGY

ACUTE PAIN FLARE/ EXACERBATION	POSTPROCEDURAL/ SURGICAL PAIN
Headache pain	Lumbar puncture
Neck pain	Craniotomy
Back pain	Spinal surgery

UROLOGY

ACUTE PAIN FLARE/ EXACERBATION	POSTPROCEDURAL/ SURGICAL PAIN
Kidney stones	Penile implants
Interstitial cystitis	Vasectomy
Epididymitis	Prostate surgery
	TURP
	Cystoscopy
	Urolift (prostate lift)
	Laser lithotripsy

PAIN MANAGEMENT

ACUTE PAIN FLARE/ EXACERBATION	INTERVENTIONAL PROCEDURES
Muscle pain	Radiofrequency ablation
Neck pain	Medial branch block
Back pain	Facet joint injection
Knee pain	Spinal cord stimulator adjustment
Headache pain	

PODIATRY

ACUTE PAIN FLARE/ EXACERBATION	POSTPROCEDURAL/ SURGICAL PAIN
Plantar fasciitis	Bunionectomy
Achilles heel tendon	Hammertoe
Bursitis	
Gout	

GYNECOLOGY

ACUTE PAIN FLARE/ EXACERBATION	POSTPROCEDURAL/ SURGICAL PAIN
Dysmenorrhea	Insertion or removal of an IUD or birth control implant
Endometriosis	Hysterectomy
Headache pain	Pelvic reconstruction
	Endometrial ablation
	Loop electrosurgical excision procedure

ORTHOPEDICS

ACUTE PAIN FLARE/ EXACERBATION	POSTPROCEDURAL/ SURGICAL PAIN
Back pain	Joint replacement
Neck pain	Arthroscopy
Muscle pain	Repair or bone fractures
	Spinal surgery

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Indications and Usage

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- **NSAIDS cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.**

Use SPRIX at the lowest effective dosage for shortest duration consistent with individual patient treatment goals.

Proven pain relief...[1,2]

SPRIX® (ketorolac tromethamine) significantly reduced pain versus placebo[3]

STUDY 1†
Postabdominal or orthopedic surgery

difference in summed pain intensity over 48 hours[1,6]

SPRIX 31.5 mg + morphine (n=199)
vs placebo + morphine (n=101)[2]

STUDY 2‡
Postabdominal surgery

difference in summed pain intensity over 48 hours[1,6]

SPRIX 31.5 mg + morphine (n=214)
vs placebo + morphine (n=107)[3]

Study 1: SPID48 Score [mean (SE)]: SPRIX 1646 (52.4) vs placebo 1374 (60.0).[6]
Study 2: SPID48 Score [mean (SE)]: SPRIX 1309 (73.2) vs placebo 1105 (113.5).[6]
SE = standard error; SPID48 = Summed Pain Intensity Difference over 48 hours.[6]

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hepatotoxicity: Elevations of ALT or AST have been reported in patients with NSAIDs. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported. Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue immediately if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop.

Hypertension: NSAIDs, including SPRIX, can lead to new onset or worsening of preexisting hypertension. Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

Heart Failure and Edema: Avoid use of SPRIX in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. If SPRIX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Please see Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

...with less opioid use[1,3]

Patients using SPRIX required less morphine than patients taking placebo over 48 hours[2,3]

SPRIX® (ketorolac tromethamine) Nasal Spray
15.75 mg per spray

STUDY 1†

less opioid[1,2]

SPRIX 31.5 mg + morphine (n=199) vs placebo + morphine (n=101)[2]

STUDY 2‡

less opioid[1,3]

SPRIX 31.5 mg + morphine (n=214) vs placebo + morphine (n=107)[3]

†Study 1 design: A phase 3, randomized, double-blind, placebo-controlled study to evaluate the analgesic efficacy and tolerability of single- and multiple-dose SPRIX in patients undergoing major abdominal or orthopedic surgery remaining in hospital for 2-5 days. Patients were randomly assigned in a 2:1 ratio to receive SPRIX 30 mg or matching placebo following surgery (day 0). All patients had access to MS via PCA beginning on day 0. The study was designed with a multidose regimen of SPRIX 30 mg or matching placebo administered 3 times per day for up to 5 days. Backup analgesia was permitted. Total hysterectomies were the majority of abdominal surgery procedures (87%). Hip replacements were the most common orthopedic procedure (72%). Other procedures were ovarian cystectomy, laminectomy, rotator cuff repair, fracture reduction and fixation, salpingo-oophorectomy, breast reconstruction, appendectomy, and knee and ankle replacement. Morphine use reduction was a secondary endpoint.[2]

‡Study 2 design: A phase 3, randomized, double-blind, placebo-controlled study to evaluate the analgesic efficacy and tolerability of SPRIX use after abdominal surgery. Adult patients were randomly assigned to receive SPRIX 31.5 mg (n=214) or placebo (n=107).[3]

MS=morphine sulfate; PCA=patient-controlled analgesia.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

Renal Toxicity and Hyperkalemia: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury and may cause a dose-dependent reduction in prostaglandin formation, which may precipitate overt renal decompensation. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of SPRIX in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function.

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs.

Exacerbation of Asthma Related to Aspirin Sensitivity: SPRIX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without known aspirin sensitivity).

Dosing[1]

Adult patients < 65 years of age:

The recommended dose is

2 **SPRAYS** (1 spray in EACH nostril)

31.5 mg = 15.75 mg spray in each nostril

Patients ≥ 65 years of age, renally impaired patients, and adult patients less than 110 lb:

The recommended dose is

1 **SPRAY** (1 spray in ONLY ONE nostril)

15.75 mg

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. SPRIX® (ketorolac tromethamine) should be administered every 6 to 8 hours. The maximum daily dose is 126 mg (4 doses).

Remember: Patients should spray, not sniff or inhale SPRIX. Use of SPRIX may result in nasal discomfort.

Ensure patients refer to the complete instructions for use that accompany each prescription.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

Serious Skin Reactions: NSAIDs, including SPRIX, can cause serious skin adverse reactions, which can be fatal. These serious events may occur without warning. Discontinue SPRIX at the first appearance of skin rash or any other sign of hypersensitivity.

Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation.

Please see Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

Safety profile

SPRIX® (ketorolac tromethamine) Nasal Spray 15.75 mg per spray

SPRIX was studied in patients enrolled in safety and efficacy studies of acute pain following major surgery[1]

	SPRIX (n=455)	Placebo (n=245)
Nasal discomfort	15%	2%
Rhinalgia	13%	<1%
Lacrimation increased	5%	0%
Throat irritation	4%	<1%
Oliguria	3%	1%
Rash	3%	<1%
Bradycardia	2%	<1%
Urine output decreased	2%	<1%
ALT and/or AST increased	2%	1%
Hypertension	2%	1%
Rhinitis	2%	<1%

ALT = alanine transaminase; AST = aspartate transaminase.

Postoperative patients with adverse reactions observed at a rate of ≥ 2% and at least twice the incidence of the placebo group

- The most frequently reported adverse reactions were related to local symptoms (eg, nasal discomfort or irritation). These reactions were generally mild and transient in nature[1]
- In controlled clinical studies, 1.5% of patients treated with SPRIX experienced serious adverse events of bleeding or hematoma at the operative site vs 0.4% treated with placebo (hematoma)[1]
- The total duration of use of SPRIX or any other ketorolac formulation must not exceed 5 days[1]

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

Hematologic Toxicity: Anemia has occurred in patients treated with NSAIDs. Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. Do not use SPRIX in patients for whom hemostasis is critical.

Limitations of Use: The total duration of use of SPRIX alone or sequentially with other forms of ketorolac is not to exceed 5 days. SPRIX should not be used concomitantly with other forms of ketorolac, aspirin, or other NSAIDs.

Adverse Reactions

The most common adverse reactions (incidence ≥2%) in patients treated with SPRIX and occurring at a rate at least twice that with placebo include: nasal discomfort; rhinalgia; increased lacrimation; throat irritation; oliguria; rash; bradycardia; decreased urine output; increased ALT and/or AST; hypertension; rhinitis.

Instructions to patients regarding SPRIX administration[1]

Spray, don't sniff or inhale SPRIX® (ketorolac tromethamine). Use of SPRIX may result in nasal discomfort.

Figure A

PREPARE[1]

Before you use SPRIX for the first time, you will need to prime the bottle. Hold the finger flange with your fingers (see Figure A), and remove the clear plastic cover with your opposite hand. Keep the clear plastic cover for later. Remove and throw away the blue plastic safety clip.

Figure B

POSITION[1]

If the clear plastic cover is improperly removed, the tip of the bottle may be pulled off of the glass vial. If this happens, place the tip back onto the glass vial by lining it up carefully and gently pushing it back on until it is back in the correct position (see Figure B). The SPRIX bottle should work properly again.

Ensure patients refer to the complete INSTRUCTIONS FOR USE that accompany each prescription.

- Spray, don't sniff or inhale SPRIX. Use of SPRIX may result in nasal discomfort
- Use as directed. If 1 spray is prescribed, only spray into your right nostril. However, if 2 sprays are prescribed, you should repeat the steps for your left nostril
- Be sure to point the spray away from the center of your nose
- When you are finished using SPRIX, replace the clear plastic cover and place the bottle in a cool, dry location out of direct sunlight, such as inside a medication cabinet. Keep out of reach of children

IMPORTANT SAFETY INFORMATION

Drug Interactions

Drugs that interfere with hemostasis: increased risk of serious bleeding with use of anticoagulants, antiplatelet agents, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs); concomitant use with pentoxifylline is contraindicated. Monitor patients for bleeding who are concomitantly taking SPRIX with drugs that interfere with hemostasis.

ACE inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers: may diminish the antihypertensive effect of these drugs; monitor blood pressure.

ACE Inhibitors and ARBs: In elderly, volume depleted, or those with renal impairment may result in deterioration of renal function; monitor for signs of worsening renal function.

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Ketorolac strength in the speed of a spray[2,3]

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Efficacy within 20–30 minutes[2,3]

Figure C

PRIME[1]

Hold the SPRIX bottle upright at arm's length away from you with your index finger on top of the finger flange and your thumb supporting the base (see Figure C). Press down on the finger flange and release the pump 5 times. You may not see spray the first few times you press down. Now the pump is primed and ready to use. You do not need to prime the pump again if you use more doses from this bottle.

Figure D

PUMP[1]

It is important to get the medication to the correct place in the nose so it will be most effective.

- Blow nose gently to clear nostrils
- Sit up straight or stand. Tilt head slightly forward
- Insert the tip of the container into your right nostril
- Point the container away from the center of your nose (see Figure D)
- Hold your breath and spray once into your right nostril, pressing down evenly on both sides of the finger flange
- Immediately after administration, resume breathing through mouth to reduce expelling the product. Also, pinch the nose to help retain the spray if it starts to drip

If only 1 spray per dose is prescribed, administration is complete. Place the clear plastic cover back on the SPRIX bottle. If a dose of 2 sprays is prescribed, repeat the process in Step 4 for your left nostril. Again, be sure to point the spray away from the center of your nose. Spray once into your left nostril. Once administration is complete, place the clear plastic cover back on the SPRIX bottle.

Watch the instructional video at SPRIX.com/patient

IMPORTANT SAFETY INFORMATION

Drug Interactions (cont'd)

Diuretics: reduces the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. During concomitant use of SPRIX with diuretics look for signs of worsening renal function and assure diuretic efficacy and antihypertensive effects.

Digoxin: has been reported to increase the serum concentration and prolong the half-life of digoxin, monitor serum digoxin levels.

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Contraindications

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- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
- In the setting of coronary artery bypass graft (CABG) surgery.
- Use in patients with active peptic ulcer disease or with recent gastrointestinal bleeding or perforation.
- Use as a prophylactic analgesic before any major surgery.
- Use in patients with advanced renal disease or patients at risk for renal failure due to volume depletion.
- Use in labor and delivery. May adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.
- Use in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, or those for whom hemostasis is critical.
- Concomitant use with probenecid or pentoxifylline.

Warnings and Precautions

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Hypertension: NSAIDs, including SPRIX, can lead to new onset or worsening of preexisting hypertension. Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

Heart Failure and Edema: Avoid use of SPRIX in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. If SPRIX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity and Hyperkalemia: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury and may cause a dose-dependent reduction in prostaglandin formation, which may precipitate overt renal decompensation. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of SPRIX in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function.

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs.

Exacerbation of Asthma Related to Aspirin Sensitivity: SPRIX is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without known aspirin sensitivity).

Serious Skin Reactions: NSAIDs, including SPRIX, can cause serious skin adverse reactions, which can be fatal. These serious events may occur without warning. Discontinue SPRIX at the first appearance of skin rash or any other sign of hypersensitivity.

Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation.

Hematologic Toxicity: Anemia has occurred in patients treated with NSAIDs. Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. Do not use SPRIX in patients for whom hemostasis is critical.

Limitations of Use: The total duration of use of SPRIX alone or sequentially with other forms of ketorolac is not to exceed 5 days. SPRIX should not be used concomitantly with other forms of ketorolac, aspirin, or other NSAIDs.

Adverse Reactions

The most common adverse reactions (incidence ≥2%) in patients treated with SPRIX and occurring at a rate at least twice that with placebo include: nasal discomfort; rhinalgia; increased lacrimation; throat irritation; oliguria; rash; bradycardia; decreased urine output; increased ALT and/or AST; hypertension; rhinitis.

Drug Interactions

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Digoxin: has been reported to increase the serum concentration and prolong the half-life of digoxin, monitor serum digoxin levels.

Use in Specific Populations

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation.

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of SPRIX in women who have difficulties conceiving.

Please see full Prescribing Information on SPRIX.com, including BOXED WARNING and MEDICATION GUIDE.

To report SUSPECTED ADVERSE REACTIONS, contact Assertio Therapeutics, Inc. at 866-458-6389 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Only available through Scripts Rx (formerly Mall Pharmacy)

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It's simple to enroll your patients in Scripts Rx. Two ways to get started:

Fax completed Scripts Rx form to **(844) 794-7275**. Write clearly to help automate processing so the prescription will reach your patients faster.

Locate Scripts Rx in your EMR system by searching:

Address	7515 Main St, Suite 180 Houston, TX 77030
NCPDP/NABP	5922595
NPI	114 473 0995

What you can expect when you fulfill through Scripts Rx[¶]

- $0 copay for commercially eligible patients (non-government)
- No prior authorization completion is required for commercially eligible patients
- Prescription delivered quickly and without contact to your patient's home
- Registered pharmacist available for 24-hour pharmacy support

[¶]Terms and conditions may apply.

Please see Important Safety Information throughout and accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

References: 1. SPRIX [Prescribing Information]. Wayne, PA: Zyla Life Sciences US Inc.; 2019. **2.** Brown C, Moodie J, Bisley E, Bynum L. Intranasal ketorolac for postoperative pain: a phase 3, double-blind, randomized study. *Pain Med.* 2009;10(6):1106-1114. **3.** Singla N, Singla S, Minkowitz HS, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. *Curr Med Res Opin.* 2010;26(8):1915-1923. **4.** McAleer SD, Majid O, Venables E, Polack T, Sheikh MS. Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. *J Clin Pharmacol.* 2007;47(1):13-18. **5.** Watts K, Balzer S, Drum M, et al. Ibuprofen and acetaminophen versus intranasal ketorolac (Sprix) in an untreated endodontic pain model: a randomized, double-blind investigation. *J Endod.* 2019;45(2):94-98. **6.** Data on file. Assertio Therapeutics, Inc.

ASSERTIO

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