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## PRESCRIBING ALERT<sup>®</sup>

Dear Healthcare Professional,

At MPR we strive to bring you important drug information in a concise and timely fashion. In keeping with this goal, we are pleased to bring you this PRESCRIBING ALERT for SPRIX<sup>®</sup> (ketorolac tromethamine) Nasal Spray, from [Regency Therapeutics](#), division of [Luitpold Pharmaceuticals, Inc.](#)

SPRIX<sup>®</sup> is an intranasal NSAID 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. SPRIX<sup>®</sup> demonstrated clinical efficacy in 2 multi-center, randomized, double-blind, placebo-controlled studies. Patients showed significant pain reduction with postoperative pain, resulting in less morphine use. The most common adverse reactions among postoperative patients were nasal discomfort and irritation.<sup>1</sup>

### IMPORTANT SAFETY INFORMATION

**WARNING: LIMITATIONS OF USE, GASTROINTESTINAL, BLEEDING, CARDIOVASCULAR, and RENAL RISK**

**Limitations of Use**—SPRIX<sup>®</sup> (ketorolac tromethamine) Nasal Spray, a nonsteroidal anti-inflammatory drug (NSAID), is indicated for short-term (up to 5 days in adults) management of moderate to moderately severe pain that requires analgesia at the opioid level. Do not exceed a total combined duration of use of SPRIX<sup>®</sup> and other ketorolac formulations (IM/IV or oral) of 5 days.

SPRIX<sup>®</sup> is not indicated for use in pediatric patients and it is not indicated for minor or chronic painful conditions.

**Gastrointestinal Risk**—Ketorolac tromethamine, including SPRIX<sup>®</sup>, can cause peptic ulcers, gastrointestinal bleeding and/or perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Therefore, SPRIX<sup>®</sup> is **contraindicated** in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. Elderly patients are at greater risk for serious gastrointestinal events.

**Bleeding Risk**—Ketorolac tromethamine inhibits platelet function and is, therefore, **contraindicated** in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding.

**Cardiovascular Risk**—NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

SPRIX<sup>®</sup> is **contraindicated** for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

**Renal Risk**—SPRIX<sup>®</sup> is **contraindicated** in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion.

SPRIX<sup>®</sup> is contraindicated in patients with known hypersensitivity or history of asthma, urticaria, or other allergic-type reactions to aspirin, ketorolac, other NSAIDs or EDTA. However, anaphylactoid reactions may occur in patients with or without a history of allergic reactions to aspirin or NSAIDs. SPRIX<sup>®</sup> is contraindicated in patients as a prophylactic analgesic prior to major surgery; or in labor, delivery, or nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates.

*(Important Safety Information continued on next page)*

SPRIX® (ketorolac tromethamine) Nasal Spray should not be used concomitantly with IM/IV or oral ketorolac, aspirin, or other NSAIDs, or with probenecid or pentoxifylline. When ketorolac is administered with aspirin, its protein binding is reduced, although the clearance of free ketorolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of SPRIX® and aspirin is not generally recommended because of the potential of increased adverse effects.

Do not use SPRIX® in patients for whom hemostasis is critical.

Clinical studies, as well as postmarketing observations, have shown that ketorolac can reduce the natriuretic effect of furosemide and thiazides in some patients.

Concomitant use of ACE inhibitors and/or angiotensin II receptor antagonists may increase the risk of renal impairment, particularly in volume-depleted patients. NSAIDs may diminish the antihypertensive effect of ACE inhibitors and/or angiotensin II receptor antagonists. Consider this interaction in patients taking SPRIX® concomitantly with ACE inhibitors and/or angiotensin II receptor antagonists.

Ketorolac can cause serious GI adverse events including bleeding, ulceration, and perforation. Elderly patients are at increased risk for serious GI events.

Use SPRIX® with caution in patients with impaired hepatic function or a history of liver disease.

The pharmacologic activity of SPRIX® in reducing inflammation and fever may diminish the utility of these diagnostic signs in detecting infections.

Avoid contact of SPRIX® with the eyes. If eye contact occurs, wash out the eye with water or saline, and consult a physician if irritation persists for more than an hour.

Ketorolac can cause renal injury. SPRIX® should be used with caution in patients with advanced renal disease or patients at risk for renal failure due to volume depletion and should be used with caution in patients taking diuretics or ACE inhibitors. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury such as interstitial nephritis and nephrotic syndrome.

NSAIDs can cause serious dermatologic adverse reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which can be fatal. These serious events may occur without warning. SPRIX® should be discontinued immediately in patients with skin reactions.

During pregnancy, use of SPRIX® beyond 30 weeks' gestation can cause premature closure of the ductus arteriosus, resulting in fetal harm (Pregnancy Category D). Prior to 30 weeks' gestation, SPRIX® should be used during pregnancy only if potential benefit justifies the potential risk to the fetus (Pregnancy Category C).

NSAIDs can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. Fluid retention, edema, retention of NaCl, oliguria, and elevations of serum urea nitrogen and creatinine have been reported in clinical trials with ketorolac. Only use SPRIX® very cautiously in patients with cardiac decompensation or similar conditions.

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

Treat patients for the shortest duration possible, and do not exceed 5 days of therapy with SPRIX®.

**Please see the Important Safety Information and complete [Prescribing Information](#), including **Boxed Warning**.** For additional information, please call 1-888-354-4855 or visit [www.sprix.com](http://www.sprix.com).

More information about the use of SPRIX® is available in the current edition of *MPR*.

Sincerely,



Madonna Krawczyk, PharmD  
Director of Clinical Communications  
MPR Custom Programs

## REFERENCE

1. SPRIX® [package insert]. Shirley, NY: Regency Therapeutics; 2011.

SP047  
Iss. 9/2011

# SPRIX®

## (ketorolac tromethamine) Nasal Spray

15.75 mg per spray

Rx

**WARNING: LIMITATIONS OF USE, GASTROINTESTINAL, BLEEDING, CARDIOVASCULAR, and RENAL RISK**

See full prescribing information for complete boxed warning.

**Limitations of Use** – The total duration of use of SPRIX® and other ketorolac formulations should not exceed 5 days.

**Gastrointestinal (GI) Risk** – Ketorolac can cause peptic ulcers, GI bleeding, and/or perforation of the stomach or intestines, which can be fatal. SPRIX® is CONTRAINDICATED in patients with peptic ulcer disease or history of GI bleeding.

**Bleeding Risk** – SPRIX® inhibits platelet function and is CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, or high risk of bleeding.

**Cardiovascular (CV) Risk** – NSAIDs may cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with CV disease or risk factors for CV disease may be at greater risk. SPRIX is CONTRAINDICATED for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

**Renal Risk** – SPRIX® is CONTRAINDICATED in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion.

**Company:** Regency Therapeutics

**Pharmacologic Class:** NSAID (pyrrolo-pyrrole)

**Active Ingredient:** Ketorolac tromethamine 15.75mg; per 100 µL nasal spray; contains EDTA.

**Indications:** For the short-term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level.

**Adults:** ≥18yrs: 1 spray in each nostril (total dose: 31.5 mg) every 6-8 hrs; max daily dose 126 mg (4 doses). ≥65yrs, renally-impaired, or <50 kg: 1 spray in one nostril (total dose: 15.75 mg) every 6-8 hrs; max daily dose 63 mg (4 doses). Discard used bottle after 24 hrs.

**Children:** <18yrs: Not approved.

**Contraindications:** Active peptic ulcer, recent GI bleed or perforation, history of peptic ulcer or GI bleeding. Cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, or for whom hemostasis is critical. History of asthma, urticaria, aspirin allergy. Pre-op major surgery. CABG surgery. Advanced renal disease or at risk for renal failure due to volume depletion. EDTA allergy. Concomitant probenecid, pentoxifylline. Labor & delivery. Nursing mothers.

**Warnings/Precautions:** Increased risk of GI, bleeding, cardiovascular, or renal effects. Inflammatory bowel disease (eg, ulcerative colitis, Crohn's disease). Hypertension. CHF. Edema. Coagulation disorders. Post-op where hemostasis is critical. Maintain adequate hydration. Impaired heart, renal, or liver function. Avoid spraying into eyes. Debilitated. Elderly. Pregnancy (Cat.C prior to 30 weeks' gestation; Cat.D starting at 30 weeks' gestation).




*Intranasal NSAID for moderate to moderately severe pain*

**Interactions:** See Contraindications. Do not use concomitantly with other formulations of ketorolac or other NSAIDs. Increased risk of bleeding with concomitant anticoagulants, SSRIs. May diminish effects of furosemide, thiazides, ACE inhibitors, angiotensin II receptor antagonists. Possible seizures with phenytoin, carbamazepine. Possible hallucinations with fluoxetine, thiothixene, alprazolam. Monitor for lithium, methotrexate toxicity. Caution with nondepolarizing muscle relaxants (apnea).

**Adverse Reactions:** Nasal discomfort, rhinalgia, increased lacrimation, throat irritation, oliguria, rash, bradycardia, decreased urine output, increased ALT/AST, hypertension, rhinitis; GI bleed/ulceration/perforation (discontinue if occurs), anaphylactoid reactions, serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis; may be fatal), severe hepatic reactions (eg, jaundice, fulminant hepatitis, liver necrosis, hepatic failure; discontinue if develops), severe renal effects (eg, renal papillary necrosis, interstitial nephritis, nephrotic syndrome; with long-term use). See literature re: risk of cardiovascular events.

**How Supplied:** Single-day nasal spray bottle (8 sprays/1.7 g bottle)—Boxes with 5 bottles

 **A non-narcotic option for patients who require analgesia at the opioid level**

- SPRIX® 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<sup>1</sup>

*Please see the Important Safety Information and complete Prescribing Information, including Boxed Warning.*

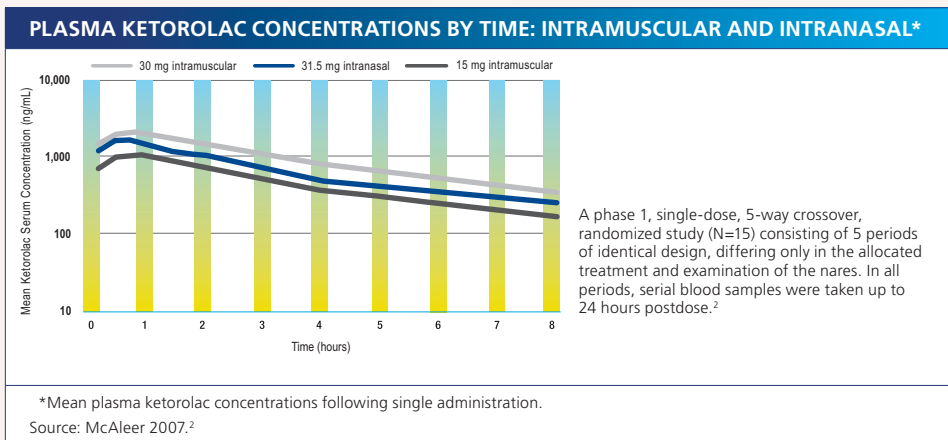
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## ✓ Innovative delivery of ketorolac<sup>1</sup>

- SPRIX® (ketorolac tromethamine) Nasal Spray is absorbed through the nasal mucosa
- Maximum plasma concentration reached in as little as 30 minutes (median  $t_{max}$  of 45 minutes) (Figure 1)<sup>2</sup>
- Plasma half-life of 5.24 hours with a standard deviation of 1.33 hours<sup>2</sup>

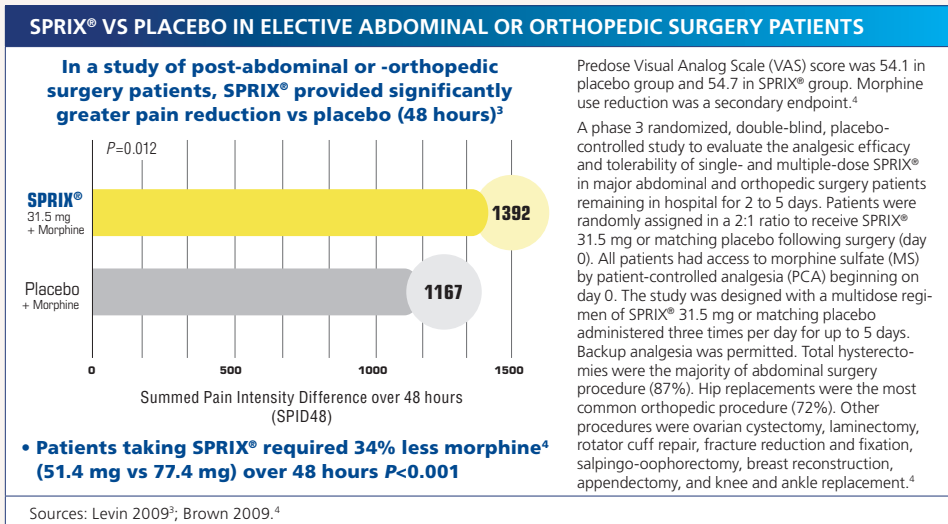
Figure 1



## ✓ SPRIX® reduces the need for narcotics to manage pain

- In a study of post-abdominal or post-orthopedic surgery patients, SPRIX® provided significantly greater pain reduction vs placebo (48 hours) (Figure 2)<sup>3</sup>

Figure 2



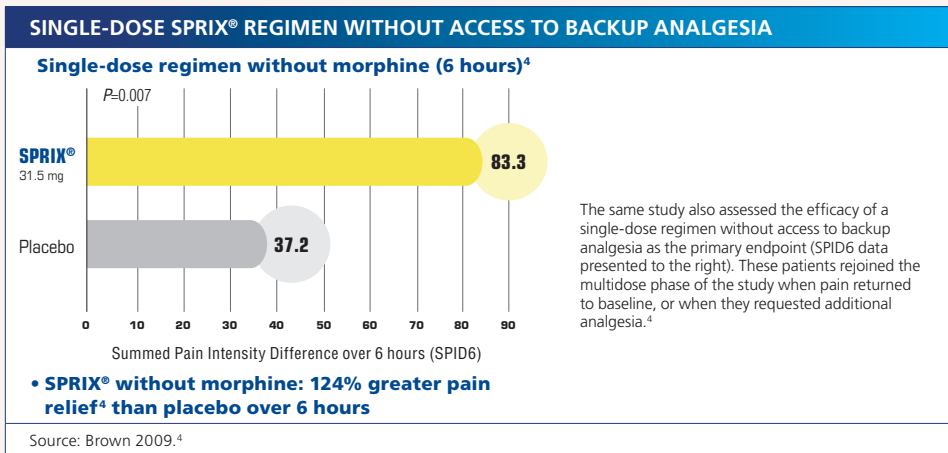
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- ✓] SPRIX® (ketorolac tromethamine) Nasal Spray proven efficacious as a single agent or in combination with opioids
- The same study evaluated the efficacy of a single-dose regimen without morphine (Summed Pain Intensity Difference over 6 hours [SPID6]) (Figure 3)<sup>3</sup>

Figure 3



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## IMPORTANT SAFETY INFORMATION (continued)

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## REFERENCES

1. SPRIX® [package insert]. Shirley, NY: Regency Therapeutics; 2011.
2. McAleer SD, Majid O, Venables E, et al. Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. *J Clin Pharmacol*. 2007;47(1):13-18.
3. Levin RA. Clinical Review of NDA 22.382. FDA Center for Drug Evaluation and Research. October 5, 2009.
4. Brown C, Moodie J, Bisley E, et al. Intranasal ketorolac for postoperative pain: a phase 3, double-blind, randomized study. *Pain Med*. 2009;10(6):1106-1114.