Patients are frequently anxious about oral and maxillofacial surgery procedures. This anxiety is likely based on a previous negative experience, but evidence suggests that patient perception of the “dental environment” also contributes to fear and anxiety. Unmanaged anxiety can contribute to postoperative complications: highly anxious patients report higher intensity and longer duration of pain.

Common oral surgery procedures such as third molar extractions are associated with pain that lasts for a couple of days, with an impact on activities of daily living, such as sleeping and eating. Traditional pain management strategies almost always involve the use of opioids, but patients may need alternatives, based on their medical history or personal preferences. Many patients prefer a non-opioid

A survey study found that 57% of surgical patients prefer a non-opioid, and 30% of patients were worried about becoming addicted through exposure to opioids for management of acute postsurgical pain. Furthermore, certain populations, such as the elderly, are at higher risk of complications associated with use of opioids, and patients with a medical history of sleep apnea may also have a greater risk of respiratory complications associated with opioid use. In addition, dentists are the highest prescribers of opioids for adolescents and young adults 10 to 19 years of age, some of whom may be at an increased risk of misuse or abuse of prescription opioids. Lastly, patients with a medical history of chronic pain may require special attention with regard to pain management strategies if they have built up a tolerance to opioids.

Patient education is important

Acknowledgement of a patient’s anxiety or fear can help establish a rapport. Educating patients and their caregivers about the importance of pain management and setting realistic expectations can contribute to a more comfortable recovery.

“Our patients need to know that we care [and] that we understand. Perhaps the procedure is somewhat elective in nature…or it may not be, but in spite of that, we do want them to be comfortable.”

EXPAREL is indicated for administration into the surgical site to produce postsurgical analgesia.

Important Safety information

EXPAREL is contraindicated in obstetrical paracervical block anesthesia. EXPAREL has not been studied for use in patients younger than 18 years of age. Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL. Monitoring of cardiovascular and neurological status as well as vital signs should be performed during and after injection of EXPAREL as with other local anesthetic products. Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting.

Please see Brief Summary of Prescribing Information at the end of this advertisement.
A survey conducted in 2010 found that 85% of oral surgeons prescribe opioids for pain following third molar extractions.10 The survey also revealed that, on average, 20 pills are prescribed to patients, and approximately 41% of surgeons believe that patients will have pills left over from that initial 20.11 This is corroborated by a 2015 study in which patients undergoing third molar extraction (N=48) were asked about postprocedure pain management.12 It was determined that all patients had been prescribed an opioid combination analgesic.12 A median of 8 out of 20 tablets was consumed over a 7-day period to control pain.12 The study captured what happened to the leftover pills, with the most common response being “medicine cabinets.”12 Leftover opioid pills in a patient’s home may lead to diversion of the medication for a non-medical use or abuse.12 A survey conducted by the Substance Abuse and Mental Health Services Administration revealed that the majority of non-medical uses of opioids are due to obtaining pills from a relative or friend (Figure 1.1) In the United States, there is an epidemic with respect to abuse of opioid prescription medications, which has increased 4.5 million people suffering from substance use disorders related to pain relievers.13

As such, many professional healthcare organizations and government agencies are promoting opioid minimization.1 The American Association of Oral and Maxillofacial Surgeons is advocating for states to establish and fund prescription monitoring programs and is offering a free course to help dental specialists prevent prescription opioid abuse, entitled “Safe Opioid Prescribing for Acute Dental Pain.”14 The state of Massachusetts recently enacted regulations that limit opioid prescriptions to a 7-day supply for patients recovering from surgery.15 There are currently more than 300 bills under consideration in state legislatures nationwide that are attempting to limit the population’s exposure to opioids.16 As such, there are challenges with ensuring patients have adequate pain control using opioids alone. Exploring new ways to manage pain may help to address some of these challenges.

**NEW OPTIONS TO MANAGE PAIN AND MEET PATIENT NEEDS**

“Pain control is obviously one of the things that you can positively affect, if you can find an alternative...some patients don’t like the feeling of being loopy on the narcotics.”

Alternative strategies that utilize non-opioid options and provide optimal pain control following oral surgery procedures may be needed.17 Using multiple therapeutic options that disrupt both nociceptive and inflammatory pathways can help control pain.13,18 A systematic review of the literature demonstrated that monotherapy with any one class of drug (ie, opioid, NSAID, acetaminophen) was not as effective as combination therapy.12 Local anesthetics can be used as part of a multimodal strategy to control pain at the site of surgery, via nerve block or local infiltration.19,20 Infiltration with local anesthetics into the surgical site is safe and effective, but analgesic efficacy is limited to the short duration of action of the local anesthetic.21 EXPAREL® (bupivacaine liposome injectable suspension) is a liposomal formulation of bupivacaine, and it is indicated for single-dose administration into a surgical site to produce postsurgical analgesia.22 It is a 1.3% solution of bupivacaine, available in 20 mL vials.23 EXPAREL is not indicated for use in a nerve block, nor is it indicated for anesthesia.24 The maximum dose is 268 mg and it is not based on a patient’s weight.24

Determining the dose of EXPAREL depends on the size of the surgical site, individual patient factors that may impact the safety of an amide local anesthetic, and the volume needed to adequately cover the area.25 Upon administration, bupivacaine is slowly released from DepoFoam® drug delivery technology.26 DepoFoam is composed of multivesicular liposomes that encapsulate bupivacaine.22 As multivesicular liposomes break down in the surgical site, bupivacaine is released over time to provide prolonged postsurgical analgesia.26,27 The administration technique can impact analgesic effects in surgical site infiltration; therefore, EXPAREL should be injected slowly into all relevant tissue layers with a 25-gauge or larger-bore needle, using a series of injections that cover the entire surgical area.28

“They’d rather have something that’s going to keep them more alert and awake. So, there are a lot of different reasons for wanting to have different products available to you.”

EXPAREL can be used as part of a multimodal approach to managing pain following surgical procedures, and it has been used in more than 2 million patients undergoing many different surgical procedures.29 Multimodal pain management strategies can help reduce reliance on any singular therapy, and they are proven to reduce opioid use, which may contribute to smoother recovery from oral surgery procedures.26 Having a variety of systemic and locally acting therapeutic options available to oral surgeons can help customize pain management regimens to your patients’ needs.24,28

**Important Safety Information (cont’d)**

by the liver, EXPAREL should be used cautiously in patients with hepatitis disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting.

Please see Brief Summary of Prescribing Information at the end of this advertisement.

### References

**EXPAREL**
(bupivacaine liposome injectable suspension)

**Brief Summary**
(Full prescribing information refer to package insert)

**INDICATIONS AND USAGE**
EXPAREL is indicated for administration into the surgical site to produce postoperative analgesia. EXPAREL has not been studied for use in patients younger than 18 years of age.

**CONTRAINDICATIONS**
EXPAREL is contraindicated in obstetrical paracervical block anesthesia. While EXPAREL has not been studied with this technique, the use of bupivacaine HCl with this technique has resulted in fetal bradycardia and death.

**WARNINGS AND PRECAUTIONS**

**Warnings and Precautions Specific for EXPAREL**
As there is a potential for serious life-threatening adverse effects associated with inadvertent intravenous administration of bupivacaine HCl, EXPAREL should be administered in a setting where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity.

Caution should be taken to avoid accidental intravenous injection of EXPAREL. Convulsions and cardiac arrest have occurred following accidental intravenous injection of bupivacaine and other amide-containing products. Using EXPAREL followed by other bupivacaine formulations has not been studied in clinical trials. Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL.

EXPAREL has not been evaluated for use in the following populations and, therefore, is not recommended for these anesthetics or routes of administration.
- Epidural
- Intrathecal
- Regional nerve blocks
- Intravascular or intrathecral use

EXPAREL has not been used for an evaluation in the following patient populations:
- Children
- Pregnant or lactating women

The ability of EXPAREL to achieve effective anesthesia has not been studied. Therefore, EXPAREL is not indicated for pre- or percutaneous diagnostic techniques requiring bupivacaine that require deep and complete sensory block in the area of administration.

**ADVERSE REACTIONS**

**Clinical Trial Experience**
The safety and efficacy of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 patients undergoing various surgical procedures. Patients were administered EXPAREL from 10 to 20 mg/mL (equivalent to 0.5 to 1 mg/mL bupivacaine HCl solution) in liquid for EXPAREL. In these studies, the most common adverse reactions (incidence greater than or equal to 10%) following EXPAREL administration were nausea, constipation, and pruritus.

The common adverse reactions (incidence greater than or equal to 2% to less than 10%) following administration of EXPAREL were pyrexia, edema, peripheral anesthesia, pruritus, paresthesia, tachycardia, headache, insomnia, anorexia, postoperative muscle spasms, hemorraghic anemia, back pain, somnolence, and procedure pain.

**DRUG INTERACTIONS**
EXPAREL should be administered in the ready to use suspension or diluted to a concentration of up to 0.88 mg/mL, (i.e., 1:1.4 dilution by volume) with normal saline. If a Ringer’s solution is used, EXPAREL must not be diluted with water or other hypotonic agents as it will result in disruption of the liposomal particles. EXPAREL should not be admixed with local anesthetics other than bupivacaine. Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.

Bupivacaine administered together with EXPAREL may impact the pharmacokinetic and/or physiochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL should not be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL, as long as the rate of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1.2.

The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to toxicity.

Other than bupivacaine as noted above, EXPAREL should not be admixed with other drugs prior to administration.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**
Risk Summary
There are no studies conducted with EXPAREL in pregnant women. In animal reproduction studies, embryo-fetal deaths were observed in rabbits at the high dose in the absence of maternal toxicity. In animal reproduction studies, embryo-fetal deaths were noted at 1.5 times the MRHD in rats and at 1.6 times the maximum dose achieved as 40 mg/kg bupivacaine hydrochloride to equivalent to 0.2, 0.5 and 1.5 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight). No embryo-fetal effects were observed in rats at the doses tested with the high dose causing increased maternal lethality. An increase in embryo-fetal deaths was observed on rats at the high dose in the absence of maternal toxicity.

Decreased pup survival was noted at 1.5 times the MRHD in a rat pre- and post-natal toxicity study, and bupivacaine can produce maternal toxicity, and the technique of drug administration. Adverse reactions in the pregnant, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

**Data Animal**
Bupivacaine hydrochloride was administered subcutaneously to rats and rabbits during the period of organogenesis (implantation to closure of the hard plate). Rat doses were 4.4, 13.3, and 40 mg/kg/day (equivalent to 0.2, 0.6, and 2.0 mg/kg/day bupivacaine HCl solution, respectively, based on the BSA comparisons and a 60 kg human weight) and rabbit doses were 1.5, 5.2, and 22.9 mg/kg/day (equivalent to 0.1, 0.4 and 1.6 times the MRHD, respectively, based on the BSA comparisons and a 60 kg human weight). No embryo-fetal effects were observed in rats at the doses tested with the high dose causing increased maternal lethality. An increase in embryo-fetal deaths was observed in rabbits at the high dose in the absence of maternal toxicity.

**Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**
Of the total number of patients in the EXPAREL surgical site infiltration clinical study, 266 mg (10 mL) EXPAREL was given to more than 65 years of age and 47 patients were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between the two age groups. The incidence of adverse events with EXPAREL has not identified differences in efficacy or safety between elderly and younger patients, but greater sensitivity of some older individuals being of special concern.

**Hepatic Impairment**
Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, patients with hepatic disease may be at the greater risk of developing toxic plasma concentrations.

**Renal Impairment**
Bupivacaine is known to be substantially excreted by the kidney, and may exhibit toxic effects on the liver, a potential toxic effect of bupivacaine in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations.

**Local Anesthesia with Concomitant Oral or Nasal Drugs**
Local infiltration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours. Systemic plasma levels of bupivacaine following administration of EXPAREL are not greater than the effective local anesthetic.

**CLINICAL STUDIES**

The efficacy of EXPAREL was compared to placebo in two multicenter, randomized, double-blinded clinical trials. One trial evaluated the treatments in patients undergoing hemorrhoidectomy while the other evaluated the treatments in patients undergoing bunionectomy.

**Study 1**
A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial evaluated the safety and efficacy of 108 mg (8 mL) EXPAREL in 153 patients undergoing bunionectomy. The mean age was 43 years (range 19 to 72).

Study medication was administered directly into the site at the conclusion of the surgery, prior to closure. There was an initial infusion of 7 mL of EXPAREL before the tissues surrounding the osteotomy and 1 mL into the subcutaneous tissue.

Pain intensity was rated by the patients on a 0-11 numeric rating scale (NRS) and compared to placebo. Postoperatively, patients were allowed rescue medication (5 mg oxycodone/325 mg acetaminophen orally every 4 to 6 hours as needed) or, if that was insufficient within the first 24 hours, 3 mg morphine sulfate intramuscularly every 3 to 4 hours.

The primary outcome measured was the area under the curve (AUC) of the NRS pain intensity scores (cumulative pain scores) collected over the first 24 hour period. There was a significant treatment effect for EXPAREL compared to placebo. EXPAREL demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours (p=0.001).

**Study 2**
A multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial evaluated the safety and efficacy of 266 mg (20 mL) EXPAREL in 189 patients undergoing hemorrhoidectomy. The mean age was 48 years (range 18 to 86).

Study medication was administered directly into the site (greater than or equal to 3 mL) at the conclusion of the surgery. Division of 20 mL of EXPAREL with 10 mL of saline, for a total of 50 mL, was divided into six 5 mL aliquots. A field block was performed by visualizing the anal clock face and slowly infiltrating one aliquot to each of the even numbers.

Pain intensity was rated by the patients on a 0 to 10 numeric rating scale (NRS) and compared to placebo. Postoperatively, patients were allowed rescue medication (morphine sulfate 10 mg intramuscular every 4 hours as needed).

The primary outcome measure was the AUC of the NRS pain intensity scores (cumulative pain scores) collected over the first 72 hour period. There was a significant treatment effect for EXPAREL compared to placebo.

**Compatibility Considerations**
Administering EXPAREL with drugs other than bupivacaine HCl prior to administration is not recommended.

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL should not be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL, as long as the rate of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1.2.
- The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to toxicity.

Other than bupivacaine as noted above, EXPAREL should not be admixed with other drugs prior to administration.

**For additional information call 1-855-RX-EXPAREL (1-855-793-9727) Rx only**
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