Pharmaceutical Approval Update

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Ramelteon (Rozerem™)

Manufacturer: Takeda Pharmaceuticals, North America

Indication: Ramelteon is used to treat insomnia characterized by difficulty with sleep onset.

Drug Class: Ramelteon acts as a selective agonist at two melatonin receptors (Mel1a/1b; MT1/MT2) in the brain’s suprachiasmatic nucleus, or “circadian clock.” This drug has demonstrated a greater affinity, selectivity, and potency than melatonin at the MT2 receptors, which are thought to regulate sleepiness.

Uniqueness of Drug: Ramelteon has shown no evidence of a potential for abuse or dependence. It is the only prescription sleep aid not designated as a Schedule IV controlled substance. The drug also can be prescribed for long-term use, and its selective mechanism of action reduces the likelihood of adverse drug events (ADEs) such as impairment of memory and motor ability.

Warnings: Patients with hypersensitivity to ramelteon or to any components of its formulation should not use this drug.

Insomnia that worsens or does not remit after a reasonable period of time or the emergence of new cognitive or behavioral abnormalities should prompt patients to see their health care providers; such symptoms may be the result of an unrecognized underlying medical disorder. Patients should be evaluated for physical and psychiatric causes of insomnia.

In primarily depressed patients, the worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotic agents. Hypnotics have been linked with cognitive and behavioral changes.

Ramelteon is not indicated for patients with severe hepatic impairment, sleep apnea, or chronic obstructive pulmonary disease.

Ramelteon may decrease testosterone levels and increase prolactin levels. The long-term effects of the drug are unknown. It should not be taken with or immediately after high-fat meals and should not be taken concomitantly with fluvoxamine (Luvox®, Solvay) or alcohol.

Patients should consult their physicians if the following events occur: cessation of menses, galactorrhea in women, decreased libido, or fertility problems. This drug is not recommended during lactation.

Patients should avoid hazardous tasks, such as driving, after taking ramelteon.

The safety and effectiveness of ramelteon have not been established in children.

Adverse Drug Effects: ADEs include headache, somnolence, fatigue, dizziness, worsening insomnia, depression, nausea, diarrhea, dysgeusia, upper respiratory tract infection, influenza, myalgia, arthralgia, and decreased blood cortisol concentrations. The most common ADEs observed that had a greater than 2% incidence of difference from placebo were somnolence, dizziness, and fatigue.

Drug Interactions: Ramelteon metabolism is affected by fluvoxamine and other cytochrome P450 (CYP450) 1A2 inhibitors; rifampin and other strong CYP450 inducers; ketoconazole and other strong CYP450 3A4 inhibitors; and alcohol.

Dosage and Administration: Ramelteon, as an 8-mg film-coated tablet, should be taken within 30 minutes before bedtime. Activities should be confined to those necessary to prepare for bed. Ramelteon should not be taken with or immediately after a high-fat meal.

Commentary: Ramelteon has a unique therapeutic mechanism of action, compared with existing insomnia treatments. The major benefits are as follows:

- The drug decreases the time to sleep onset in a wide range of patients, including older adults.
- It carries a minimal risk of rebound insomnia and dependency.
- The Food and Drug Administration (FDA) does not consider ramelteon, unlike other sleeping medications, to be a controlled substance.

The drug represents a breakthrough in the treatment of insomnia. It will be interesting to learn whether the long-term use of ramelteon will result in ADEs that have not been observed in previous clinical trials.

Source: www.rozerem.com

Lidocaine–Tetracaine Patch (Synera™)

Manufacturer: Zars

Indication: The lidocaine–tetracaine (“S-Caine”) patch is used to numb the skin before various medical procedures. Examples include superficial venous access and dermatological operations such as excision electrodesiccation and shave biopsy of skin lesions. The product is indicated for use in children and adults.

Drug Class: The patch consists of a thin, uniform layer of local anesthetic emulsion of lidocaine 70 mg and tetracaine 70 mg. An integrated, oxygen-activated heating component enhances delivery of the analgesic agent.

Uniqueness of Product: The patch uses heating pad technology and a proprietary local anesthetic formulation to increase the skin’s temperature, thus shortening the onset time of local anesthesia. When the patch is removed from its storage pouch, it begins to heat, warming the skin after an application.

The patch is more effective than placebo for reducing pain associated with superficial dermatological procedures in adults.

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and elderly patients, as assessed by scores on the Visual Analog Scale. The results of pediatric trials reinforced the patch’s efficacy in all age groups for reducing pain.

**Warnings:** Applying the patch for a longer duration than recommended, or applying multiple patches simultaneously or sequentially, can result in absorption of lidocaine and tetracaine sufficient to cause serious ADEs.

Even a used patch contains at least 90% of the initial amount of lidocaine and tetracaine. The potential exists for a child or a pet to experience serious ADEs from chewing or ingesting a new or used patch. Patients should store the patch out of the reach of children and pets and dispose of it safely.

**Precautions:** The patch should be used with caution in patients with sensitivity to the systemic effects of the drugs, such as those who are acutely ill or debilitated.

Allergic or anaphylactoid reactions associated with lidocaine and tetracaine or other components of the patch are characterized by urticaria, angioedema, bronchospasm, and shock. Allergic reactions should be managed by conventional means.

Patients should avoid contact of the patch with the eyes, as severe eye irritation has occurred with the use of similar products in animals. The loss of protective reflexes may predispose the eye to corneal irritation and potential abrasion. If the patch comes in contact with the eyes, patients should immediately wash out their eyes with water or saline. They should protect the eyes by keeping them closed and by putting a gauze patch over them as a temporary shield until sensation returns.

The lidocaine–tetracaine patch is not recommended for use on mucous membranes or on areas with a compromised skin barrier. The patch should not be cut.

Applying the patch to broken or abraded skin may result in toxic blood concentrations of lidocaine and tetracaine from increased absorption.

The risk of toxic plasma lidocaine and tetracaine concentrations is increased in patients with severe hepatic disease or pseudocholinesterase deficiency because of their inability to metabolize local anesthetics.

Because the integrated heating component contains iron powder, the patch must be removed before patients undergo magnetic resonance imaging.

**Adverse Drug Effects:** ADEs include erythema, blanching, edema, abnormal sensations of the skin, and allergic or anaphylactoid reactions.

**Dosage and Administration:** The lidocaine–tetracaine patch is applied to the intact skin of adults and children three years of age and older. Before venipuncture or intravenous cannulation, the patch is applied to intact skin for 20 to 30 minutes. Before superficial dermatological procedures, it is applied to intact skin for 30 minutes.

**Commentary:** The S-Caine Patch offers a new option in reducing the pain associated with common surgical procedures. The development of topical anesthetics has provided the family physician with multiple options in anesthetizing open and intact skin.

Several other products contain local anesthetics that are applied to the skin, although they are not technologically similar to the Synera™ patch. For instance, the eutectic mixture of local anesthetics (i.e., lidocaine, prilocaine [EMLA, AstraZeneca]) represented the first major breakthrough for dermal anesthesia on intact skin. (Eutectic refers to a mixture of two or more elements with a lower melting point than any of its constituents.) The mixture consists of lidocaine 25 mg/ml, prilocaine 25 mg/ml, a thickener, an emulsifier, and distilled water (pH, 9.4). The 5% lidocaine patch (Lidoderm®, Endo) blocks nerve endings in the skin and helps relieve the pain that often follows a case of shingles (postherpetic neuralgia).

Lidocaine can inhibit viral and bacterial growth. The effect of the patch on intradermal injections of live vaccine has not been determined.

**Source:** www.zars.com

**Insulin Detemir [recombinant DNA origin] Injection (Levemir®)**

**Manufacturer:** Novo Nordisk

**Indications:** Insulin detemir is used for the treatment of type-1 and type-2 diabetes. As an acylated, synthetic, long-acting, soluble insulin analogue, it provides up to a 24-hour duration of action and causes little weight change. Insulin detemir is injected subcutaneously once or twice daily, depending on the patient’s blood glucose control and insulin requirements throughout the day.

**Drug Class:** Insulin analogues are created through genetic engineering. Levemir® is made by recombinant DNA (rDNA) technology and is chemically different from the insulin made by the human body.

**Uniqueness of Drug:** This product is engineered to bind to human albumin, which provides slow absorption and a prolonged action. The underlying mechanism involves insulin self-association in the subcutaneous depot and albumin binding both in the subcutaneous tissue and in the circulation.

Insulin detemir has a more consistent, predictable effect on blood glucose than neutral protamine Hagedorn (NPH) insulin. It has a relatively flat action profile, and it can be used in monotherapy, as an adjunct to oral antidiabetic agents, or in combination with rapid-acting insulin.

**Precautions:** Hypoglycemia can occur with:

- the wrong insulin dose.
- medications that reduce glucose levels or increase sensitivity to insulin.
- illnesses that limit glucose reserves, lengthen the time that insulin stays in the body, or that increase sensitivity to insulin.
- insufficient intake of carbohydrate.
- overutilization of glucose by the body.

**Hyperglycemia can occur with:**

- the wrong insulin dose.
- medications that increase glucose or decrease sensitivity to insulin.
- illnesses that increase the body’s glucose production or decrease sensitivity to insulin.
- overconsumption of carbohydrate.

**Adverse Drug Effects:** Serious allergic reactions may include the development of a rash over the whole body, trou...
ble breathing, a rapid heartbeat, sweating, and local allergic reactions at the injection site (redness, swelling, itching). If serious or continual reactions occur, the patient should use another insulin product. The skin may thicken or pit at the injection site, especially if the injection site is not rotated. Vision changes may necessitate an evaluation by an ophthalmologist.

Fluid retention or swelling may affect the hands and feet. Hypokalemia may occur.

**Dosage and Administration:** Insulin detemir is injected once or twice daily subcutaneously. It is initiated in basal–bolus (depot) regimens. For patients with type-1 or type-2 diabetes, the dosage should be initiated and adjusted individually, as with other intermediate or long-acting insulins.

Patients start with an evening dose (either at dinner or bedtime) once daily (e.g., 0.2–0.5 units/kg of body weight per day). To ensure postprandial glycemic control, mealtime insulin is added, depending on individual needs.

The dose is increased until the desired morning concentrations of fasting plasma glucose have been reached. If the desired pre-dinner target cannot be achieved, the total dose of insulin detemir (morning and evening) can be split, according to the patient's needs.

**Commentary:** Insulin detemir is a very-long-acting insulin, and its chemical structure allows for a slower and more stable absorption from the injection site. Its similarity to insulin glargine (Lantus®, Aventis) makes comparisons inevitable. Both are true basal, or depot, insulins because they can maintain activity for a full 24 hours with essentially no peaks or troughs.

The major breakthrough with this new product is that no weight gain has been attributed to its use. When used in combination with insulin at mealtime (in a basal–bolus regimen), it is not associated with undesirable weight gain for people with type-1 diabetes. Compared with other insulins, it is associated with less weight gain in patients with type-2 diabetes.

Insulin detemir is available in 3-ml cartridges that can be used with the NovoPen® and all other Novo Nordisk pens that take Penfill® cartridges. It is also available in the FlexPen® preloaded device.

**Source:** www.novonordisk.com