Exenatide Injection (Byetta™)

**Manufacturer:** Amylin Pharmaceuticals, Inc./Eli Lilly

**Indication:** Adjunctive therapy to improve glycemic control in patients with type-2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but who have not achieved adequate glycemic control.

**Drug Class:** This is the first in a new class of diabetes drugs called “incretin mimetics.” Exenatide is a synthetic version of exendin-4, a naturally occurring hormone in humans. The amino acid sequence of exenatide partially overlaps with that of the human incretin hormone glucagon-like peptide-1 (GLP-1), but its half-life is longer than that of native GLP-1.

**Uniqueness of Drug:** Exenatide binds to and activates the human GLP-1 receptor *in vitro*. Having many of the same glucoregulatory effects as GLP-1, exenatide mimics natural physiology for self-regulating glycemic control. By mimicking the mechanisms of this hormone, exenatide is a diabetes self-regulating drug that stays in the blood, working actively only when blood glucose concentrations are too high. In clinical trials, exenatide regulated glucose levels. Most patients in long-term exenatide clinical studies also experienced reductions in weight.

**Precautions:** Adverse drug events (ADEs) associated with exenatide are generally mild to moderate in intensity. In clinical trials, the most frequently reported ADE was nausea, which varied with the dose. With continued therapy, the frequency and severity of nausea decreased over time in most patients.

Patients receiving exenatide in combination with a sulfonylurea may be at a higher risk of hypoglycemia. To minimize this risk, practitioners might consider reducing the sulfonylurea dosage. When patients begin taking exenatide, health care providers should explain the symptoms, treatment, and conditions that tend to result in hypoglycemia, and they should review and reinforce the patient’s usual instructions for hypoglycemia management.

Patients should also be advised that treatment with exenatide may lead to a reduction in appetite, food intake, or body weight and that there is no need to modify the dosing regimen because of these effects.

**Contraindications:** Exenatide is not a substitute for insulin. It is not indicated for patients with (1) type-1 diabetes or ketoacidosis, (2) end-stage renal disease, (3) a creatinine clearance of below 30 ml/minute, or (4) severe gastrointestinal disease, including gastroparesis.

The most common side effect is nausea. The safety and effectiveness of exenatide have not been established in children.

**Dosage:** Exenatide 5 mcg is administered subcutaneously twice daily within 60 minutes of the morning and evening meals.

**Commentary:** This agent mimics the action of GLP-1, which is secreted by the gastrointestinal tract to spearhead insulin production after a meal, when blood glucose levels are elevated. This is important, because other diabetes drugs stimulate insulin secretion even if levels are already low, leading to the risk of hypoglycemia.

Exenatide is a synthetic version of a protein found in the saliva of the Gila monster that works in a manner similar to that of human GLP-1. Exenatide was administered in conjunction with the sulfonylureas; another common diabetes drug; metformin; or in combination with earlier treatments. Adding exenatide triggered a decline of approximately 1% in glycosylated hemoglobin (HbA1c), an important measurement of blood glucose averages. This activity is consistent with the reductions caused by other diabetes drugs.

Exenatide should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption.

**Sources:** www.pharmacyonesource.com; www.lillydiabetes.com

Pregabalin (Lyrica™)

**Manufacturer:** Pfizer, Inc., Groton, CT

**Indication:** Adjunctive treatment of partial-onset seizures in adults with epilepsy.

**Drug Class:** Pregabalin is a 3-substituted analogue of gamma-aminobutyric acid (GABA), and it is a compound related to gabapentin.

**Uniqueness of Drug:** This agent is already approved for patients with pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. It is the first treatment approved by the Food and Drug Administration (FDA) for these neuropathic pain states. Pregabalin binds to calcium channels, modulating calcium influx and influencing GABAergic neurotransmission. This mode of action translates into antiepileptic, analesic, and anxiolytic effects.

**Warnings and Precautions:** Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose–galactose malabsorption should not take this medication. In accordance with current clinical practice, some diabetic patients who gain weight after taking pregabalin may need to adjust their hypoglycemic medications.

Pregabalin has been associated with dizziness and somnolence, which can increase the occurrence of accidental injury and falls in elderly patients. Patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Data are insufficient regarding the effects of the withdrawal

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of concomitant antiepileptic medicinal products, after seizures are controlled by pregabalin as an “add-on” (“second-line”) therapy; therefore, pregabalin cannot currently be used as monotherapy. If pregabalin needs to be discontinued, this should be done gradually over period of at least one week.

Side effects, such as dizziness and somnolence, are common in more than 10% of patients. Other ADEs, affecting from 1% to more than 10% of patients, include increased appetite, ataxia, blurred vision, and erectile dysfunction.

**Dosage:** Therapy can be started with pregabalin 150 mg/day. According to the individual patient’s response and tolerability, the dosage may be increased to 300 mg/day after one week. The maximum dosage of 600 mg/day may be achieved after an additional week.

**Commentary:** Over the past 15 years or so, the number of antiepileptic drugs on the market has nearly doubled. As a result, physicians have been able to offer many of their patients drugs with improved effectiveness, tolerability, and safety. Depending on the seizure type, certain standard antiseizure medications are usually used first for epilepsy (the “first-line” agents). If they are unsuccessful or if the patient becomes tolerant to the primary medications, the newer add-on or second-line drugs are tried, usually in combination with standard drugs.

The newer-generation antiepileptic drugs have several theoretical advantages over their predecessors: they have well-characterized mechanisms of action and improved tolerability, and their simpler pharmacokinetic properties are more predictable, especially when the agent is given in combination. In addition, pregabalin is not metabolized and does not bind to protein. Its linear and expected absorption is an advantage because of its predictable efficacy, and its side-effect profile is favorable.

The efficacy of 600 mg of pregabalin was reported to be clearly greater than that of 150 mg, but all ADEs occurred more often with 600 mg than with 150 mg. Somnolence, dizziness, ataxia, and weight gain were clearly dose-related.

**Source:** www.pharmacyonesource.com

**Tigecycline (Tygacil™)**

**Manufacturer:** Wyeth Pharmaceuticals, Madison, NJ

**Indications:** Treatment of complicated skin and skin structure infections (cSSSIs) in adults. This agent is also approved for adults with complicated intra-abdominal infections (cIAIs) caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

**Drug Class:** This is the first approved antibiotic in a new class called glyclcyclines.

**Uniqueness of Drug:** This intravenous (IV) antibiotic has a broad spectrum of antimicrobial activity, including activity against the drug-resistant bacteria methicillin-resistant *Staphylococcus aureus* (MRSA). Tigecycline can be used as an empirical monotherapy to treat a variety of hospital-acquired and community-acquired infections (e.g., complicated appendicitis, infected burns, intra-abdominal abscesses, deep soft-tissue infections, and infected ulcers).

**Precautions and Contraindications:** Tigecycline is contraindicated in patients with known hypersensitivity to this agent. It should be administered with caution in patients with known hypersensitivity to the tetracycline class of antibiotics, and it may have adverse effects similar to those of the tetracyclines. In clinical trials, the most common treatment-emergent ADEs were nausea (29.5%) and vomiting (19.7%).

Tigecycline may cause fetal harm when administered during pregnancy. The safety and effectiveness of tigecycline in patients younger than 18 years of age and in lactating women have not been established.

The use of tigecycline during tooth development may cause permanent discoloration of the teeth.

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range from mild to life-threatening.

Monotherapy should be used with caution in patients with clinically apparent intestinal perforation.

**Dosage:** The recommended dosage of tigecycline is 100 mg infused over 30–60 minutes followed by 50 mg infused every 12 hours for 5–14 days. The length of treatment should be guided by the severity of the infection, the patient’s bacteriological response, and the patient’s clinical progress.

Patients with severe liver impairment should receive a starting dose of 100 mg, followed by 25 mg every 12 hours. No dosage adjustment is needed for patients with mild or moderate liver impairment.

The dosage does not need to be adjusted in renally impaired patients, and the drug is conveniently administered every 12 hours.

**Commentary:** Tigecycline is an agent that restores some faith in the tetracyclines, given its enhanced activity against resistant organisms and its broad spectrum of activity. It is a novel glyclycline antibiotic with activity against a broad range of gram-positive, gram-negative, atypical, anaerobic and antibiotic-resistant bacteria. Its activities are typical of earlier tetracyclines, and it is more potent against tetracycline-resistant organisms.

The glyclcyclines, which were designed to overcome the development of acquired resistance normally associated with tetracycline antibiotics, are the result of adding dimethylglyclamido or tertiary butylglyclamido groups to tetracycline structures.

Although tetracycline is bacteriostatic *in vitro*, its effectiveness in clinical trials suggests that traditional laboratory thinking about using bacteriostatic drugs in serious infections needs to be revised. Unlike existing tetracyclines, tigecycline is available only as an IV preparation. It is administered twice daily, although its long half-life and post-antibiotic effect may make once-daily dosing a possibility.

Tigecycline appears to have good tissue penetration (e.g., under the skin). No dose adjustment is needed in patients with renal or hepatic disease.

In three clinical trials, the drug was well tolerated despite an increased frequency of nausea and vomiting.

**Sources:** www.wyeth.com; http://salesandmarketingnetwork.com