Drug Class Review Monograph – GPI Class 30 – Endocrine and Metabolic Agents, Miscellaneous

Review Time Frame: 11/2015 – 04/2017

Previous Class Review: 02/2016

Background:

The drugs reviewed in this class include the following:

- **Bone Density Regulators**: These agents, which include bisphosphonates, calcitonin, and parathyroid hormone derivatives, regulate bone density. Bisphosphonates attach to calcium salts on bony surfaces, thereby inhibiting osteoclast bone resorption. Similarly, calcitonin inhibits bone resorption by binding to osteoclasts as well as maintains calcium homeostasis. Parathyroid hormone and its derivatives, such as teriparatide, act as primary regulators of calcium and phosphate metabolism in the bone.
- **Selective Estrogen Receptor Modulators (SERMs)**: SERMs are competitive inhibitors of estrogen binding to estrogen receptors. They have mixed agonist and antagonist activity, depending on the target tissue. SERMs provide protection against menopausal bone loss, presumably due to their partial agonist activity and lower serum total and low-density lipoprotein (LDL)-cholesterol.
- **Fertility Regulators**: Clomiphene is a selective estrogen receptor modulator (SERM) that competes with estradiol for estrogen receptors at the hypothalamus. It prevents estrogen from lowering the output of gonadotropin-releasing hormone (GnRH). As GnRH increases, the pituitary gland releases follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn stimulate the ovaries to develop oocyte follicles.
- **Luteinizing hormone-releasing hormone (LHRH)/Gonadotropin-releasing hormone (GnRH) Agonist Analog Pituitary Suppressants**: Nafarelin is a synthetic agonistic analog of GnRH that is almost 200 times more potent than endogenous GnRH. Like GnRH, nafarelin stimulates the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Unlike GnRH, nafarelin reduces production of FSH and LH over time due to down-regulation of the GnRH receptors (caused by continuous administration of nafarelin versus GnRH which is released in pulses).
- **Somatostatic Agents**: Somatostatin is a key regulatory peptide that inhibits a variety of gastrointestinal processes. Pasireotide is a somatostatin analog that binds to and actives somatostatin receptors, resulting in inhibition of corticotropin secretion. This leads to lower cortisol secretion, thereby managing Cushing's disease. Pasireotide also inhibits other pituitary hormones such as growth hormone; this property enables it to be used in managing acromegaly.
- **Posterior Pituitary Hormones**: Desmopressin acts similarly to vasopressin, an antidiuretic hormone secreted by the hypothalamus. Both increase resorption of water at the renal collecting ducts, ultimately reducing urine flow and increasing urine osmolality. Unlike vasopressin, desmopressin does not have an effect on visceral smooth muscle contraction. It does, however, have increased hemostatic effects compared to vasopressin, which supports its use in congenital or acquired bleeding disorders.
- **Prolactin Inhibitors**: High levels of prolactin can lead to loss of libido, amenorrhea, infertility, galactorrhea, gynecomastia, and impotence. Cabergoline is a centrally-acting

synthetic ergot alkaloid that causes dose-dependent suppression of prolactin levels through stimulation of dopamine-2 receptors in the anterior pituitary. By normalizing prolactin levels, it is able to correct the symptoms listed above.

- **Abortifacient – Progesterone Receptor Antagonists**: Progesterone is important for the establishment of pregnancy. Mifepristone acts as a competitive antagonist with progesterone at the progesterone receptor. It functions as an abortifacient by interrupting progesterone support to the endometrium and sensitizing the myometrium to prostaglandins. This ultimately leads to menstrual bleeding, disruption of placental function, and ultimately termination of pregnancy.
- **Metabolic Modifiers:** Metabolic modifiers include carnitine replenisher agents (e.g., L-carnitine), vitamin D analogs (e.g., calcitriol), calcimimetic agents (e.g., cinacalcet), urea cycle disorder agents (e.g., sodium phenylbutyrate, glycerol phenylbutyrate), and phenylketonuria (PKU) agents (e.g., sapropterin). These agents replace or correct metabolic abnormalities in various conditions, including primary and secondary carnitine deficiencies, hyperparathyroidism, urea cycle disorders, and PKU.

New treatment guideline recommendations:

- Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline
  - For women with a history of breast cancer presenting with dyspareunia, the Endocrine Society recommends against ospemifene.
  - For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, the Endocrine Society suggests a trial of ospemifene.
- American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 2.
  - Treatment for women with polycystic ovary syndrome (PCOS) and anovulatory infertility should begin with an oral agent such as clomiphene citrate or letrozole, an aromatase inhibitor.
- Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency
  - The Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society recommend the use of insulin-like growth factor-1 (IGF-I) therapy to increase height in patients with severe primary IGF-I deficiency (PIGFD). (Strong recommendation)
- Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline
  - The Endocrine Society suggests the standard dose (250 μg for adults and children ≥ 2 years of age, 15 μg/kg for infants, and 125 μg for children < 2 years of age) IV corticotropin stimulation (30 or 60 min) test over other existing diagnostics tests to establish the diagnosis of adrenal insufficiency.

Newly approved drugs:

- Approved 04/27/2017: Brineura (cerliponase alfa): 30 mg/mL; availability anticipated in June 2017.
- Approved 02/07/2017: Parsabiv (etelcalcetide) 2.5mg/0.5mL, 5mg/mL, 10mg/2mL solution, intravenous; anticipated commercial availability unknown.
- Approved 12/08/2015: Kanuma (sebelipase alfa) 20 mg/10 mL injection; currently commercially available.

Newly approved formulations:

- Approved 03/03/2017: Noctiva (desmopressin acetate) 0.00083 mg/spray (nasal); anticipated commercial availability unknown.
- Approved 06/17/2016: Rayaldee (calcifediol) 0.03 mg extended release capsule; currently commercially available.
- Approved 04/22/2016: Orfadin (nitisinone) 4 mg/mL suspension; currently commercially available.
- Approved 02/04/2016: Paricalcitol (paricalcitol) 0.002 mg/mL, 0.005 mg/mL, 0.01 mg/2mL solution; currently commercially available.
- Approved 12/28/2015: Zoledronic acid (zoledronic acid) 0.04 mg/mL solution; currently commercially available.

Newly approved generics:

- Approved 02/24/2016: Ammonul (sodium phenylacetate and sodium benzoate) 10%/10% solution for injection; currently commercially available.

Discontinued drugs:

- None identified

FDA Safety Alerts/black box warnings:

- None identified

Pipeline alerts:

Agents pending FDA approval include:

- Evenity (romosozumab): treatment of osteoporosis in postmenopausal women at increased risk of fracture; PDUFA: 07/19/2017.
- Signifor LAR (pasireotide long-acting release): treatment of Cushing's disease; PDUFA: 09/01/2017.
- Sensipar (cinacalcet): the treatment of secondary hyperparathyroidism in pediatric patients with chronic kidney disease on hemodialysis; PDUFA: 10/01/2017.

References:

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4. Neil F. Goodman, Rhoda H. Cobin, Walter Futterweit, Jennifer S. Glueck, Richard S. Legro, and Enrico Carmina (2015) American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 2. Endocrine Practice: December 2015, Vol. 21, No. 12, pp. 1415-1426.
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