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New Drugs: Farxiga, Hetlioz, Northera, and Vimizim

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Dr. Thomas A. Gossel has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide information on dapagliflozin (Farxiga™), droxidopa (Northera™), elosulfase alfa (Vimizim™), and tasimelteon (Hetlioz™).

Objectives. At the completion of this activity, the participant will be able to:

1. recognize signs and symptoms, and key features of targeted pathologies including information on their prevalence in the population;
2. recognize important therapeutic uses for the drugs and their applications in specified pathologies;
3. select the indication(s), pharmacologic action(s), clinical application(s), dosing regimens, mode of administration, and availability for each drug;
4. demonstrate an understanding of adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug interactions reported for each agent; and
5. list important counseling advice to convey to patients and/or their caregivers.

The four new-molecular entity drugs discussed in this lesson are indicated to treat a wide variety of pathologies (Table 1). This lesson provides a brief introduction to the therapeutic agents, and its depth is not intended to extend beyond an overview of the topic. The reader is, therefore, urged to consult the products' full prescribing information leaflet (package insert), *Medication Guide* when available, and other published sources for detailed descriptions.

Dapagliflozin (Farxiga)

Due to the progressive nature of Type 2 diabetes mellitus (T2DM), over time therapy with oral agents is often associated with a high failure rate. Current treatments for T2DM are also often limited by significant adverse effects. The traditional focus of therapeutic strategies has long been on developing drugs that improve insulin sensitivity, enhance endogenous insulin secretion, or both. Research efforts in recent years have pursued development of therapies with alternative mechanisms of action. This effort led to a novel class of agents, the sodium-glucose cotransporter 2 (SGLT2) inhibitors. Dapagliflozin is the second agent in this new class that represents a promising treatment pathway. The first was canagliflozin (Invokana) approved in March 2013.

Indications and Use. Farxiga (far-SEE-guh) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It should not be used for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

Diabetes Mellitus. The World Health Organization reports that diabetes affects more than 346 million people worldwide, approximately 70 percent of whom live in low- and middle-income regions. With three new cases of diabetes diagnosed somewhere in the world every ten seconds, the number is projected to soar by 6.5 percent per year, with 439 million afflicted by year 2030. Approximately 24 million individuals in the United States have diabetes, with T2DM accounting for more than 90 percent of cases diagnosed in this country. T2DM is associated with progressive beta-cell failure and increasing insulin resistance. It often necessitates treatment intensification to maintain glycemic control. Many available therapies for T2DM, especially those with an insulin-dependent mechanism of action, are associated with troublesome adverse effects such as weight gain and hypoglycemia.

The consequences of uncontrolled diabetes are multisystem complications and comorbidities, including nephropathy and peripheral neuropathy; glaucoma, cataracts, and retinopathy; limb amputations; bacterial and fungal infections, and other dermatologic pathologies; digestive irregularities; sexual dysfunction; periodontal disease; depression; cardiovascular disease and myocardial infarction; cerebrovascular disease, and stroke. In 2010, 6 to 8 percent of all deaths worldwide were attributed to diabetes. Since people with diabetes are living longer and the number of ethnic minority groups

Table 1
Selected new drugs

Generic Name	Distributor	Indication	Dose*	Dosage Form	Most Common Side Effects	Medication Guide±
Dapagliflozin (Farxiga)	Bristol-Myers Squibb Company	adjunct to diet and exercise in type 2 diabetes mellitus	5 mg once daily	5, 10 mg tablets	(≥5%): female genital mycotic infections, nasopharyngitis, urinary tract infections	Yes
Elosulfase alfa (Vimizim)	BioMarin Pharmaceutical	mucopolysaccharidosis type IVA	2 mg/kg once weekly	1 mg/mL (requiring dilution) infusion	(≥10% and at higher incidence than placebo): fever, vomiting, headache, nausea, abdominal pain, chills, fatigue	No
Droxidopa (Northera)	Chelsea Therapeutics	neurogenic orthostatic hypotension	100 mg to 600 mg 3 times daily	100, 200, 300 mg capsules	(>5%): headache, dizziness, nausea, hypertension, fatigue	No
Tasimelteon (Hetlioz)	Vanda Pharmaceuticals	non-24-hour sleep-wake disorder	20 mg prior to bedtime	20 mg capsules	(>5% and at least twice as high as placebo): headache, increased alanine aminotransferase, nightmares or unusual dreams, upper respiratory or urinary tract infection	No

*Recommended dose for most patients ±Availability at the time of publication of this lesson

at high risk for diabetes is increasing, the U.S. Centers for Disease Control and Prevention estimates that as many as one in three adults in this country will have diabetes by 2050.

The kidneys play a pivotal role in glucose homeostasis through glomerular filtration and reabsorption in the proximal convoluted tubule. A normal, healthy adult filters approximately 180 grams of glucose each day. Most is reabsorbed with less than 1 percent of the glucose excreted into the urine. The normal tubular glucose load is approximately 120 mg/min. Glucosuria occurs when the tubular glucose load exceeds 220 mg/min, which corresponds to a plasma glucose concentration of approximately 200 mg/dL.

The plasma glucose concentration is an important modulator of SGLT2 expression within the kidney and its activity. By blocking the action of SGLT2 in the proximal convoluted tubules, increased urinary glucose excretion with correspondingly reduced plasma glucose levels can be achieved. A potential benefit of this action is the caloric load of approximately 200 to 300 kcal/day that accompanies the reduced glucose resorption.

Mechanism of Action. SGLT2 is a high-capacity, low affinity transporter that is overexpressed and over-activated in persons with T2DM. It is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen, thus assuring that glucosuria does not occur in normal individuals. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion that leads to glucosuria.

This action confers a number of potential clinical advantages. First, the drug's pharmacodynamic effect is dependent on plasma glucose concentration and renal function; therefore, it has a low intrinsic propensity to cause hypoglycemia. Second, because the pharmacodynamic effect is independent of beta-cell function, and insulin secretion and sensitivity, efficacy has been established in patients with different durations of disease. Dapagliflozin is effective as monotherapy in patients with diminished beta-cell function; as add-on therapy in patients with inadequate glycemic control with therapy such as metformin (Glucophage, and others), sulfonylureas, pioglitazone (Actos), glimepiride (Amaryl), and sitagliptin (Januvia); and as add-on therapy in persons with advanced disease receiving high-dose insulin. Third, dapagliflozin-induced urinary glucose excretion is associated with caloric loss, thus decreasing body weight, body fat mass, and waist circumference. Additionally, the mild diuretic effect produced by the renal loss of glucose is associated with a modest decrease in blood pressure.

Efficacy and Safety. The drug's safety and efficacy were evaluated in 16 clinical trials involving more than 9,400 patients

with T2DM. The trials showed significant improvement in glycosylated hemoglobin (HbA1c), a measure of long-term blood glucose control, when used as stand-alone therapy or in combination with other antidiabetic drugs. An increased number of bladder cancers was diagnosed among Farxiga users and, in fact, an FDA advisory panel voted against approval in 2011 because of this. Because the drug causes osmotic diuresis, it can cause dehydration leading to hypotension that can result in dizziness and/or fainting, and a decline in renal function. Patients especially at risk include the elderly, those with impaired renal function, and persons taking loop diuretics to treat other conditions. Overall, the drug seems to be well tolerated with no serious adverse effects. The most common adverse effects reported in clinical trials were genital mycotic infections and urinary tract infection. Nonetheless, FDA is requiring six post-marketing studies:

- a cardiovascular outcomes trial (CVOT) to evaluate the cardiovascular risk in patients with high baseline risk of cardiovascular disease;
- a double-blind, randomized, controlled assessment of bladder cancer risk in patients enrolled in the CVOT;
- an animal study evaluating the role of Farxiga-induced urinary flow/rate and composition changes on bladder tumor promotion in rodents;
- two clinical trials to assess the pharmacokinetics, efficacy, and safety in pediatric patients; and
- an enhanced pharmacovigilance program to monitor reports of liver abnormalities and pregnancy outcomes.

Warnings, Precautions and Contraindications. The following **warnings** and **precautions** are listed:

- *Hypotension:* Before initiating the drug, assess volume status and correct hypovolemia in the elderly, in patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.
- *Impairment in renal function:* Evaluate renal function prior to initial therapy and during therapy. The drug should not be initiated in patients with eGFR <60 mL/min/1.73m^2.
- *Hypoglycemia:* In patients using insulin or an insulin secretagogue with Farxiga, consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.
- *Genital mycotic infections:* Monitor and treat if indicated.
- *Increased LDL-C:* Monitor and treat per standard of care.
- *Bladder cancer:* Farxiga should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.
- *Macrovascular outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Farxiga or any other antidiabetic drug.

Two **contraindications** are listed: (1) history of serious hypersensitivity reactions to Farxiga; and (2) severe renal impairment, end-stage renal disease, or dialysis.

Drug Interactions. In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide (the drug's major [inactive] metabolite) neither inhibited CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Administration, Dosing, and Availability. The recommended starting dose is 5 mg once daily, taken in the morning, with or without food. In patients who require additional glucose control, the dose can be increased to 10 mg daily. Farxiga is available as 5 mg and 10 mg tablets.

Patient Counseling Information. An FDA-approved *Medication Guide* must be dispensed

Table 2
Patient counseling information for Farxiga

Inform patients:
- to read the FDA-approved *Medication Guide* with each prescription refill;
- to be aware of potential risks and benefits of the medicine, and of alternative modes of therapy, about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications; to seek medical advice promptly during periods of stress such as fever, trauma, infection, dehydration, or surgery since medication requirements may change;
- to take the medicine only as instructed. If a dose is missed, take it as soon as possible, but if it is almost time for the next dose, not to take two doses at the same time. Do not change the dose without physician approval;
- of common adverse effects such as vaginal yeast infections and urinary tract infections; (Males may experience yeast infections of the penis such as rash or redness of the glans or foreskin.)
- (females) to immediately inform the physician if she is pregnant or plans to become pregnant, and if she is breastfeeding or planning to breastfeed;
- that symptomatic hypotension (low blood pressure) may occur and to contact their healthcare provider if they experience symptoms of low blood pressure;
- to immediately inform the physician if signs or symptoms suggesting allergic reactions or angioedema appear, and not to take any more drug until they have consulted the physician;
- that their urine may test higher than expected for glucose and to check with the physician for further information.

Table 3
Patient counseling information for Vimizim

Inform patients:
- that anaphylactic reactions may occur when receiving Vimizim treatment. Inform patients of the signs and symptoms of anaphylaxis and have them seek medical care at once should symptoms occur. Patients with acute respiratory illness may be at particular risk.
- of the Morquio A Registry established in order to better understand the variability and progression of the disease as a whole, and to monitor and evaluate long-term treatment effects of Vimizim. Encourage patients to participate; their participation is voluntary. Tell them to contact MARS@bmrn.com or call 1.800.983.4587.

with Farxiga. Specific points for counseling are summarized in Table 2.

Elosulfase alfa (Vimizim)

Indications and Use. Vimizim (VIM-ee-zim) is the first drug approved to treat mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). It is a formulation of elosulfase alfa, which is a purified human enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line.

Mucopolysaccharidosis Type IVA. The mucopolysaccharidoses comprise a group of lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). MPS IVA is characterized by absence or marked reduction in N-acetylgalactosamine-6-sulfatase activity. This deficiency allows for the accumulation of GAG substrates throughout the body that leads to a cascade of multisystemic disease manifestations, including widespread cellular, tissue, and organ dysfunction including problems with bone development, growth, and mobility.

MPS IVA is a progressive condition that mainly affects the skeleton. Signs and symptoms usually appear in early childhood with life expectancy dependent on severity of disease. There are approximately 800 patients in the United States with the disease.

Mechanism of Action. Elosulfase alfa provides the exogenous enzyme that will be taken up into the lysosomes and increase catabolism of the GAG substrates.

Efficacy and Safety. Safety and effectiveness of Vimizim were established in a clinical trial involving 176 participants with MPS IVA, ranging in age from five to 57 years. Patients treated with Vimizim showed greater improvement in a six-minute walk test than those treated with placebo. On average, patients treated with Vimizim in the trial walked 22.5 meters farther in six minutes compared to those receiving placebo. Safety and effectiveness of Vimizim have not been established in pediatric patients less than five years of age.

The most common adverse reactions seen in premarketing trials (≥10 percent of patients, and occurring at a higher incidence than placebo-treated patients) were fever, vomiting, headache, nausea, abdominal pain, chills, and fatigue.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

- *Anaphylaxis and hypersensitivity reactions:* Life-threatening anaphylaxis and hypersensitivity reactions have been observed. If they occur, the infusion should be stopped and appropriate medical treatment initiated. A boxed warning advises of the risk of anaphylaxis.
- *Risk of acute respiratory complications:* Patients with acute febrile or respiratory illness may be at higher risk of life-threatening complications from hypersensitivity reactions.

No **contraindications** or **drug interactions** are listed.

Administration, Dosing, and Availability. The recommended dose is 2 mg/kg infused intravenously over a minimum period of 3.5 to 4.5 hours, based on infusion volume, once every week. Pre-treatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to starting the infusion. Vimizim is supplied in single use vials containing 5 mg elosulfase alfa/5 mL.

Patient Counseling Information. Excerpts from the FDA-approved Patient Prescribing leaflet are shown in Table 3.

Droxidopa (Northera)

Persons with neurogenic orthostatic hypotension (NOH) are often severely restricted in their ability to perform routine daily activities that require walking or standing. Since there are limited treatment options for people with this relatively rare condition, FDA approved Northera with orphan-product status because it is intended to treat a rare disease or condition.

Indications and Use. Northera is indicated for treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (e.g., Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.

Effectiveness beyond two weeks of treatment has not been demonstrated. The continued effectiveness of Northera should be assessed periodically.

Neurogenic Orthostatic Hypotension. This is a rare, chronic, and often debilitating drop in blood pressure upon standing that is associated with Parkinson's disease, multiple system atrophy, and pure autonomic failure. Symptoms include dizziness, lightheadedness, blurred vision, fatigue, and fainting.

Norepinephrine is the body's primary neurotransmitter released at most postganglionic sympathetic nerve terminals. Its action is terminated predominantly by

reuptake into presynaptic sympathetic neurons. There is also some norepinephrine spillover into the plasma. Standing provokes the release of norepinephrine into the synaptic cleft and results in a two- to three-fold increase in plasma norepinephrine. The major deficit in NOH is a reduction in norepinephrine or the inability to release norepinephrine appropriately from sympathetic neurons.

On standing, a gravitational volume shift causes an instant redistribution of circulating blood by pooling of 500 to 1,000 mL within the capacitance vessels located below the diaphragm. As a result, the venous return to the right atrium and the thoracic blood and stroke volume are all reduced, and reflex vasoconstrictive responses mediated by increased sympathetic outflow and decreased vagal activity compensate to maintain arterial pressure in the upper body at the pre-orthostatic level, respectively. Transcapillary filtration in the subdiaphragmatic space additionally reduces the central blood volume by about 15 percent, and the cardiac output by nearly 20 percent. In a healthy patient, however, mean arterial pressure is preserved because of compensatory increases in vascular tone in splanchnic, musculocutaneous and renal areas. The rapid circulatory adjustments are governed by autonomic neural pathways, whereas circulatory changes that occur during the prolonged orthostatic challenge involve neurohumoral mechanisms, such as activation of the renin-angiotensin system. Failure of any of these adaptive reflexes may result in a temporary or persistent fall in blood pressure while in the upright position.

Mechanism of Action. The exact mechanism of action in NOH is unknown. This new drug is a synthetic amino acid analog that is metabolized to norepinephrine by the enzyme dopa-decarboxylase, which is distributed throughout the body. Droxidopa is believed to exert its pharmacologic effects through norepinephrine and not through the parent molecule or other metabolites. Droxidopa increases blood pressure by inducing small and transient rises in plasma norepinephrine, thereby causing peripheral arterial and venous vasoconstriction.

Adverse Effects. Adverse reactions noted in participants enrolled in premarketing trials at an incidence of >5 percent (with at least 3 percent greater incidence in the Northera group than in persons receiving placebo) included headache, dizziness, nausea, hypertension, and fatigue.

Efficacy and Safety. Effectiveness of Northera was established through two clinical trials of two weeks duration, one trial of eight weeks duration, and two long-term studies in people with NOH. Subjects taking Northera reported a decrease in dizziness, lightheadedness, feeling faint, or feeling as if they might lose consciousness compared to those taking a placebo.

Warnings, Precautions and Contraindications. The following **warnings** and **precautions** are listed:

• *Supine hypertension:* Northera may cause or exacerbate supine (lying on the back) hypertension in patients with NOH. Patients should be advised to elevate the head of the bed when resting or sleeping. Blood pressure, both in the supine position and in the recommended head elevated sleeping position should be monitored. The dosage should be reduced or the drug discontinued if supine hypertension persists. If the condition is not well managed, Northera may increase the risk of cardiovascular events.

• *Hyperpyrexia and confusion:* Postmarketing cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported. Patients should be observed carefully when the dosage of Northera is changed or when coadministered levodopa is reduced abruptly or discontinued. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes.

• *Exacerbation of symptoms:* The drug may exacerbate symptoms in patients with existing ischemic heart disease, arrhythmias, and congestive heart failure.

• *Allergic reactions:* The product contains FD+C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in susceptible persons.

There are no **contraindications** listed.

Drug Interactions. Administration of drugs that increase blood pressure (e.g., norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension, and should be used cautiously with droxidopa. Dopa-decarboxylase inhibitors may require dose adjustments for droxidopa.

Table 4
Patient counseling information for Northera

Inform patients:
• that the drug causes elevations in blood pressure and increases the risk of supine hypertension, which could lead to strokes, heart attacks and death; to rest and sleep in an upper-body elevated position and monitor blood pressure; how to manage observed blood pressure elevations; to take the late afternoon dose at least three hours before bedtime to reduce the risk of supine hypertension;
• about the concomitant use of drugs to treat other conditions that may have an additive effect with Northera;
• to consult a physician if they are nursing, pregnant, or planning to become pregnant while taking Northera;
• that they should take Northera the same way each time, either with food or without food, and to swallow the capsules whole;
• that if a dose is missed, patients should take the next dose at the regularly scheduled time and should not double the dose.

Administration, Dosing, and Availability. The recommended starting dose is 100 mg taken orally three times daily: upon arising in the morning, at midday, and in the late afternoon at least three hours prior to bedtime to reduce the potential for supine hypertension during sleep. It should be taken consistently, either with food or without food, and the capsules swallowed whole. Patients should be titrated to symptomatic response, in increments of 100 mg three times daily every 24 to 48 hours up to a maximum dose of 600 mg three times daily (i.e., a maximum total daily dose of 1800 mg). Northera is available in three strengths: capsules containing 100 mg, 200 mg, and 300 mg droxidopa.

Patient Counseling Information. Excerpts from the FDA-approved Patient Prescribing leaflet are shown in Table 4.

Tasimelteon (Hetlioz)

FDA approved Hetlioz (HeT-lee-ōz) to treat Non-24-Hour Sleep-Wake Disorder (Non-24). Non-24 (formerly known as free-running rhythm disorder) occurs in persons who are completely blind. The drug was reviewed under priority review. Priority review provides for an expedited review of drugs that treat serious conditions and have the potential to provide significant improvement in safety or effectiveness of the treatment, diagnosis, or prevention of such serious conditions. Hetlioz also received orphan-product designation because it is intended to treat a rare disease or condition.

Indications and Use. Hetlioz is indicated for treatment of Non-24. The drug can improve the ability to sleep at night and to be active during the day. Because of individual differences in circadian rhythms, drug benefit may not be achieved for weeks or months.

Melatonin and the Non-24-Hour Sleep-Wake Disorder. The serotonin derivative, melatonin, is an ubiquitous (existing everywhere, omnipresent) molecule with functional activity occurring in unicellular organisms, plants, fungi, and animals. In humans, melatonin is synthesized primarily in the pineal gland. This is an endocrine gland about the size of a grain of rice located within the brain. The gland resembles a pine cone, hence its name. It is regulated by the environmental light-dark cycle via the hypothalamic suprachiasmatic nucleus (SCN). Light reaching the retina is relayed to the SCN, which then signals the pineal gland to increase or decrease melatonin release. The pineal gland secretes melatonin during the dark phase of the light-dark cycle and, consequently, melatonin is often called the "hormone of darkness." Melatonin is principally secreted at night and is centrally involved in sleep regulation, as well as in a number of other cyclical body functions. Melatonin is exclusively involved in signaling the "time of day" and "time of year" (hence, considered to help both clock and calendar functions) to all tissues. Melatonin is, therefore, referred to as the body's chronological pacemaker.

Melatonin has obvious physiological effects. Non-24 occurs in persons who are completely blind. Since light does not enter their eyes, and they cannot entrain (synchronize their biological clock) to the 24-hour light-dark environment, the disorder can prevent blind individuals from following the normal daily schedule that sighted persons take for granted. Typically, a consistent daily drift (usually to later and later times) of sleep-onset and wake-up times occurs. As a consequence, persons with Non-24 suffer from periodic daytime somnolence and nighttime insomnia, as the circadian rhythms in alertness and sleep propensity drift in and out of synchrony with the 24-hour day. Simply put, these patients are periodically trying to maintain sleep or wakefulness in opposition to their own biological clocks.

Approximately half of people who are blind have sleep disturbances related to Non-24. Non-24 is thought to be rare in sighted persons.

Although melatonin is a popular treatment for patients with circadian rhythm sleep disorders, two caveats exist. First, melatonin products available OTC cannot be favored for daily use over a long period because their potency, purity, and safety are not regulated by FDA. Second, despite substantial evidence that exogenous melatonin and melatonin agonists promote sleep and entrain endogenous circadian rhythms, the data remain unclear and controversial. Negative study results may have resulted from variations in quality and content of individual melatonin preparations, and absence of large, randomized controlled trials.

Mechanism of Action. The precise mechanism by which tasimelteon exerts its therapeutic effect in patients with Non-24 remains unclear. It is believed that it is an agonist for melatonin MT_1 and MT_2 receptors, with greater affinity for MT_2 than MT_1 receptors. Melatonin effects are mediated by the MT_1 and MT_2 receptors, although the precise role of each receptor subtype in circadian phase shifting and sleep promotion is unknown. Preclinical studies are reported to show that tasimelteon has similar phase-shifting properties as melatonin, but with fewer vasoconstrictive effects.

Efficacy and Safety. Drug effectiveness of Hetlioz was evaluated in 104 participants in two clinical trials of totally blind individuals with Non-24. In the trials, treatment with Hetlioz resulted in significant improvement compared to placebo, both in increasing nighttime sleep and decreasing daytime sleep duration.

In the trials, the most common adverse effects reported by patients treated with Hetlioz were headache, elevated liver enzymes (alanine aminotransferase) in the blood, nightmares or unusual dreams, disturbed night's sleep, upper respiratory or urinary tract infection, and drowsiness. The drug can impair activities that require complete mental alertness. The

Table 5
Patient counseling information for Hetlioz

Inform patients:
- to take the drug before bedtime at the same time every night;
- that because a high-fat meal can reduce blood levels of this medicine, it should be taken without food;
- to skip a dose if they cannot take Hetlioz at approximately the same time on a given night;
- that, after taking the drug, he/she should limit activities to preparing for going to bed because it can potentially impair the performance of activities requiring mental alertness;
- that because of individual differences in circadian rhythms, daily use for several weeks or months may be necessary before drug benefit is observed;
- to swallow the capsule whole.

risk of adverse reactions may be greater in persons >65 years compared to younger persons because exposure to tasimelteon is increased by approximately two-fold compared to younger individuals.

Warnings, Precautions and Contraindications. The following **warnings** and **precautions** are listed:

- *May cause somnolence:* After taking Hetlioz, patients should limit their activity to preparing for going to bed, because the drug can impair the performance of activities requiring complete mental alertness.

No **contraindications** are listed.

Drug Interactions. Strong CYP1A2 inhibitors (e.g., fluvoxamine) may increase exposure of tasimelteon and present a greater risk of adverse reactions. Strong CYP3A4 inducers (e.g., rifampin) may reduce exposure of tasimelteon and, thus, cause reduced drug efficacy. Likewise, smoking induces CYP1A2 levels to reduce tasimelteon exposure.

Efficacy of Hetlioz in treating Non-24 may be reduced in subjects with concomitant administration of beta-adrenergic receptor antagonists.

Administration, Dosing, and Availability. The dose is 20 mg prior to bedtime, at the same time every night. The drug should be taken without food. Hetlioz is available as capsules containing 20 mg tasimelteon.

Patient Counseling Information. Excerpts from the FDA-approved Patient Prescribing leaflet are shown in Table 5

Overview and Summary

This lesson describes four newly-approved drugs to treat a variety of afflictions. The drugs should offer renewed hope to persons being treated for these disease states.

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The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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CE Hours: 1.5 (0.15 CEU)

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continuing education quiz

New Drugs: Farxiga, Hetlioz, Northera, and Vimizim

1. The number of persons in the U.S. who have diabetes is approximately:
   a. 18 million. c. 24 million.
   b. 20 million. d. 30 million.

2. A healthy adult filters approximately how much glucose through the kidneys daily?
   a. 90 grams c. 250 grams
   b. 180 grams d. 300 grams

3. Which of the following is the mechanism of action of dapagliflozin?
   a. Insulin secretion stimulation
   b. SGLT2 activity inhibition
   c. Gluconeogenesis inhibition
   d. Incretin levels enhancement

4. Farxiga should not be used in patients with an active case of which of the following cancers?
   a. Bladder c. Thyroid
   b. Breast d. Liver

5. Vimizim is administered by IV infusion over a minimum of:
   a. 30-60 minutes. c. 3.5-4.5 hours.
   b. 60-120 minutes. d. 4-6 hours.

6. Which disease affects approximately 800 patients in the U.S.?
   a. Diabetes c. NOH
   b. Non-24 d. MPS IVA

7. The major deficit in neurogenic orthostatic hypotension is a decreased ability to release which of the following neurotransmitters from sympathetic neurons?
   a. Dopamine c. Gamma-aminobutyric acid
   b. Ephedrine d. Norepinephrine

Completely fill in the lettered box corresponding to your answer.

1.	[a]	[b]	[c]	[d]	6.	[a]	[b]	[c]	[d]	11.	[a]	[b]	[c]	[d]
2.	[a]	[b]	[c]	[d]	7.	[a]	[b]	[c]	[d]	12.	[a]	[b]	[c]	[d]
3.	[a]	[b]	[c]	[d]	8.	[a]	[b]	[c]	[d]	13.	[a]	[b]	[c]	[d]
4.	[a]	[b]	[c]	[d]	9.	[a]	[b]	[c]	[d]	14.	[a]	[b]	[c]	[d]
5.	[a]	[b]	[c]	[d]	10.	[a]	[b]	[c]	[d]	15.	[a]	[b]	[c]	[d]

❑ **I am enclosing $5 for this month's quiz made payable to: Ohio Pharmacists Association.**

1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
2. Did it meet each of its objectives? ❑ yes ❑ no
   If no, list any unmet_____
3. Was the content balanced and without commercial bias?
   ❑ yes ❑ no
4. Did the program meet your educational/practice needs?
   ❑ yes ❑ no
5. How long did it take you to read this lesson and complete the quiz? _____
6. Comments/future topics welcome.

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8. The debilitating drop in blood pressure upon standing that is associated with Parkinson's disease is best treated with:
   a. Farxiga. c. Northera.
   b. Hetlioz. d. Vimizim.

9. Melatonin is a derivative of:
   a. dopamine. c. norepinephrine.
   b. ephedrine. d. serotonin.

10. All of the following statements are true about Hetlioz EXCEPT:
   a. its approval included FDA's orphan-product designation.
   b. it stimulates the suprachiasmatic nucleus to release melatonin.
   c. its mechanism of action is believed to be as an agonist for MT_1 and MT_2 receptors.
   d. it has been shown to increase blood levels of alanine aminotransferase.

11. Which of the following substances is referred to as the body's *chronological pacemaker*?
   a. Dopamine c. Melatonin
   b. Ephedrine d. Norepinephrine

12. Specific postmarketing studies are required by FDA for which of the following drugs?
   a. Farxiga c. Northera
   b. Hetlioz d. Vimizim

13. The drug label that contains a warning of supine hypertension is:
   a. Farxiga. c. Northera.
   b. Hetlioz. d. Vimizim.

14. Which of the following drugs should be taken without food?
   a. Farxiga c. Northera
   b. Hetlioz d. Vimizim

15. Which of the following drugs should be taken three times daily, with the third dose at least three hours prior to bedtime?
   a. Farxiga c. Northera
   b. Hetlioz d. Vimizim

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