New Drug Update 2014*

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Objectives:

After attending this program, the participant will be able to:

1. Identify the indications and routes of administration of the new therapeutic agents.
2. Identify the important pharmacokinetic properties and the unique characteristics of the new drugs.
3. Identify the most important adverse events and precautions of the new drugs.
4. Compare the new drugs to the older therapeutic agents to which they are most similar in activity.
5. Identify information regarding the new drugs that should be communicated to patients.

New Drug Comparison Rating (NDCR) system

5 = important advance
4 = significant advantage(s) (e.g., with respect to use/effectiveness, safety, administration)
3 = no or minor advantage(s)/disadvantage(s)
2 = significant disadvantage(s) (e.g., with respect to use/effectiveness, safety, administration)
1 = important disadvantage(s)

Additional information

The Pharmacist Activist monthly newsletter: www.pharmacistactivist.com

Dapagliflozin propanediol (Farxiga – Bristol-Myers Squibb; AstraZeneca) Antidiabetic Agent

2014 New Drug Comparison Rating (NDCR) =

Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Comparable drug: Canagliflozin (Invokana)

Advantages:
--May be less likely to cause hypersensitivity reactions and hyperkalemia
--May be less likely to interact with other medications
--May be used in patients with severe hepatic impairment, whereas canagliflozin has not been studied in patients with severe hepatic impairment and use is not recommended

Disadvantages:
--Bladder cancer has been infrequently reported in clinical studies and should not be used in patients with active bladder cancer
--Recommendations for use in patients with impaired renal function are more restrictive (e.g., treatment should not be initiated in patients with an estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m^2, whereas treatment with canagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2)

Most important risks/adverse events: Renal function impairment (contraindicated in patients with severe renal impairment; renal function should be monitored during therapy); hypersensitivity reactions (contraindicated in patients with a history of a serious hypersensitivity reaction); hypotension (risk is increased in patients with impaired renal function or low systolic blood pressure, the elderly, and in patients treated with a diuretic); hypoglycemia (when used concomitantly with insulin or an insulin secretagogue [e.g., a sulfonylurea]); bladder cancer (reported infrequently in clinical studies but at a higher rate that in patients treated with comparator antidiabetic agents or placebo; should not be used in patients with active bladder cancer)

Most common adverse events (and the incidence in patients treated with a dosage of 10 mg daily): Female genital mycotic infections (7%; e.g., vulvovaginal candidiasis), nasopharyngitis (6%), urinary tract infections (4%), increased urination (4%), back pain (4%), male genital mycotic infections (3%; e.g., balanitis), nausea (3%), dyslipidemia (3%; e.g., increased LDL-C)

Usual dosage: Initially, 5 mg once a day in the morning; in patients who tolerate treatment and require additional glycemic control, dosage may be increased to 10 mg once a day in the morning; treatment should not be initiated in patients with an eGFR less than 60 mL/min/1.73 m^2, and treatment should be discontinued if the eGFR is persistently below this value

Products: Film-coated tablets – 5 mg, 10 mg

Comments: Sodium-glucose cotransporter 2 (SGLT2) is expressed in the proximal renal tubules and is responsible for the reabsorption of the majority of glucose filtered by the kidney, Dapagliflozin is the second SGLT2 inhibitor, joining canagliflozin, and these agents reduce the reabsorption of filtered glucose, thereby increasing urinary glucose secretion and lowering blood glucose and glycosylated hemoglobin (hemoglobin A1c [HbA1c]) concentrations. Its effectiveness has been demonstrated in studies in which it has been used as monotherapy, or in combination regimens with metformin, glipizide, glimepiride, pioglitazone, sitagliptin (Januvia), or insulin. The use of dapagliflozin resulted in reductions in HbA1c and fasting plasma glucose (FPG) concentrations and, in many patients, weight reduction. In a placebo-controlled study, the percentage of patients achieving a HbA1c of less than 7% was 44% and 51% in patients receiving daily doses of 5 mg and 10 mg of dapagliflozin, respectively, compared with 32% of those receiving placebo. The use of dapagliflozin in combination with other antidiabetic agents resulted in greater reductions in HbA1c and FPG concentrations. Patients treated with regimens that included dapagliflozin typically lost an average of 1 to 3 kg of body weight over a 24-week period, whereas those who were treated with other antidiabetic agents usually either lost less weight or experienced weight gain.

Empagliflozin (Jardiance – Boehringer-Ingelheim; Lilly) Antidiabetic Agent

2014 New Drug Comparison Rating (NDCR) =

Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Comparable drugs: Canagliflozin (Invokana), dapagliflozin (Farxiga)

Advantages:
--Recommendations for use in patients with impaired renal function are less restrictive (compared with dapagliflozin)
--May be used in patients with severe hepatic impairment (compared with canagliflozin that has not been studied in patients with severe hepatic impairment and use is not recommended)
--Has not been associated with reports of patients experiencing bladder cancer (compared with dapagliflozin)

Disadvantages:
--Additive benefit when used in combination regimens may be less pronounced (although agents have not been directly compared in clinical studies)
--Not available in a combination formulation with metformin (compared with canagliflozin)

Most important risks/adverse events: Renal function impairment (contraindicated in patients with severe renal impairment; renal function should be monitored during therapy); hypersensitivity reactions (contraindicated in patients with a history of a serious reaction); hypotension (risk is increased in patients with impaired renal function or low systolic blood pressure, the elderly, and in patients treated with a diuretic); hypoglycemia (when used concomitantly with insulin or an insulin secretagogue [e.g., a sulfonylurea]); positive urine glucose test results (alternative methods to monitor glycemic control should be used)

Most common adverse events: Urinary tract infection (9%), female genital mycotic infection (5%; e.g., vulvovaginal candidiasis), dyslipidemia (4%; e.g., increased LDL-C), increased urination (3%), male genital mycotic infection (3%; e.g., balanitis), upper respiratory tract infection (3%)

Usual dosage: 10 mg once a day in the morning; in patients who tolerate treatment and require additional glycemic control, dosage may be increased to 25 mg once a day; treatment should not be initiated in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2, and treatment should be discontinued if the eGFR is persistently below this value

Products: Film-coated tablets – 10 mg, 25 mg

Comments: Sodium-glucose cotransporter 2 (SGLT2) is expressed in the proximal renal tubules and is responsible for the reabsorption of the majority of glucose filtered by the kidneys. Empagliflozin is the third SGLT2 inhibitor, joining canagliflozin and dapagliflozin, and these agents reduce the reabsorption of filtered glucose, thereby increasing urinary glucose excretion and lowering blood glucose and glycosylated hemoglobin (hemoglobin A1c [HbA1c]) concentrations. Its effectiveness has been demonstrated in studies in which it has been used as monotherapy, or in combination regimens with metformin, glimepiride, pioglitazone, or insulin. The use of empagliflozin resulted in reductions in HbA1c and fasting plasma glucose (FPG) concentrations and, in many patients, weight reduction. In a placebo-controlled study, the percentage of patients achieving an HbA1c of less than 7% at Week 24 was 35% and 44% in patients receiving daily doses of 10 mg and 25 mg of empagliflozin, respectively, compared with 12% of those receiving placebo. Patients treated with empagliflozin lost an average of approximately 3 kg of body weight, compared with an average loss of 0.4 kg in those receiving placebo. The reductions in HbA1c and FPG in patients treated with combination regimens that included empagliflozin, as well as the percentage of patients achieving an HbA1c of less than 7%, were generally similar to those attained with empagliflozin monotherapy.

Albiglutide (Tanzeum – GlaxoSmithKline) Antidiabetic Agent

2014 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Comparable drugs: Exenatide (Byetta), exenatide extended-release (Bydureon), liraglutide (Victoza)

Advantages:
--Less frequent administration (once a week; compared with liraglutide [once a day] and exenatide [twice a day]; exenatide extended-release is also administered once a week)

Disadvantages:
--Less reduction in glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG) (compared with liraglutide; comparative studies with exenatide have not been conducted))
--Less weight loss (compared with liraglutide
--More likely to cause injection site reactions (compared with exenatide and liraglutide)
--Formulation requires reconstitution (compared with exenatide and liraglutide; exenatide extended-release also requires reconstitution)

Most important risks/adverse events: Thyroid C-cell tumors have been reported in rodents (boxed warning; contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2); pancreatitis (treatment should be discontinued if pancreatitis is suspected; other antidiabetic therapies should be considered in patients with a history of pancreatitis); hypersensitivity reactions; hypoglycemia (when used concomitantly with insulin or an insulin secretagogue [e.g., a sulfonylurea]); risk in patients with severe gastrointestinal disease including severe gastroparesis (use is not recommended in patients with pre-existing severe GI disease; renal function should be monitored in patients with renal impairment experiencing severe GI adverse events); slows gastric emptying and may alter absorption of concomitantly administered oral medications

Most common adverse events: Upper respiratory tract infection (14%), diarrhea (13%), nausea (11%), injection-site reaction (11%)

Usual dosage: Administered subcutaneously in the abdomen, thigh, or upper arm; 30 mg once a week on the same day each week; dosage may be increased to 50 mg once a week if the glycemic response is not adequate; if a dose is missed, the patient should administer it as soon as possible within 3 days after the missed dose; thereafter, doses should be administered on the usual day of administration

Products: Pen-injectors – 30 mg, 50 mg of lyophilized powder that is reconstituted with diluent included in the pen device (should be stored in a refrigerator)

Comments: Albiglutide is the third glucagon-like peptide-1 (GLP-1) receptor agonist, joining exenatide (marketed initially in an immediate-release formulation and subsequently in an additional extended-release formulation) and liraglutide. The new drug is a recombinant fusion protein comprised of two tandem copies of modified human GLP-1 genetically fused in tandem to human albumin. A human GLP-1 fragment sequence has been modified to confer resistance to dipeptidyl peptidase 4 (DPP-4) mediated proteolysis. The human albumin moiety of the protein, together with the DPP-4 resistance, provides a longer half-life that permits administration of doses just once a week.

The effectiveness of albiglutide was demonstrated in 8 clinical trials that included more than 2,000 patients with type 2 diabetes. Albiglutide was evaluated as a stand-alone therapy, as well as in combination with metformin, glimepiride, pioglitazone, or insulin (but not prandial insulin). Its use resulted in reduction of HbA1c and FPG concentrations. In a study in which albiglutide was compared with liraglutide, the new drug provided less of an HbA1c reduction (0.8%) than liraglutide (!.0%), and the between-treatment difference did not meet the pre-specified, non-inferiority margin.

Umeclidinium bromide/vilanterol trifenatate (Anoro Ellipta – GlaxoSmithKline)

Bronchodilator

2014 New Drug Comparison Rating (NDCR) =

Indication: For oral inhalation for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

Comparable drugs: Other long-acting muscarinic antagonists (LAMA) that are used as bronchodilators via oral inhalation: Aclidinium (Tudorza Pressair); tiotropium (Spiriva HandiHaler)

Advantages:
--Is the first combination formulation for oral inhalation that includes a LAMA and a long-acting beta$_2$-adrenergic agonist (LABA)
--More convenient administration and lesser likelihood of problems associated with administration (compared with tiotropium that is supplied in capsules that are placed in a device for oral inhalation)
--Is administered less frequently (compared with aclidinium that is administered twice a day)

Disadvantages:
--Indication does not include use to reduce exacerbations of COPD (whereas the labeled indication for tiotropium includes use to reduce exacerbations)
--Umeclidinium is not available as a single agent (has been subsequently approved in a formulation as a single agent [Incruse Ellipta])

Most important risks/adverse events: Contraindicated in patients with severe hypersensitivity to milk proteins or hypersensitivity to any of the components of the formulation; paradoxical bronchospasm (treatment should be discontinued); worsening narrow-angle glaucoma; worsening urinary retention; must not be used for the relief of acute bronchospasm (i.e., rescue therapy); action may be increased by other agents with anticholinergic activity and concurrent use should be avoided; increased risk of asthma-related death (attributable to vilanterol; boxed warning; not indicated for the treatment of asthma); other risks and adverse events attributable to vilanterol are included in the labeling

Most common adverse events: Pharyngitis (2%), diarrhea (2%), pain in extremity (2%)

Usual dosage: One inhalation (umeclidinium/vilanterol: 62.5 mcg/25 mcg) once a day via oral inhalation; should be administered at the same time every day, and should not be used more than 1 time every 24 hours

Product: Inhaler containing 2 blister strips of powder for oral inhalation, each with 30 blisters; one strip contains 62.5 mcg of umeclidinium in each blister and the other contains 25 mcg of vilanterol in each blister; inhaler unit is supplied in a moisture-protective foil tray and removed immediately before initial use – should be discarded when the dose counter reads "0" after all blisters have been used, or 6 weeks after opening the foil tray, whichever comes first

Comments: Umeclidinium is the third long-acting anticholinergic agent, also designated as long--acting muscarinic antagonists (LAMA), to be approved for use via oral inhalation as bronchodilators in the treatment of patients with COPD, joining tiotropium and aclidinium. It was initially approved in a formulation with the LABA vilanterol, and is the first combination formulation to include both a LAMA and LABA. Therefore, patients who do not experience adequate benefit with the use of one inhaled bronchodilator can be treated with two bronchodilators with one dose from the same delivery device. Although a combination formulation (Combivent Respimat) of ipratropium and albuterol is also available, these agents have a shorter duration of action and must be administered more frequently.

The effectiveness of umeclidinium/vilanterol was demonstrated in studies in which the new combination formulation provided a larger increase in FEV_1 (forced expiratory volume in the first second of expiration) at 24 weeks than either of the individual components or placebo.

Vortioxetine hydrobromide (Brintellix – Lundbeck; Takeda) Antidepressant

2013 New Drug Comparison Rating (NDCR) =

Indication: Treatment of major depressive disorder

Comparable drugs: Other serotonin reuptake inhibitors (e.g., selective serotonin reuptake inhibitors [SSRIs]; escitalopram [e.g., Lexapro] is the specific agent to which comparisons are made)

Advantages:
--In addition to inhibiting serotonin reuptake, has a unique combination of actions on multiple serotonin receptor types
--May be more effective in some patients (however, the contribution of its additional actions on serotonin receptors has not been established and the clinical relevance is not known)
--May be less likely to cause sexual dysfunction

Disadvantages:
--Has not been directly compared with other antidepressants in clinical studies
--Labeled indications are more limited (escitalopram is also indicated for the treatment of generalized anxiety disorder, and fluoxetine, paroxetine, and sertraline have multiple additional labeled indications)
--Has not been evaluated in patients less than 18 years of age (whereas escitalopram is indicated in the treatment of depression in adolescent patients aged 12-17 years)
--Interacts with CYP2D6 inhibitors (e.g., quinidine) and CYP inducers (e.g., carbamazepine)
--Dosage titration is needed

Most important risks/adverse events: Risk of suicidal thinking and behavior in children, adolescents, and young adults to 24 years (boxed warning); concurrent use with a monoamine oxidase inhibitor (MAOI; e.g., tranylcypromine, linezolid [Zyvox], intravenous methylene blue) is contraindicated (an MAOI for the treatment of a psychiatric disorder should not be initiated within 21 days after stopping treatment with vortioxetine); serotonin syndrome (risk is increased by the use of other agents having serotonergic activity (e.g., SSRIs and certain other antidepressants, triptans, tramadol, tryptophan, St. John's wort); activation of mania/hypomania; hyponatremia; abnormal bleeding (risk is increased in patients being treated with an anticoagulant, aspirin, or an NSAID); may cause CNS effects and patients should not engage in potentially hazardous activities until they have observed how the medication affects them; action may be increased by the concurrent use of a strong CYP2D6 inhibitor (e.g., bupropion, quinidine) and decreased by a strong CYP inducer (e.g., carbamazepine, rifampin)

Most common adverse events (and incidence reported with a dosage of 20 mg once a day): Nausea (32%), dizziness (9%), vomiting (6%), constipation (6%)

Usual dosage: Recommended starting dosage – 10 mg once a day; should be subsequently increased to 20 mg once a day as tolerated; in patients known to be CYP2D6 poor metabolizers, the maximum recommended dosage is 10 mg once a day; dosage should be reduced by one-half in patients treated with a strong CYP2D6 inhibitor; discontinuation of treatment with dosages of 15 mg or 20 mg a day should involve an initial reduction of dosage to 10 mg once a day for one week

Products: Tablets – 5 mg, 10 mg, 15 mg, 20 mg

Comments: The primary mechanism of vortioxetine is inhibition of serotonin (5-HT) reuptake. In addition, it acts as an agonist at 5-HT1A receptors, a partial agonist at 5-HT1B receptors, and an antagonist at 5-HT3, 5-HT1D, and 5-HT7 receptors. It is the only antidepressant with this combination of actions at serotonin receptors, but the contribution of any of these additional actions to the antidepressant effect has not been established. Its effectiveness has been demonstrated in 6 placebo-controlled, short-term studies, one of which was conducted in elderly patients. In addition, it was evaluated in a long-term study in which its use resulted in a longer time to recurrence of depressive episodes, compared to placebo.

Apremilast (Otezla – Celgene) Anti-inflammatory Agent

2014 New Drug Comparison Rating (NDCR) =

Indication: Treatment of adult patients with active psoriatic arthritis

Comparable drugs: Tumor necrosis factor (TNF) blockers (adalimumab [Humira], certolizumab [Cimzia], etanercept [Enbrel], golimumab [Simponi], infliximab [Remicade]), and the interleukin-12 and -23 inhibitor ustekinumab (Stelara)

Advantages:
--Has a unique mechanism of action (is a phosphodiesterase-4 [PDE4] inhibitor)
--May be effective in some patients who have not experienced an adequate response or satisfactorily tolerated other treatments
--Is administered orally (whereas comparable drugs are administered subcutaneously or intravenously)
--Less risk of infection

Disadvantages:
--Has not been directly compared with other medications in clinical studies
--Appears to be less effective based on data from noncomparative studies
--Labeled indications are more limited (e.g., labeled indications for adalimumab also include plaque psoriasis, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis)
--May cause the emergence or worsening of depression
--Dosage titration is complex

Most important risks/adverse events: Depression and suicide ideation/behavior (caution should be observed in deciding whether the drug should be used in patients with a history of these experiences; patients and caregivers should be alert for the emergence or worsening of these responses); weight loss (if excessive weight loss occurs, discontinuation of treatment should be considered); is a substrate for the CYP3A4 metabolic pathway and effectiveness may be reduced by the concurrent use of a strong cytochrome P450 enzyme inducer (e.g., rifampin, carbamazepine; concurrent use is not recommended); dosage should be reduced in patients with severe renal impairment

Most common adverse events: Nausea (9%), diarrhea (8%), headache (6%)

Usual dosage: Dosage is titrated over the first 5 days of treatment to reduce gastrointestinal symptoms; on Day 1, a dose of 10 mg is administered in the morning, on Day 2, 10 mg is administered in both the morning and evening, on Day 3, 10 mg is administered in the morning and 20 mg in the evening, on Day 4, 20 mg is administered in both the morning and evening, on Day 5, 20 mg is administered in the morning and 30 mg in the evening, and on Day 6 and thereafter, the recommended maintenance dosage of 30 mg in both the morning and evening is administered; in patients with severe renal impairment, the morning doses should be administered, but not the evening doses, with a recommended maintenance dosage of 30 mg once a day

Products: Film-coated tablets – 10 mg, 20 mg, 30 mg

Comments: Phosphodiesterase-4 (PDE4) mediates the conversion of cyclic adenosine monophosphate (cAMP) to AMP that can contribute to the occurrence of inflammation. By inhibiting PDE4, apremilast increases intracellular cAMP concentrations resulting in a reduced inflammatory response. The effectiveness of apremilast was evaluated in three placebo-controlled studies in patients with active psoriatic arthritis despite prior or current therapy with a disease-modifying antirheumatic drug (DMARD). Some patients had been previously treated with a biologic, including a TNF blocker. The percentages of patients treated with apremilast who achieved an American College of Rheumatology (ACR) 20 response (representing at least a 20% improvement from baseline in most measures of disease activity) at Week 16 were 38%, 32%, and 41%, compared with 19%, 19%, and 18%, respectively, in patients receiving placebo. The patients treated with apremilast experienced improvement in each of the seven components of the ACR evaluation (e.g., number of tender joints, number of swollen joints, patient's assessment of pain).

Vedolizumab (Entyvio – Takeda) Agent for Inflammatory Bowel Disease

2014 New Drug Comparison Rating (NDCR) =

Indications: Administered by intravenous infusion for the treatment of adult patients with moderately to severely active ulcerative colitis, or moderately to severely active Crohn's disease, who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator (e.g., azathioprine, mercaptopurine, cyclosporine); or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids; in patients with ulcerative colitis, it is indicated for inducing and maintaining clinical response, inducing and maintaining clinical remission, improving the endoscopic appearance of the mucosa, and achieving corticosteroid-free remission; in patients with Crohn's disease, it is indicated for achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission

Comparable drug: Natalizumab (Tysabri)

Advantages:
--Labeled indications include the treatment of patients with ulcerative colitis
--Action as an integrin receptor antagonist appears to be limited to the gastrointestinal tract
--Appears unlikely to be associated with the occurrence of progressive multifocal leukoencephalopathy (PML)

Disadvantages:
--None

Most important risks/adverse events: Hypersensitivity reactions (contraindicated in patients with a history of a severe hypersensitivity reaction to the drug); increased risk of infection (treatment should not be initiated in patients with an active, serious infection until the infection is controlled; if a severe infection occurs during treatment, withholding therapy should be considered; all immunizations should be up to date before initiating treatment); potential risk for PML based on mechanism of action (there were no reports of PML in the clinical studies but patients should be monitored for any new onset, or worsening, of neurological signs or symptoms); elevations of transaminase and/or bilirubin concentrations

Most common adverse events: Nasopharyngitis (13%), headache (12%), arthralgia (12%), nausea (9%), pyrexia (8%), upper respiratory tract infection (7%), fatigue (6%), cough (5%)

Usual dosage: Administered as an intravenous infusion over 30 minutes; should be administered by a health professional and patients should be observed during the infusion; 300 mg at zero, 2, and 6 weeks, and then every 8 weeks thereafter; if there has not been evidence of therapeutic benefit by week 14, treatment should be discontinued

Product: Vials – 300 mg (should be stored in a refrigerator); contents of vial should be reconstituted with 4.8 mL of Sterile Water for Injection; 5 mL of reconstituted solution should be withdrawn from the vial and added to 250 mL of 0.9% Sodium Chloride Injection

Comments: Vedolizumab is a humanized monoclonal antibody that acts as an integrin receptor antagonist by specifically binding to alpha-4 beta-7 integrin receptors. These receptors are expressed on the surface of a subset of memory T-lymphocytes that preferentially migrate into the gastrointestinal (GI) tract. The alpha-4 beta-7 integrin receptors interact with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) that is mainly expressed on gut endothelial cells and plays a significant role in the concentrating of of inflammatory T-lymphocytes in gut tissue. This interaction has been implicated as an important contributor to the chronic inflammation that characterizes ulcerative colitis and Crohn's disease. By blocking the interaction of the integrin receptors with MAdCAM-1, vedolizumab inhibits the migration of memory T-l;ymphocytes across the endothelium into inflamed GI parenchymal tissue. Its effectiveness was demonstrated in placebo-controlled studies in which a significantly higher percentage of patients treated with the drug experienced improvement in the parameters reflected by its labeled indications compared with the response in those receiving placebo. Unlike natalizumab, vedolizumab does not bind to alpha-4 beta-1 integrins and is not likely to exhibit activity in the central nervous system (CNS) or be associated with the occurrence of PML, a rare but often fatal opportunistic viral infection of the CNS.

Simeprevir sodium (Olysio – Janssen) Antiviral Agent

2013 New Drug Comparison Rating (NDCR) =

Indication: Treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen (efficacy has been established in combination with peginterferon alfa and ribavirin, in hepatitis C virus (HCV) genotype 1 infected patients with compensated liver disease [including cirrhosis])

Comparable drugs: Boceprevir (Victrelis), telaprevir (Incivek)

Advantages:
--May be effective in some patients who have experienced an inadequate response with regimens including the comparable drugs
--Is less likely to be associated with the occurrence of anemia
--Is less likely to cause serious skin reactions (compared with telaprevir)
--Is less likely to cause hypersensitivity reactions (compared with boceprevir)
--Is administered once a day (whereas telaprevir is administered twice a day and boceprevir three times a day)

Disadvanatages:
--Is less effective in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism
--May be more likely to cause photosensitivity reactions
--Has greater systemic exposure and risk of adverse events in patients of East Asian ancestry

Most important risks/adverse events: Contraindicated in women who are pregnant and in men whose female partners are pregnant (because the ribavirin component of the regimen may cause birth defects and fetal death; negative pregnancy test must be obtained; two effective methods of contraception should be used during treatment and for 6 months after completion of treatment); photosensitivity reactions (sun exposure should be limited and sun protective measures taken; tanning devices should be avoided); rash (treatment should be discontinued if severe rash occurs); is a substrate of CYP3A and action may be increased by moderate or strong inhibitors of CYP3A (e.g., clarithromycin) and decreased by moderate or strong inducers of CYP3A (e.g., carbamazepine) – concurrent use of interacting agents is best avoided

Most common adverse events: Rash (including photosensitivity; 28%), pruritus (22%), nausea (22%)

Usual dosage: 150 mg once a day with food for 12 weeks; should be used in combination with peginterferon alfa and ribavirin; treatment-naïve and prior relapser patients should receive an additional 12 weeks of treatment with peginterferon alfa and ribavirin (for a total treatment duration of 24 weeks); prior non-responder patients (including partial and null-responders) should receive an additional 36 weeks of treatment with peginterferon alfa and ribavirin (for a total treatment duration of 48 weeks)

Product: Capsules – 150 mg

Comments: Simeprevir is a direct-acting antiviral agent against the hepatitis C virus (HCV). Like boceprevir and telaprevir that were first marketed in 2011, it is an inhibitor of the HCV NS3/4A protease that is necessary for replication of the virus. The effectiveness of simeprevir was demonstrated in studies designed to measure whether a patient's HCV was no longer detected in the blood at least 12 weeks after finishing treatment (sustained virologic response [SVR]). Eighty percent of treatment-naïve patients treated with simeprevir, peginterferon alfa, and ribavirin achieved a SVR, compared to 50% of those treated with peginterferon alfa and ribavirin. In a study in prior relapser patients, 79% of patients treated with the 3-drug regimen achieved a SVR, compared with 37% of those treated with peginterferon alfa and ribavirin. In another study, the regimen with simeprevir improved response rates in partial responders and those who did not respond to prior therapy (null responders). A reduction in the effectiveness of simeprevir was observed in patients infected with the genotype 1a HCV with an NS3 Q80K polymorphism, a strain that is commonly found in the US. Patients should be screened for this strain prior to initiating therapy.

Sofosbuvir (Sovaldi – Gilead) Antiviral Agent

2013 New Drug Comparison Rating (NDCR) =

Indication: Treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen (efficacy has been established in patients with hepatitis C virus (HCV) genotype 1, 2, 3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection)

Comparable drugs: Boceprevir (Victrelis), telaprevir (Incivek), simeprevir (Olysio)

Advantages:
--Has a unique mechanism of action (is a HCV nucleotide analog NS5B polymerase inhibitor)
--Is effective in some patients in combination antiviral regimens that do not include interferon
--Is effective in some patients with HCV genotypes 2 and 3 infection
--Is effective in some patients awaiting liver transplantation, and in some patients with HCV/HIV-1 co-infection
--Activity has not been reported to be reduced in patients with HCV genotype 1a with an NS3 Q80K polymorphism (compared with simeprevir)
--Is less likely to cause serious skin reactions (compared with telaprevir), hypersensitivity reactions (compared with boceprevir), and photosensitivity (compared with simeprevir)
--Interacts with fewer medications
--Is administered once a day (compared with telaprevir that is administered twice a day and boceprevir that is administered three times a day)
--Used in shorter treatment regimens (12 weeks) for many patients

Disadvantages:
--May be more likely to cause fatigue and nausea
--Safety and dosage recommendations have not been established for patients with severe renal impairment

Most important risks/adverse events: Contraindicated in women who are pregnant and in men whose female partners are pregnant (because the ribavirin component of the regimen may cause birth defects and fetal death; negative pregnancy test must be obtained; two non-hormonal methods of contraception should be used during treatment and for 6 months after completion of treatment); action may be reduced by potent intestinal P-glycoprotein inducers (e.g., rifampin, St. John's wort), and concurrent use should be avoided; action may also be reduced by the concurrent use of other transporter and/or enzyme inducers (e.g., carbamazepine)

Most common adverse events: when used in combination with ribavirin – fatigue (38%), headache (24%); when used in combination with ribavirin and peginterferon alfa – fatigue (59%), headache (36%), nausea (34%), insomnia (25%), anemia (21%)

Usual dosage: 400 mg once a day with ribavirin for 12 weeks in patients with genotype 2 CHC, and for 24 weeks in patients with genotype 3 CHC; 400 mg once a day with ribavirin and peginterferon alfa for 12 weeks in patients with genotype 1 or 4 CHC; use with ribavirin for 24 weeks is an option for patients with genotype 1 infection who are ineligible to receive an interferon-based regimen; in patients with hepatocellular carcinoma awaiting liver transplantation, is used in combination with ribavirin for up to 48 weeks or until the time of liver transplantation

Product: Tablets – 400 mg

Comments: Sofosbuvir is a direct-acting antiviral agent against the hepatitis C virus (HCV) and has a unique mechanism of action as a nucleotide analog inhibitor of HCV NS5B polymerase, a protein needed for the virus to replicate. It is extensively metabolized in the liver to form an active derivative. It is the first drug to be approved for the treatment of certain types of HCV infection in a regimen that does not include interferon, and the FDA has designated it as a breakthrough therapy. Treatment for 12 weeks with regimens that include sofosbuvir have achieved a sustained virologic response (SVR) of 90% in some studies, and treatment has been effective in many patients with HCV infection who have not experienced an adequate response with other treatment regimens.

Avanafil (Stendra – Auxilium; Vivus) Agent for Erectile Dysfunction

2014 New Drug Comparison Rating (NDCR) =

Indication: Treatment of erectile dysfunction

Comparable drugs: Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra, Staxyn)

Advantages:
--May have a faster onset of action (is administered approximately 15 minutes before sexual activity whereas sildenafil and vardenafil are usually taken approximately 60 minutes before sexual activity)
--Less risk of problems associated with QT interval prolongation (compared with vardenafil)
--Dosage adjustment is not needed in patients with mild to moderate hepatic impairment (compared with sildenafil and tadalafil with which dosage adjustment may be needed)

Disadvantages:
--Labeled indications are more limited (compared with tadalafil that is also indicated for use once a day in a lower dosage for erectile dysfunction, and for the treatment of benign prostatic hyperplasia)
--Has a shorter duration of action (compared with tadalafil)
--Use is not recommended in patients with severe renal impairment (whereas comparable drugs can be used with dosage adjustments and/or appropriate precautions)

Most important risks/adverse events: May potentiate the hypotensive effects of nitrates (e.g., nitroglycerin) and concurrent use with any form of an organic nitrate is contraindicated (if a nitrate is considered necessary in a life-threatening situation, at least 12 hours should elapse after a dose of avanafil before a nitrate is administered); may increase the blood pressure-lowering action of alpha-adrenergic blocking agents (e.g., tamsulosin) and antihypertensive agents; consumption of alcoholic beverages may increase the risk of orthostatic signs and symptoms (e.g., decrease in standing blood pressure, dizziness); use should be avoided in patients in whom sexual activity is inadvisable due to their cardiovascular status/risk; prolonged erection (greater than 4 hours)/priapism (emergency treatment should be obtained); sudden loss of vision (may be related to non-arteritic ischemic optic neuropathy (NAION); sudden decrease or loss of hearing; is a CYP3A4 substrate and concurrent use with a strong CYP3A4 inhibitor (e.g., clarithromycin, ritonavir) should be avoided; use is not recommended in patients with severe hepatic impairment or severe renal impairment

Most common adverse events: Headache (7%), flushing (4%), nasal congestion (3%), nasopharyngitis (3%), back pain (2%)

Usual dosage: Initially, 100 mg, taken as needed approximately 15 minutes before sexual activity; based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or reduced to 50 mg; maximum recommended dosing frequency is once a day; in patients who are stabilized on therapy with an alpha-blocker, initial dose should be 50 mg; in patients treated with a moderate CYP3A4 inhibitor (e.g., diltiazem), the maximum recommended dose is 50 mg

Products: Tablets – 50 mg, 100 mg, 200 mg

Comments: Avanafil is the fourth phosphodiesterase type 5 (PDE5) inhibitor to be approved for the treatment of erectile dysfunction, joining sildenafil, tadalafil, and vardenafil. Erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Inhibition of PDE5 enhances the effect of NO. Avanafil and the other PDE5 inhibitors have been demonstrated to be significantly more effective than placebo in the treatment of erectile dysfunction in clinical trials. The drugs have not been compared with each other in clinical studies but avanafil appears to have a faster onset of action than the other agents and most patients can take it approximately 15 minutes before sexual activity. Tadalafil has the slowest onset of action of the four agents but also the longest duration of action. It is also used in a lower dosage once a day for the treatment of erectile dysfunction. Tadalafil is also indicated for the treatment of benign prostatic hyperplasia, and formulations of both sildenafil (Revatio) and tadalafil (Adcirca) are also approved for the treatment of pulmonary arterial hypertension.

Bazedoxifene acetate/conjugated estrogens (Duavee – Pfizer) Agent for Menopause-associated Conditions

2014 New Drug Comparison Rating (NDCR) =

Indications: In women with a uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause, and the prevention of postmenopausal osteoporosis

Comparable drug: Raloxifene (Evista)

Advantages:
--Labeled indications include treatment of vasomotor symptoms associated with menopause
--Is the only combination formulation with an estrogen agonist/antagonist and estrogen

Disadvantages:
--Labeled indication for postmenopausal osteoporosis is limited to prevention (whereas the indication for raloxifene also includes treatment)
--Labeled indications do not include a reduction in risk of invasive breast cancer
--Labeling includes a boxed warning regarding an increased risk of endometrial cancer
--Bazedoxifene is only available in a fixed-dose combination product and not as a single agent

Most important risks/adverse events: Contraindications and other risks include problems that could result from the use of estrogen alone (i.e., the conjugated estrogens component); contraindicated in patients with undiagnosed abnormal uterine bleeding, known or suspected breast cancer or estrogen-dependent neoplasia, active or history of thromboembolism, hepatic impairment or disease, or during pregnancy (Pregnancy Category X); increased risk of stroke, deep vein thrombosis, dementia, and endometrial cancer (boxed warning); should not be used with additional estrogens (boxed warning) or with progestins or other estrogen agonist/antagonists; estrogen therapy has also been associated with an increased risk of hypertriglyceridemia, gallbladder disease, visual abnormalities, and hypothyroidism (thyroid function should be monitored)

Most common adverse events: Muscle spasms (8%), nausea (8%), diarrhea (8%), dyspepsia (7%), upper abdominal pain (7%), oropharyngeal pain (7%), neck pain (5%), dizziness (5%)

Usual dosage: One tablet daily (20 mg of bazedoxifene and 0.45 mg of conjugated estrogens); in the prevention of osteoporosis, supplemental calcium and/or vitamin D should be taken if daily intake is not adequate

Product: Tablets – 20 mg of bazedoxifene and 0.45 mg of conjugated estrogens

Comments: Estrogen is effective in reducing menopausal symptoms but, when used alone, it increases the risk of endometrial hyperplasia that may be a precursor to endometrial cancer. To reduce the risk of endometrial problems, a progestin has been used in combination with an estrogen, but additional risk may also be experienced. Bazedoxifene is an estrogen agonist/antagonist, also designated as a selective estrogen receptor modulator (SERM), that activates estrogen receptors in some tissues while inhibiting estrogen activity in others (e.g., the uterus). Its use in combination with conjugated estrogens provides the first combination product that includes an estrogen agonist/antagonist instead of a progestin to reduce the risk of endometrial hyperplasia.

The effectiveness of bazedoxifene/conjugated estrogens in the treatment of vasomotor symptoms was demonstrated in a placebo-controlled study in which the new product significantly reduced the number and severity of hot flashes. In studies in which it was evaluated for the prevention of postmenopausal osteoporosis, it significantly increased lumbar spine bone mineral density (BMD) and total hip BMD. When considered solely for the prevention of postmenopausal osteoporosis, the new product should only be used in women at significant risk of osteoporosis and non-estrogen medication should be carefully considered.

Other estrogen agonist/antagonists that are indicated for use in postmenopausal women include raloxifene that is indicated for the treatment and prevention of osteoporosis, and for the reduction in risk of invasive breast cancer, as well as ospemifene (Osphena) that was marketed in 2013 for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.