"New Drugs: 2013-2014"

May 2014

In this lesson, we will specifically review 2 of the 3 new breakthrough drugs. Additionally, we will discuss a few of the other new drugs that are being seen most frequently in the pharmacy. (See our website---www.wfprofessional.com---for a full list of all 27 drugs approved in 2013. Go to the website; click on 'Courses,' Click on '2014,' open the most recent lesson, and scroll to the list of New Approved Drugs 2013).

The objectives of this lesson are such that upon completion:

Pharmacists will be able:

1. Describe the 2013 new approved drugs.
2. Discuss the role of these agents in therapy.
3. List adverse effects of these new agents.
4. Recommen specific counseling points.

Technicians will be able to:

1. Recognize the 2013 new approved drugs.
2. List the primary indication for the new drugs.
3. Recall the more significant problems, if any, associated with use of these new drugs.

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To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

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INTRODUCTION

The Food and Drug Administration (FDA) approved 27 new drugs in 2013, down from 39 new agents in 2012. Despite this decline in approvals, FDA officials stated that the number of innovative products is in line with the historical trend. On average, the FDA has approved 28 new drugs annually over the past five years.[1]

In this lesson, we will specifically review 2 of the 3 new breakthrough drugs. Additionally, we will discuss a few of the other new drugs that are being seen most frequently in the pharmacy. (See our website---www.wfprofessional.com---for a full list of all 27 drugs approved in 2013. Go to the website; click on 'Courses,' Click on '2014,' open the most recent lesson, and scroll to the list of New Approved Drugs 2013).

Newly Approved Drugs -2013[1]

GENERIC NAME	BRAND NAME	MANUFACTURER	DESCRIPTION	USE/REVIEW STATUS
Respiratory/Pulmonary Agents				
Fluticasone and vilanterol inhalation powder	Breo Ellipta	Glaxo Smith Kline	Corticosteroid/ long acting beta 2 agonist combination	Chronic obstructive pulmonary disease (COPD)
Riociguat	Adempas	Bayer	Soluble guanylate cyclase (sGC) stimulator	Pulmonary hypertension ***Priority Review***
Umeclidinium and vilanterol inhalation powder	Anora Ellipta	Glaxo Smith Kline	Anticholinergic/ long acting beta 2 agonist combination	Chronic obstructive pulmonary disease (COPD)
Macitentan	Opsumit	Actelion	Endothelin receptor antagonist (ERA)	Pulmonary arterial hypertension (PAH) ***Orphan Drug***
Cardiovascular Agents Cardiovascular Agents				
Mipomersen	Kynamro	Genzyme	Inhibitor of apolipoprotein B-100 synthesis	Homozygous familial Hypercholesterolomia (HoFH) ***Orphan Drug***
Endocrinology				
Alogliptin	Nesina	Takeda	DPP4 inhibitor	Type 2 Diabetes
Ospemifene	Osphena	Shionogi	Estrogen agonist/ antagonist	Moderate to severe dyspareunia
Canagliflozin	Invokana	Janssen	Sodium-glucose co-transporter 2 (SGLT2) inhibitor	Type 2 Diabetes
Conjugated estrogens/ bazedoxifene	Duavee	Pfizer	Conjugated estrogens and estrogen agonist/antagonis	Moderate to severe hot flashes
Neurology/Psychiatry				
Dimethyl fumarate	Tecfidera	Biogen	Activator of Nuclear factor-like pathway	Relapsing forms of multiple sclerosis (MS)

GENERIC NAME	BRAND NAME	MANUFACTURER	DESCRIPTION	USE/REVIEW STATUS
Vortioxetine	Brintellix	Takeda	SSRI	Major Depressive disorder
Eslicarbazepine	Aptiom	Sunovion	Dibenzazepine	Seizures
Oncology/Hematology				
Pomalidomide	Pomalyst	Celgene	Thalidomide analogue	Multiple myeloma ***Orphan Drug*** ***Accelerated approval***
Ado-trastuzumab emtansine	Kadcyla	Genentech	HER2-targeted antibody and microtubule inhibitor conjugate	HER2-positive, late-stage (metastatic) breast cancer ***Priority review***
Radium Ra223 dichloride	Xofigo	Bayer	Radium 223 dichloride	Symptomatic late-stage (metastatic) castration-resistant prostate cancer that has spread to bones but not to other organs ***Priority review***
Dabrafenib	Tafinlar	Glaxo Smith Kline	Kinase inhibitor	Melanoma in tumors that express the BRAF V600E gene mutation. ***Orphan Dug***
Obinutuzumab	Gazyva	Genentech	CD20-directed cytolytic antibody	Combined with chlorambucil to treat patients with previously untreated chronic lymphocytic leukemia (CLL) ***Breakthrough Drug*** ***Orphan drug***
Trametinib	Mekinist	Glaxo Smith Kline	Kinase inhibitor	Tumors that express the BRAF V600E or V600K gene mutations
Ibrutinib	Imbruvica	Pharmacyclics	Kinase inhibitor	Mantle cell lymphoma (MCL) ***Breakthrough Drug*** ***Orphan drug***
Afatinib	Gilotrif	Boehringer-Ingelheim	Kinase inhibitor	Late stage (metastatic) non-small cell lung cancer (NSCLC) whose tumors express specific types of epidermal growth factor receptor (EGFR) gene mutations, as detected by an FDA-approved test ***Orphan drug***
Infectious Diseases/Immunology				
Dolutegravir	Tivicay	ViiV Healthcare	Integrase inhibitor	HIV-1 infection
Luliconozole	Luzu	Valeant Pharmaceuticals	Azole antifungal	Topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis

GENERIC NAME	BRAND NAME	MANUFACTURER	DESCRIPTION	USE/REVIEW STATUS
Simeprevir	Olysio	Janssen	Protease inhibitor	Chronic Hepatitis C infection
Sofosbuvir	Sovaldi	Gilead	Protease inhibitor	Chronic Hepatitis C infection ***Breakthrough Drug***
Diagnostic Agents				
Technetium Tc 99m tilmanocept	Lymphoseek	Navidea	Radioactive diagnostic imaging agent	Locate lymph nodes in patients with breast cancer or melanoma
Gadoterate meglumine	Dotarem	Guerbet	Paramagnetic diagnostic imaging agent	Magnetic resonance imaging (MRI) of the brain, spine and associated tissues of patients ages 2 years and older
Flutementamol F 18	Vizamyl	GE Healthcare	Radioactive diagnostic imaging agent	Radioactive diagnostic drug for use with positron emission tomography (PET) imaging of the brain in adults being evaluated for Alzheimer's disease (AD) and dementia

SOFOSBUVIR (SOLVALDI)

Sofosbuvir is the first oral agent to be approved by the FDA for the treatment of hepatitis C virus (HCV) infection without the need for interferon. It was also designated as a breakthrough drug indicating that it provides substantial improvement over current therapy.

Pharmacology/Pharmacokinetics

Sofosbuvir is a direct-acting antiviral agent against the hepatitis C virus.[4] It inhibits HCV-NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a prodrug which is converted in the body to its active form GS-461203. Dephosphorylation of GS-461203 results in GS-331007, a metabolite that lacks anti-HCV activity. Sofosbuvir is well absorbed after oral ingestion and absorption is not affected by meals. The dose is excreted primarily (78%) in the urine. The elimination half-life is 27 hours.

Indications

Sofosbuvir is indicated for the treatment of chronic hepatitis C infection (CHC) as part of a combination antiviral regimen.[4] It is effective in individuals with HCV genotype 1, 2, 3 or 4 including patients awaiting liver transplant. It is also effective in individuals with HCV and HIV co-infection.

Dosing

Sofosbuvir is administered as a 400 mg tablet once a day without regard to food.[4,5]

The recommendations for length of therapy with sofosbuvir.[5] are: Genotype 1 or 4---treat with sofosbuvir and peg-interferon alfa and ribavirin for 12 weeks; **Genotype 2**---treat with sofosbuvir

and ribavirin for 12 weeks; **Genotype 3**---treat with sofosbuvir and ribavirin for 24 weeks.

In patients with genotype 1 who are not candidates for interferon therapy, sofosbuvir may be administered in combination with ribavirin for 24 weeks.[4] No dose recommendation can be made at this time for patients with severe renal impairment or end-stage renal disease.

Contraindications

When sofosbuvir is used in combination with peginterferon alfa/ribavirin or ribavirin alone, the contraindications associated with peginterferon alfa and/or ribavirin apply to sofosbuvir combination therapy.[4]

Ribavirin may cause birth defects and fetal death, so the use of sofosbuvir in any combination with ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant.

Drug Interactions: PLEASE CHECK THE LITERATURE FOR FULL PRESCRIBING DETAILS & DESCRIPTIONS OF INTERACTIONS.

Sofosbuvir is a substrate of the drug transporter P-gp.[4] Drugs that are potent P-gp inducers may decrease the effectiveness of sofosbuvir. Drugs that are potent P-gp inhibitors may increase the drug's effectiveness.

Warnings

Patients must have a negative pregnancy test prior to initiating therapy because of the teratogenicity of ribavirin.[4] Patients should use at least 2 effective non-hormonal methods of contraception during therapy and for at least 6 months after completing treatment. Women of childbearing potential should have monthly pregnancy tests during treatment of CHC.

Adverse Effects

The most common adverse effects with sofosbuvir and ribavirin combination therapy are headache and fatigue.[4] When given in combination with interferon and ribavirin, adverse effects reported were fatigue, headache, nausea, insomnia and anemia.

Pregnancy and Lactation

Sofosbuvir is pregnancy category X because it is used in combination with ribavirin.[4] All combination therapies with ribavirin should be avoided in pregnancy. As described above, 2 effective forms of birth control should be used during therapy.

It is not known if sofosbuvir is excreted in human milk.[4] Because of the unknown risk, breastfeeding should be discontinued or therapy for CHC should be stopped. This is a risk benefit decision that must take into account the importance of treatment for the mother.

Counseling the patient

When discussing hepatitis C treatment, it is important for patients to understand the importance of compliance with therapy to avoid development of resistance. Explain that they need to take the sofosbuvir in combination with ribavirin (and possibly interferon) so that the medications can be effective. Be sure they understand that they should never take sofosbuvir alone for

single drug treatment of hepatitis C.

It is important to discuss the risk of birth defects with hepatitis C therapy. Instruct women and men to use 2 effective forms of birth control to prevent pregnancy. If pregnancy occurs, they should inform their doctor as soon as possible.

Role in therapy

The FDA granted sofosbuvir its priority review and breakthrough therapy designation, which is granted to investigational drugs that may offer major advances in treatment over existing options.[2] Approval of sofosbuvir was supported by data from four Phase 3 studies, NEUTRINO, FISSION, POSITRON and FUSION, which evaluated 12 or 16 weeks of treatment with sofosbuvir combined with either ribavirin or ribavirin/interferon.[4] In genotype 1 patients, the addition of sofosbuvir to peginterferon plus ribavirin yielded SVR12 of about 90% with slightly lower levels in patients with cirrhosis. In genotype 2, sofosbuvir combined with ribavirin for 12 weeks resulted in SVR12 of 90% or better. Patients with genotype 3 were less responsive to 12 weeks of sofosbuvir plus ribavirin, especially in the presence of cirrhosis. It is anticipated that sofosbuvir will become an important component of first line treatment for Hepatitis C infection.

IBRUTINIB (IMBRUVICA)

Ibrutinib is another drug designated by the FDA as a breakthrough agent.[2] This designation was awarded because of the overall response rate (ORR) and duration of response (DOR) reported in the phase II trials with this agent in the treatment of mantle cell lymphoma (MCL). Mantle cell lymphoma is a subtype of B-cell Non-Hodgkin's Lymphoma. Approximately 2,900 individuals are diagnosed with MCL annually. Current therapy does not halt this aggressive type of cancer for more than 5 months.

Pharmacology/Pharmacokinetics

Ibrutinib inhibits Burton's tyrosine kinase (BTK).[6,7] BTK is a critical molecule of the B-cell receptor and is important for malignant B cells to grow. Ibrutinib blocks malignant B cells from growing and dividing in an uncontrollable fashion.

Ibrutinib is well absorbed following oral ingestion. It is metabolized via the cytochrome p450 CYP 3A system to several inactive metabolites. Approximately 90% of a dose of ibrutinib is excreted through the feces as inactive metabolites.

Indications

Ibrutinib is approved for the treatment of mantle cell lymphoma (MCL) in patients who have received at least one prior therapy.[6]

Dosing

The dosing of ibrutinib is 560 mg (four of the 140 mg capsules) taken by mouth once a day.[6] If a patient develops a Grade 3 or higher non-hematological, neutropenia with fever or infection (Grade 3) or Grade 4 hematological toxicity, stop ibrutinib. Once the toxicity has resolved to at least Grade 1, therapy can be restarted at the normal dose. If the toxicity reoccurs, reduce the dose by one 140 mg capsule. A second reduction may be required of toxicity recurs or persists.

Contraindications

There are no specific contraindications to the use of ibrutinib.[6]

Drug Interactions: PLEASE CHECK THE LITERATURE FOR FULL PRESCRIBING DETAILS & DESCRIPTIONS OF INTERACTIONS.

Warnings

Patients with mantle cell lymphoma are at risk for **bleeding**.[6] Grade 3 or higher bleeding occurs in 5% of patients with MCL. These events can present as hematuria, gastric bleeding, or subdural hematoma. Approximately 48% of patients receiving ibrutinib reported bleeding of any grade while receiving therapy. Although the mechanism of these bleeding events is unclear, the benefit to risk should be considered when prescribing anticoagulants or antiplatelet drugs to patients using ibrutinib. Ibrutinib should be discontinued at least 3-7 days before and after surgery.

Serious **renal impairment (toxicity)** has been reported in patients who receive ibrutinib.[6] An increase in creatinine up to 1.5 times the upper limit of normal was reported in 67% of patients, and increases above 1.5 to 3 times the upper limit of normal were reported in 9% of patients. Creatinine levels should be monitored and patients should be well hydrated while taking ibrutinib.

Adverse Effects

The most common adverse effects reported with ibrutinib include diarrhea, thrombocytopenia, neutropenia, anemia, muscle pain, peripheral edema, upper respiratory tract infection, nausea, bruising, and shortness of breath, constipation, rash, stomatitis, vomiting, and decreased appetite. The most common serious adverse events (Grade 3 or 4) include pneumonia, atrial fibrillation, diarrhea, fatigue, abdominal pain and skin infections.

The most frequent adverse reaction that led to discontinuation of ibrutinib was subdural hematoma. Approximately 14% of patients in clinical trials required a dose reduction of ibrutinib due to adverse reactions.

Lymphocytosis has been reported in one third of patients in clinical trials with ibrutinib. This temporary lymphocytosis resolves in the first 2 months of treatment.

Pregnancy and Lactation

Ibrutinib is pregnancy category D and should be avoided in pregnancy.[6] This drug has been associated with heart and major vessel malformations in rats given a dose 14 times the expected exposure in humans. Women who may be pregnant while taking ibrutinib should be told of the potential hazard to the fetus.

It is not known if ibrutinib is excreted in breastmilk. Nursing mothers should discontinue breastfeeding or discontinue ibrutinib.

Counseling the patient

Since bleeding is a serious risk for patients, they should be counseled on the signs and symptoms of bleeding including blood in the urine or stool, bleeding gums, easy bruising. Discuss the risks

of taking antiplatelet or anticoagulants with ibrutinib.

Since renal toxicity has been reported with ibrutinib, practitioners should counsel patients about maintaining adequate hydration while taking this medication. Diarrhea was reported in about half of the patients taking ibrutinib during clinical trials. Discuss the proper management of diarrhea and the need to contact the physician if it becomes severe.

This medication should be swallowed whole and should not be opened up or chewed because of the risk of injury to the mouth.

Role in therapy

Ibrutinib is approved for use in CML patients who have had one prior treatment. With an overall response rate (ORR) of 69%, this agent will be considered first line therapy for patients with MCL. It is currently being studied for use in chronic lymphocytic leukemia (CLL) and approval for this indication is expected in 2014.

CANAGLIFLOZIN (INVOKANA)

Canagliflozin is the first sodium-glucose co-transporter 2 (SGLT2) inhibitor to be approved by the FDA.[8] Another SGLT2 inhibitor, dapagliflozin, has been available in Europe; however, the FDA denied approval of this agent because of concerns regarding an increased risk of breast and bladder cancer.[9]

Pharmacology/Pharmacokinetics

SGLT2 is a membrane protein found primarily in the kidney and responsible for reabsorption of filtered glucose from the proximal renal tubule into the tubular epithelial cells.[8] SGLT2 inhibitors decrease this glucose reabsorption, increase excretion of glucose in urine and lower blood glucose.

Canagliflozin is well absorbed after oral administration with a peak plasma concentration occurring within 1-2 hours of ingestion.[8,9] The half-life of canagliflozin is 10.6 hours with the 100 mg dose, and 13 hours with the 300 mg dose. Canagliflozin is metabolized by UDP-glucoronosyltransferase (UGT) 1A9 and 2B4 to inactive metabolites. Approximately 40% of a dose is excreted in the feces with 30% excreted in the urine.

Indications

Canagliflozin is indicated for the treatment of type 2 diabetes in conjunction with diet and exercise.[8] It is not approved for use in Type 1 diabetes or diabetic ketoacidosis.

Dosing

The initial dose of canagliflozin is 100 mg orally before the first meal of the day.[8] The dose may be increased to 300 mg/day in patients with an eGFR of 60 mL/min/1.73m2 or greater. In moderate renal failure (eGFR 45-59 mL/min/1.73m^2) the dose should not exceed 100 mg/day. If a patient's renal function drops below 45 mL/min/1.73 m^2, the drug should be stopped. Canagliflozin should be avoided in patients with renal failure.

Contraindications

Canagliflozin is contraindicated in patients with an allergy to any component of the product.[8]

It is also contraindicated in patients with severe renal impairment, ESRD (end stage renal disease) or on dialysis.

Drug Interactions: PLEASE CHECK THE LITERATURE FOR FULL PRESCRIBING DETAILS & DESCRIPTIONS OF INTERACTIONS.

Warnings

Symptomatic hypotension may occur because of volume depletion with canagliflozin.[8] Patients at risk of hypotension include the elderly, those on diuretic medications, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, patients with renal dysfunction (eGFR < 60 mL/min/1.73m2) and those with low blood pressure.

Canagliflozin has been associated with hyperkalemia.[8] Patients with moderate renal dysfunction or those taking ACE/ARBs or potassium sparing diuretics are at higher risk for hyperkalemia. Since canagliflozin can increase serum creatinine and reduce eGFR, patients are at risk for developing renal dysfunction. In patients with eGFR < 60 mL/min/1.73m^2, more frequent monitoring of renal function may be needed.

Hypersensitivity reactions, which may be severe, have been reported.[8] This presents as a generalized urticaria within hours to days after initiating therapy. The drug should be stopped immediately.

Canagliflozin may increase the risk of hypoglycemia when used in combination with insulin or insulin secretagogues.[8] A lower dose of these agents may be needed to prevent hypoglycemia.

Adverse Effects

Genital mycotic infections have been reported in 3-11% of men and 10-15% of women taking canagliflozin.[8,9] Urinary tract infections were reported in 5% of patients in clinical trials. Other adverse effects include a diuretic effect which can result in volume depletion, increased serum creatinine and elevated potassium, magnesium, and phosphate. There was a slight increase in the risk of fracture. The incidence of hypoglycemia is similar to placebo (3%) in clinical trials.

Pregnancy and Lactation

Canagliflozin is pregnancy category C and should be avoided in pregnancy.[8] There are no well-controlled trials in pregnant women; however, animal studies indicate that canagliflozin may affect renal development and maturation. It is not known if canagliflozin is excreted in breastmilk. The drug is secreted into the milk of lactating rats at 1.4 times the maternal plasma level. Nursing mothers should discontinue breastfeeding or discontinue canagliflozin.

Counseling the patient

It is important to discuss lifestyle changes in all diabetic patients and encourage good eating habits and exercise.

Specifically for patients taking this drug, remind them to take canagliflozin before the first meal of the day.[8] In patients beginning therapy with canagliflozin, discuss the risk of generalized urticaria that may occur early in therapy and the need to discontinue the medication and contact their doctor if this occurs. Patients need to maintain adequate hydration and have regular assessment of their renal function and electrolytes to prevent complications. Patients should be aware of the risk for genital mycotic infections and how to identify these infections.

Role in therapy

The current management of Type 2 diabetes includes lifestyle modifications, including diet and exercise. The initial drug therapy recommended by the guidelines is metformin. After metformin, there is no agreement among the experts on which agent should be added. Canagliflozin offers a modest reduction in HbA1c with a low risk of hypoglycemia. Of concern is the incidence of genital mycotic infections and the long term safety of this agent is still not determined.

DIMETHYL FUMARATE (TECFIDERA)

Dimethyl fumarate is the third oral agent to be approved by the FDA for the treatment of multiple sclerosis (MS). This agent has been available for several years in Europe for the treatment of psoriasis.

Pharmacology/Pharmacokinetics

The mechanism of action of dimethyl fumarate is not established.[10,11] It activates (Nrf2) antioxidant response pathway which provides primary cellular defense against oxidative stress. Dimethyl fumarate is well absorbed following oral administration. When taken with a high fat, high calorie meal, the incidence of flushing is reduced by 25%. The half-life is 2-2.5 hours. The drug is metabolized by esterases in the GI tract, blood and tissue. It is converted to the active metabolite monomethyl fumarate which is then further metabolized to an inactive metabolite. Sixty percent of the dose is excreted by exhalation of CO2 and 16% excreted in the urine.

Indications

Dimethyl fumarate is approved for the treatment of relapsing forms of MS.[10]

Dosing

The initial dose is 120 mg orally twice a day for 7 days.[10] The dose is then increased to 240 mg twice a day. This medication should be taken with food to reduce the incidence of flushing.

Contraindications

There are no contraindications to the use of dimethyl fumarate.[10]

Drug Interactions: PLEASE CHECK THE LITERATURE FOR FULL PRESCRIBING DETAILS & DESCRIPTIONS OF INTERACTIONS.

Warnings

Dimethyl fumarate can reduce lymphocyte counts by 30% in the first year of treatment.[10] Patients should receive a complete blood count prior to starting treatment to determine if they have a pre-existing low lymphocyte count. This drug should not be given to patients with a low lymphocyte count. In addition, therapy should not be initiated if the patient has a serious infection.

Adverse Effects

The most frequently reported side effect is flushing[10], which was reported in 40% of patients in the clinical trials. Other adverse effects include abdominal pain, nausea and diarrhea. A 30% reduction of the mean lymphocyte count was reported during the first year of treatment with a grade 3 lymphopenia occurring in 6% of patients. There have been 4 cases of progressive multifocal leukoencephalopathy (PML) linked with fumaric acid used for psoriasis. No reports of PML in its use for MS have been seen.

Pregnancy and Lactation

Dimethyl fumarate is pregnancy category C and should be avoided in pregnancy.[10] There are no well-controlled trials in pregnant women; however, in animal studies, neurobehavioral function, sexual maturation and poor growth were reported. There is a pregnancy registry available from the manufacturer to monitor for adverse pregnancy outcomes in women exposed to dimethyl fumarate. It is not known if dimethyl fumarate is excreted in breastmilk. Nursing mothers should discontinue breastfeeding or discontinue dimethyl fumarate.

Counseling the patient

When receiving an initial prescription for dimethyl fumarate, it is important to verify that the patient has had a complete blood test within the last 6 months to ensure they do not have a pre-existing low lymphocyte count.[10] Patients should understand that flushing and GI effects are common, especially early in therapy. Taking the medication with food can reduce the incidence of these side effects.

Women of child-bearing age should be counseled about avoiding pregnancy while taking dimethyl fumarate. If a woman becomes pregnant while taking this medication, there is a Pregnancy Registration that should be considered.

Role in therapy

In a clinical trial, two dose regimens of dimethyl fumarate were compared to glatiramer and placebo.[11] The dimethyl fumarate regimens reduced the relapse rate by 44% and 51% compared to placebo. The glatiramer group reduced the rate by 29%. Neither drug significantly slowed progression of disability. Other clinical trials of teriflunomide and fingolimod reduce relapse rate by 31% and 55% respectively. Although there are no direct comparisons, dimethyl fumarate appears to be more effective than teriflunomide and better tolerated than fingolimod.

DOLUTEGRAVIR (TIVICAY)

Dolutegravir is the third integrase strand transfer inhibitor (INSTI) approved by the FDA. Previously approved INSTIs include raltegravir (Isentress) and elvitegravir (a component of Stribild).

Pharmacology/Pharmacokinetics

Dolutegravir blocks HIV-1 integrase and also blocks the strand transfer step of retroviral DNA integration, which is required for HIV replication.[12] Dolutegravir is well absorbed following oral administration with peak plasma concentrations observed 2 to 3 hours after dosing. Dolutegravir is highly plasma protein bound (> 98%) and has a half-life of 14 hours. Dolutegravir is metabolized primarily by UGT1A1 with a small amount via CYP3A. Approximately 53% of a dose is excreted through the feces as unchanged drug with 31% excreted as inactive metabolites via the urine.

Indications

Dolutegravir is approved for treatment of HIV1 in combination with other antiviral agents in adults and children> 12 years who weigh at least 40 kg.[12]

Dosing

In patients who have never taken an INSTI, the dose of dolutegravir is 50 mg once a day with or without food. [5,12,13] In patients who are INSTI-naïve, but combining dolutegravir with efavirenz, rifampin, or ritonavir boosted fosamprenavir or tipranavir, the dose of dolutegravir should be increased to 50 mg twice a day. INSTI-experienced patients with certain INSTI-associated resistance substitutions or suspected INSTI-resistance should also receive 50 mg twice a day.

This drug has not been evaluated in patients with severe hepatic impairment.

Contraindications

Dolutegravir is contraindicated for use with dofetilide.[12] It should not be used in patients with a previous allergy to dolutegravir.

Drug Interactions: PLEASE CHECK THE LITERATURE FOR FULL PRESCRIBING DETAILS & DESCRIPTIONS OF INTERACTIONS.

Warnings

Dolutegravir has been associated with a hypersensitivity reaction that includes severe rash, flu-like symptoms, conjunctivitis, shortness of breath, oral lesions and possible liver damage.[12,13] If a patient develops any of these symptoms, dolutegravir should be discontinued immediately. Patients with a previous hypersensitivity to dolutegravir should not receive the drug.

In patients with co-infection of hepatitis B or C, use of dolutegravir may result in elevated or worsening transaminase levels.[12] These elevations are consistent with hepatitis reactivation or immune reconstitution syndrome. Patients with hepatitis should be monitored closely for signs of liver toxicity while taking dolutegravir.

Adverse Effects

Dolutegravir is generally well tolerated compared to other agents used to treat HIV.[12]

Hypersensitivity reactions described above are reported in less than 1% of patients. Elevations or worsening of transaminase levels have been reported in patients with co-infection with Hepatitis B or C.

The most common adverse reactions reported (> 2%) were insomnia and headache.[5,12] Less frequently reported adverse effects include abdominal pain, increased flatulence, nausea, and fatigue.

Pregnancy and Lactation

Dolutegravir is pregnancy category B and should be avoided in pregnancy.[12] There are no well-controlled trials in pregnant women. Breastfeeding should be avoided in women who are HIV positive due to the risk of transmission of the HIV virus to the infant.

Counseling the patient

When counseling a patient with HIV about medication therapy, it is important to discuss compliance and the risk of drug resistance. Identification and reduction of barriers to compliance is critical with this population. Discuss when the medication should be taken, once or twice a day. Discuss what the patient should do if they miss a dose of dolutegravir.

It is important to review the hypersensitivity risks reported with dolutegravir.[12] Although the risk is low, it is important to explain to the patient the importance of stopping the medication and discussing the reaction with their physician. Also in patients who are co-infected with hepatitis B or C, describe the potential risk of worsening transaminase levels.

Role in therapy

The first approved INSTI, raltegravir (Isentress), was included as a preferred first-line option in the February 2013 revision of the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. That version also included Stribild (elvitegravir/cobicistat/tenofovir/emtricitabine) as an alternative regimen for patients with normal kidney function. In the latest change of the guidelines, released October 30, 2013, Healthcare and Human Services now recommend 4 integrase inhibitor-based combinations as preferred regimens for initial antiretroviral treatment:[14] (1) Raltegravir 400 mg twice-daily plus tenofovir/emtricitabine: (2) Stribild (elvitegravir/cobicistat/tenofovir/emtricitabine) once-daily for patients with estimated creatinine clearance >70 mL/min; (3) Dolutegravir 50 mg once-daily plus abacavir/lamivudine once-daily for patients who test negative for the HLA B*5701 abacavir hypersensitivity gene variant; (4) Dolutegravir 50 mg once-daily plus tenofovir/emtricitabine once-daily.

FLUTICASONE/VILANTEROL (BREO ELLIPTA)

This is the only once daily fixed dose combination product for COPD. It is the first approved indication for vilanterol. This agent is approved for the treatment of chronic obstructive pulmonary disease (COPD). Fluticasone is an inhaled corticosteroid (ICS), and vilanterol is a long-acting beta 2 adrenergic agonist (LABA).

Pharmacology/Pharmacokinetics

Vilanterol stimulates adenyl cyclase, the enzyme that converts adenosine triphosphate (ATP) to cyclic AMP.[5,15] Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from mast cells. Although beta-2 receptors are generally found in bronchial smooth muscle and beta 1 receptors are in the heart, there are a significant number of beta-2 receptors in the heart. This accounts for the potential cardiovascular effects that may be seen with LABAs.

Fluticasone is a trifluorinated corticosteroid with anti-inflammatory activity. The mechanism through which fluticasone improves COPD symptoms is not known. Corticosteroids have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

Following oral inhalation there is some systemic absorption of fluticasone/vilanterol primarily from the percent of the dose that reaches the lung.[15] Both agents are metabolized primarily by CYP3A4. Fluticasone is excreted primarily via the feces while 70% of the dose of vilanterol

is excreted in the urine.

Indications

Fluticasone/vilanterol is approved for long term, once daily treatment of airflow obstruction in patients with COPD.[15] It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations. It is not approved for treatment of acute bronchospasm or treatment of asthma.

Dosing

The dose of fluticasone/vilanterol is one inhalation daily. Fluticasone/vilanterol should not be used as a rescue inhaler. It has not been studied in patients under 18 years of age.

Contraindications

The only contraindication to fluticasone/vilanterol is in patients with allergy to milk protein or any other component of the product.

Drug Interactions: PLEASE CHECK THE LITERATURE FOR FULL PRESCRIBING DETAILS & DESCRIPTIONS OF INTERACTIONS.

Warnings

There is an increased risk of asthma-related death with any LABA, including vilanterol. There is a black box warning regarding the use of LABA in asthma.[15] The safety and effectiveness of fluticasone/vilanterol has not been evaluated in asthma and should not be used in this population.

Adverse Effects

The most common side effects reported with fluticasone/vilanterol are nasopharyngitis, headache, oral candidiasis and upper respiratory tract infection.[5,15] Other serious side effects include pneumonia, and reduced bone density which may increase fracture risk.

Pregnancy and Lactation

Fluticasone/vilanterol is pregnancy category C and should be avoided in pregnancy.[7,15] There are no well-controlled trials in pregnant women; however, there is an increased risk of teratogenicity in animal studies. Breastfeeding should be avoided. Other corticosteroids/LABAs have been shown to be excreted into human milk.

Counseling the patient

It is important to verify that the patient understands how to use the inhaler. Have the patient demonstrate how they use the inhaler. Be sure that they understand that this inhaler should be used every day, and that it is not intended for use as a rescue inhaler. Ensure that the patient understands how to keep the inhaler properly cleaned to prevent oral thrush or other complications.

Review the patient's medication regimen and review any potential drug-drug interactions. Stress the importance of the patient talking to you before initiating any new prescription or nonprescription medication. Discuss the risk of pregnancy with any women of child-bearing potential.

Role in therapy

The current GOLD guidelines recommend the use of ICS plus LABA for moderate to severe COPD.[16] Two 6-month, randomized, double-blind, placebo-controlled, parallel-group, lung function studies demonstrated sustained 24-hour bronchodilator efficacy of fluticasone/vilanterol in moderate to severe COPD. Two additional 12-month randomized, parallel-group exacerbation studies showed that treatment with fluticasone/vilanterol resulted in a lower annual rate of moderate/severe COPD exacerbations compared with vilanterol alone.[7]

SIMEPREVIR (OLYSIO)

Simeprevir is an oral protease inhibitor (PI) for use in hepatitis C. It is the third oral PI to be approved for use in combination with peg-interferon and ribavirin for the treatment of hepatitis C.

Pharmacology/Pharmacokinetics

Simeprevir is an NS3/4A protease inhibitor and is a direct acting antiviral agent.[17,18] It is well absorbed following oral administration with a peak plasma level 4 to 6 hours after administration. Simeprevir is highly plasma-protein bound (>99.9%) and is metabolized in the liver via the CYP3A system. Approximately 91% of a dose is excreted in the stool. The half-life is 41 hours.

Indications

Simeprevir is approved for the treatment of hepatitis C in combination with peg-interferon and ribavirin.[18] Patients with HCV genotype 1 should be screened for NS3Q80K polymorphism. If this polymorphism is present, alternative therapy should be considered.

Dosing

The dose of simeprevir is 150 mg taken orally once a day for 12 weeks with food. Simeprevir must be given in combination with peg-interferon and ribavirin. The peg-interferon and ribavirin must be continued for an additional 12 weeks in treatment-naïve or patients who have relapsed. In patients who are non-responders, the peg-interferon and ribavirin combination should be continued for an additional 36 weeks. Proper dosing regimens for patients of East Asian descent or those with moderate to severe liver impairment cannot be provided.

If the HCV RNA is ≥ 25 IU/mL at 4, 12 or 24 weeks, the patient has an inadequate viral response, and all therapy should be discontinued.

Contraindications

There are no specific contraindications for simeprevir; however, the same contraindications for peg-interferon and ribavirin apply when combining simeprevir with these agents. This includes avoiding use of ribavirin in pregnant women or in men whose female partners are pregnant.

Drug Interactions: PLEASE CHECK THE LITERATURE FOR FULL PRESCRIBING DETAILS & DESCRIPTIONS OF INTERACTIONS.

Warnings

Photosensitivity reactions have been reported when simeprevir is given in combination with peg-interferon and ribavirin.[18] Ensure that patients use sun protection. Rash has been reported with this drug combination. Discontinue simeprevir if severe rash occurs.

Adverse Effects

The most common adverse effects reported with simeprevir (20% of patients) include rash, pruritus, photosensitivity and nausea.[5,18] Other adverse reactions include myalgia, and dyspnea.

Pregnancy and Lactation

Simeprevir is classified as pregnancy category C; however, ribavirin is pregnancy category X.[18] Since these agents are used together, simeprevir is contraindicated in pregnancy. There is no data available regarding the excretion of simeprevir in human milk. Breast feeding should be avoided with simeprevir.

Counseling the patient

Patients should be counseled regarding the use of effective birth control while taking simeprevir due to the teratogenicity and embryocidal effects of ribavirin/peg-interferon. Women should use 2 effective forms of birth control. Female partners of men taking this combination should take the same precautions.

Discuss the risk of rash related to simeprevir in combination with peg-interferon and ribavirin. Patients should understand the rash may become severe. Patients should contact their physician if the rash is severe. Discontinue simeprevir only if physician advises patient to stop.

Explain that simeprevir should only be taken in combination with peg-interferon/ribavirin. If peg-interferon/ribavirin is discontinued, simeprevir should be stopped as well.

Role in therapy

The combination of peg-interferon, ribavirin and simeprevir results in sustained virologic response rates in HCV genotype 1 patients.[17] It appears to be as effective as telaprevir (Incivek) or boceprevir (Victrelis) except in those patients with the NS3 Q80K mutation. It does not worsen the anemia seen with peg-interferon; however, the rash reactions can be severe. It does offer the advantage of once daily administration.

CONCLUSION

The FDA has approved 27 new drugs this past year, which is about average to what is approved annually. Three agents did receive breakthrough status. Pharmacists & technicians are encouraged to review these new agents and be prepared to counsel patients regarding proper use of these agents.

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LESSON EVALUATION
Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?

Describe 2013 approved drugs	YES NO
Discuss the role of these in therapy	YES NO
List adverse effects of the new drugs	YES NO
Recommend counseling points	YES NO

2. Was the program independent & non-commercial YES NO

	Low Relevance						Very Relevant
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like most about this lesson?_____
5. What did you like least about this lesson?_____

Please Mark the Correct Answer(s)

1. **In 2013 the FDA approved _____new drugs:**
   A. 39 B. 28
   C. 27 D. 34
2. **Which of these does not have to be administered in combination with peg-interferon in treating HCV?**
   A. Simeprevir B.Boceprevir
   C. Sofosbuvir D. Telapravir
3. **Canagliflozin is an excellent new drug for Type I diabetes mellitus.**
   A. True B. False
4. **Genital mycotic infections are an adverse effect associated with:**
   A. Canagliflozin B. Alogliptin
   C. Dabrafenib D. Ibrutinib
5. **The most frequent adverse effect reported with dimethyl fumarate is:**
   A. Lymphocytosis B. Hypotension
   C. Flushing D. Diarrhea
6. **Ibrutinib is approved for treating:**
   A. Chronic lymphocytic leukemia
   B. Hepatic carcinoma
   C. Hemolytic anemia
   D. Mantle cell lymphoma
7. **Dolutegravir is a:**
   A. Protease inhibitor
   B. Integrase strand transfer inhibitor
   C. Non-nucleoside reverse transcriptase inhibitor
   D. None of these
8. **Fluticasone/vilanterol has been associated with an increased risk of bone fractures**
   A. True B. False
9. **If a drug is designated as a breakthrough drug by FDA:**
   A. Development & review are expedited
   B. It provides substantial benefit over current therapy
   C. Treats a serious or life threatening condition
   D. All of these
10. **Which of these is the most frequent reason to discontinue ibrutinib?**
    A. Dizziness & fainting
    B. Hypotension
    C. Subdural hematoma
    D. Hypertension

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Contributing Author
Mary Lynn Moody, BS Pharm
Clinical Assistant Professor
Director, Business Development
Drug Information Group
University of Illinois, Chicago
College of Pharmacy

Executive Editor
William J. Feinberg,
BS Pharm, MBA

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