CE PRN

PHARMACY CONTINUING EDUCATION FROM WF PROFESSIONAL ASSOCIATES

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"Part 2: New Drugs Approved in 2016"

August 2017

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The FDA approved only 22 new molecular entities (NME) in 2016. In this lesson, and the previous one, we focus on some of the newer agents that are of interest to pharmacy practitioners. Information is provided that includes dosing guidelines, common adverse effects, contraindications and key counseling points.

This lesson provides 1.25 (0.125 CEUs) contact hours of credit, and is intended for pharmacists & technicians in all practice settings. **The program ID # for this lesson is 707-000-17-008-H01-P for pharmacists & 707-000-17-008-H01-T for technicians.**

Participants completing this lesson by July 31, 2020 may receive full credit. Release date for this lesson is August 1, 2017.

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.

If you have any comments, suggestions or questions, contact us at the above address, or call 1-847-945-8050. **Please write your name, NABP eProfile (CPE Monitor®) ID Number & birthdate (MM/DD) in the indicated space on the quiz page.**

The objectives of this lesson are such that upon completion participants will be able to:

For Pharmacists:

1. List the new drugs approved by FDA in 2016.
2. Discuss the role of these agents in therapy.
3. Summarize adverse effects associated with these agents.
4. Recommend counseling points associated with these drugs.

For Technicians:

1. List new drugs approved in 2016.
2. Discuss the uses of these new drugs.

CE PRN® (ISSN 0199-5006) is owned and published by W-F Professional Associates, Inc. 400 Lake Cook Road, Suite 207, Deerfield, Illinois 60015. William J. Feinberg, President. CE PRN® is published eleven times per year, monthly, January through November.

INTRODUCTION

Only 22 new molecular entities (NME) were approved in 2016. (Table 1)[1]. This number is lower than the 45 products approved in 2015 or the 29 drug approvals per year which have been seen over the last decade. One reason cited is that the FDA's Center for Drug Evaluation and Research approved 5 products in 2015 ahead of their scheduled approval date in 2016.[2] In this lesson, and in last month's, we focus on the newer agents that have been approved by the FDA. Information is provided that includes dosing guidelines, common adverse effects, contraindications and key counseling points.

Table 1–New drugs of 2016[1].

Generic Name	Brand Name	Approval Date	Indication
Elbasvir and grazoprevir	Zepatier	1-28-2016	Chronic hepatitis C (HCV) genotypes 1 and 4 infection
Brivaracetam	Briviact	2-18-2016	Partial onset seizures
Obiltoxaximab	Anthim	3-18-2016	Inhalational anthrax
Ixekizumab	Taltz	3-22-2016	Moderate to severe plaque psoriasis
Reslizumab	Cinqair	3-23-2016	Severe asthma
Defibrotide sodium	Defitelio	3-30-2016	Hepatic veno-occlusive disease following stem cell transplant
Venetoclax	Venclexta	4-11-2016	Chronic lymphocytic leukemia in patients with a specific chromosomal abnormality
Pimavanserin	Nuplazid	4-29-2016	Treatment of hallucinations and delusions from psychosis in Parkinson's disease
Atezolizumab	Tecentriq	5-18-2016	Urothelial type bladder cancer
Daclizumab	Zinbryta	5-27-2016	Multiple sclerosis
Obeticholic acid	Ocaliva	5-27-2016	Rare chronic liver disease
Fluciclovine F 18	Axumin	5-27-2016	Diagnostic imaging agent for recurrent prostate cancer detection
Gallium Ga 68 dotatate	NETSPOT	6-1-2016	Diagnostic imaging agent for rare neuroendocrine tumors
Sofosbuvir and velpatasvir	Epclusa	6-28-2016	Treatment of all 6 major forms of hepatitis C virus
Lifitegrast	Xiidra	7-11-2016	Treat signs and symptoms of dry eye
Lixisenatide	Adlyxin	7-27-2016	Diabetes type 2
Eteplirsen	Exondys 51	9-19-2016	Duchenne muscular dystrophy
Olaratumab	Lartruvo	10-19-2016	Soft tissue sarcoma
Bezlotoxumab	Zinplava	10-21-2016	Reduce the recurrence of *Clostridium difficile* infection in adults
Crisaborole	Eucrisa	12-14-2016	Atopic dermatitis in patients two years of age or older
Rucaparib	Rubraca	12-19-2016	Ovarian cancer
Nusinersen	Spinraza	12-23-2016	Spinal muscular atrophy

In last month's lesson (Part 1" New Drugs of 2016), we discussed:

- Lixisenatide
- Elbasvir + grazoprevir
- Sofosbuvir 400 mg + velpatasvir 100 mg

In this lesson, we discuss:

- Eteplirsen
- Ixekizumab
- Lifitegrast
- Daclizumab
- Pimavanserin

Almost 75% of the NMEs approved in 2016 qualified for at least one of the FDA's designations to expedite the approval process (See Table 2)[2].

Table 2–FDA Programs to shorten the drug approval process[2]

Program Title	Description	Percent of drugs	Drugs approved under program
First in Class	Mechanism of action different from existing therapies	36% (8/22)	Defitelio, Exondys 51, Ocaliva, Spinraza, Venclexta, Xiidra, Zinbryta, Zinplava
Orphan Drugs	Drug for disease affecting less than 200,000 Americans	41% (9/22)	Anthim, Defitelio, Exondys 51, Lartruvo, Netspot, Ocaliva, Rubraca, Spinraza, Venclexta
Fast Track	Potential to address unmet medical need	36% (8/22)	Anthim, Defitelio, Epclusa, Exondys 51, Lartruvo, Ocaliva, Spinraza, Zinplava
Breakthrough	Drug may result in substantial improvement in at least one clinically significant endpoint over available drugs	32% (7/22)	Epclusa, Lartruvo, Nuplazid, Rubraca, Tecentriq, Venclexta, Zepatier
Priority	Potentially provide a significant advance in medical care. Drug is reviewed in 6 months versus standard 10 months.	68% (15/22)	Axumin, Defitelio, Epclusa, Exondys 51, Lartruvo, Netspot, Nuplazid, Ocaliva, Rubraca, Spinraza, Tecentriq, Venclexta, Xiidra, Zepatier, Zinplava
Accelerated	Early approval of drug for serious or life-threatening illness that offers benefit over current treatment	27% (6/22)	Exondys 51, Lartruvo, Ocaliva, Rubraca, Tecentriq, Venclexta

ETEPLIRSEN (EXONDYS 51)

Eteplirsen was approved by the FDA on September 9, 2016 under the accelerated approval pathway as an orphan drug. The manufacturer also received a rare pediatric disease priority review voucher which encourages development of new drugs and biologics for the prevention and treatment of rare pediatric diseases. This is the seventh rare pediatric disease priority review voucher issued. Eteplirsen was approved for use in Duchenne Muscular Dystrophy (DMD). DMD is a genetic disorder that results in progressive muscle degeneration and weakness. This disease occurs in about one out of every 3,600 male infants worldwide. DMD primarily affects boys. It is caused by an absence of dystrophin, a protein that helps keep skeletal muscle cells intact.

Symptoms often appear in childhood between ages 3 to 5 years. These symptoms start in the hips, thighs and shoulders and progress to skeletal muscles of arms, legs and trunk. Most patients have heart and respiratory muscle involvement by their teen years and succumb to the disease in the twenties to thirties. This is the first drug approved specifically for DMD. Therapy with high dose prednisone has been used to slow the progression of the disease. Eteplirsen is available as 50 mg/mL single dose vials in 2 mL (100 mg) and 10 mL (500mg).[20,21]

Pharmacology/Pharmacokinetics

Eteplirsen is an antisense oligonucleotide that binds to exon 51 in the RNA that codes for dystrophin. This allows "skipping" of exon 51 and the formation of a partially functional dystrophin protein.[5,21]

Eteplirsen is rapidly absorbed following intravenous administration and peak plasma levels were reached at the end of the infusion (1 hour). The plasma protein binding of eteplirsen is low and ranges from 6-17%. The volume of distribution of the drug is 600 mL/kg. The drug is primarily excreted through the kidneys and the elimination half- life is 3 to 4 hours.[21]

Indications

Eteplirsen is indicated for individuals who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13% of the population with DMD. A clinical benefit has not been established. The continued availability of the drug will be determined following confirmatory trials.[21]

Dosing

Eteplirsen is administered at a dose of 30 mg/kg of body weight once a week. The drug is infused over 35 to 60 minutes. The drug should be diluted in 0.9% sodium chloride to a final volume of 100 to 150 mL. The drug has not been studied in patients with liver or kidney disease so dose adjustments are not reported.[5,21]

Efficacy

The approval of eteplirsen has been dogged by controversy. The FDA Advisory Committee did not support the approval of eteplirsen. The FDA scientists stated that there was not enough evidence to support the efficacy of the drug. The Director of the Center for Drug Evaluation and Research (CDER) and the FDA Commissioner approved the agent in spite of this lack of scientific support.

The pivotal clinical trial of eteplirsen for FDA approval included only 12 boys with DMD who were randomized to receive eteplirsen or placebo. The study evaluated the surrogate end-point of dystrophin increase in skeletal muscle not clinical improvement. Although the FDA approved the use of eteplersin in DMD, they did note that there were substantial flaws in the initial clinical trial submitted. FDA requires the manufacturer to submit a randomized controlled trial comparing eteplirsen 30 mg/kg once a day to 30 mg/kg once a week to determine if the drug provides clinical benefit. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.[21,22]

Contraindications/Warnings

There are currently no contraindications or warnings to the use of eteplirsen.[21]

Drug Interactions

There are no documented drug interactions with eteplirsen.[21]

Adverse Effects

The most common side effects reported in clinical trials with eteplirsen include problems with balance (38%), vomiting (38%) and skin rash (25%). Other adverse events that have been reported in ≥10% of patients include confusion, arthralgia, severe itching, catheter site pain, and upper respiratory tract infection. There have also been some reports of transient erythema, facial flushing, and elevated temperature on the days that eteplirsen was administered.[5,21]

Pregnancy and Lactation

There is no data on the effects of eteplirsen in pregnancy or lactation. DMD primarily affects male boys and no data is available on its effects on sperm.[21]

Counseling the patient

The pharmacist should counsel the parent/guardian of the child with DMD. The drug is administered intravenously once a week. The pharmacist should work with the parent/guardian to determine if the product should be prepared and delivered by a specialty pharmacy or will the parent/guardian prepare and administer the dose to the child. The drug is infused intravenously over 35 to 60 minutes. In some cases, it might be necessary to apply an anesthetic cream to the infusion site to reduce the risk of pain and itching at the infusion site.[21]

Role in therapy

Eteplirsen is the first drug to be approved for treatment of Duchenne muscular dystrophy (DMD). It slightly increased dystrophin levels in the muscle cells of patients with specific mutations of the dystrophin gene that occur in about 13% of DMD cases. Some insurance providers are limiting use of this drug due to the limited clinical benefit and extremely high cost which ranges from $500,000 to 1 million per patient per year.[21,22]

Examples of possible criteria are:

- Patients with confirmed mutation of the DMD gene that is amenable to exon 51 skipping
- Patient has some physical function that can be maintained (e.g. upper limb function or ambulation)
- Patient is receiving glucocorticoid therapy or glucocorticoid treatment was discontinued at the recommendation of the treating physician
- Patient has stable pulmonary function (e.g. absence of invasive ventilation or tracheostomy) and cardiac function
- Medication is prescribed by or in consultation with a pediatric neurologist or other provider with expertise in treating DMD

As a condition of FDA approval, the manufacturer of eteplirsen will have to conduct a two-year, randomized controlled trial to confirm the clinical effectiveness of the drug. The purpose is to determine whether the drug actually improves motor function. If the trial fails, the FDA could decide to withdraw the drug from the market.[20]

IXEKIZUMAB (TALTZ)

Ixekizumab was approved by the FDA on March 22, 2016 for the treatment of moderate to severe plaque psoriasis. Ixekizumab is the second IL-17A antagonist to be approved for this indication in the United States. Psoriasis is a chronic inflammatory, immune-mediated condition. Approximately 7.5 million people suffer from psoriasis in the US. Patients with psoriasis are at

an increased risk for psoriatic arthritis, heart disease, stroke, hypertension, type 2 diabetes, eye disorders, and obesity. It is not just a cosmetic condition. Initial therapy for mild to moderate disease includes topical corticosteroids, vitamin D and retinoid products. Moderate to severe psoriasis can be treated with methotrexate, cyclosporine, phosphodiesterase inhibitors such as apremilast and the TNF inhibitors etanercept, adalimumab and infliximab. Additional therapies include IL-12/23 inhibitor ustekinumab, and the IL-17A antagonist secuinumab. [23]

Pharmacology/Pharmacokinetics

Interleukin-17 is involved in normal immune and inflammatory responses. Ixekizumab is a recombinant monoclonal antibody that binds and neutralizes IL-17A preventing the release of inflammatory cytokines.[24]

Ixekizumab is 60-80 % bioavailable following subcutaneous administration. It appears to have a volume of distribution of approximately 7 liters. The time to the peak effect of ixekizumab is about 4 days. It is expected that the metabolism of this drug would be similar to the metabolism of IgG. The elimination half-life of ixekizumab is 13 days. [5,24]

Indications

Ixekizumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. [24]

Dosing

The recommended dose of ixekizumab is 160 mg (two 80 mg injections) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, followed by 80 mg every 4 weeks. It is administered by subcutaneous injection. Patients should be assessed for tuberculosis infection prior to initiating treatment with ixekizumab. Ixekizumab is available as an 80 mg/mL solution in a single-dose prefilled autoinjector or a prefilled syringe.[24]

Efficacy

Three trials (UNCOVER-1, UNCOVER-2 and UNCOVER-3) compared ixekizumab administered every 2 or 4 weeks to etanercept or placebo. A total of 2570 patients with moderate to severe psoriasis were included in the trials. The co-primary endpoints of the studies was a > 75% reduction in the psoriasis area and severity index (PASI) score at 12 weeks and a Physician Global Assessment (PGA) score of 0 or 1 and at least a 2 point improvement from baseline. In all studies combined, 87-90% of the ixekizumab patients had improvement in their PASI 75 and 81-83% had a PGA score of 0 to 1. The placebo treated patients experienced minimal response with less than 7% achieving the primary endpoints.[25]

Contraindications/Warnings

Ixekizumab is contraindicated in patients who are allergic to the drug or any of its components.[24]

Before treatment with ixekizumab, patients should be evaluated for tuberculosis (TB). The drug should be avoided in patients with an active TB infection. Serious infections have been reported with this drug, including Crohn's disease and ulcerative colitis. Individuals with inflammatory bowel disease should be monitored closely when ixekizumab is initiated.[24]

Drug Interactions

Patients should avoid receiving live vaccines while taking ixekizumab. When starting or stopping ixekizumab, providers should monitor drug levels of CYP450 substrates with a narrow

therapeutic index such as warfarin or cyclosporine.[24]

Adverse Effects

The most common adverse effects reported with ixekizumab include injection site reactions, upper respiratory tract infections, nausea, and tinea infections. Serious adverse reactions include thrombocytopenia and neutropenia, conjunctivitis and antibody development to ixekizumab.[24]

Pregnancy and Lactation

There is no clinical data on the effects of ixekizumab on pregnancy or lactation. This drug should be used only after weighing the benefits to the mother and the risk to the fetus.[24]

Counseling the patient

The pharmacist should review the dose and frequency of administration of ixekizumab. Be sure to have the patient demonstrate the subcutaneous injection. Be sure that patient rotates the sites of injections with each dose to reduce the chance for injection site reactions and infections.[24] Discuss the proper disposal of ixekizumab to reduce the risk for needle stick injuries. The pharmacist should discuss the adverse effects of ixzekizumab including upper respiratory infections, oral candidiasis, conjunctivitis and tinea infections.

Role in therapy

Ixekizumab offers an additional IL-17A agent for the treatment of moderate to severe psoriasis. Therapy with IL-17A antagonists is generally reserved for patients who have failed other systemic therapy with TNF agents.

Studies have shown that ixekizumab is safe and effective for short term use but additional data is needed to determine its long term safety and efficacy. The wholesale acquisition cost of ixekizumab is about $12,300 for 12 weeks of treatment.

LIFITEGRAST (XIIDRA)

Lifitegrast was approved by the FDA on July 12, 2016 for the treatment of Dry Eye Disease (DED). Dry eye disease is estimated to affect 5 million Americans over the age of 50 years and is twice as common in women compared to men.[26]

Lifitegrast had originally been submitted to FDA in 2015 and the FDA declined to approve the drug based on the need for additional clinical data. The clinical trials OPUS-1 and OPUS-2 showed inconsistent clinical outcomes. The manufacturer submitted results from OPUS-3 that demonstrated significant improvement in the symptoms of dry eye. Lifitegrast is the first medication in a new class of drugs, called lymphocyte function-associated antigen 1 (LFA-1) antagonists.[27]

Pharmacology/Pharmacokinetics

Lifitegrast binds to LFA-1, a cell surface protein found on leukocytes. It blocks the interaction of LFA-1 with intercellular adhesion molecule-1 (ICAM-1). ICAM-1 may be overexpressed in corneal and conjunctival tissues in dry eye disease. The exact mechanism of action of lifitegrast in dry eyes is not known.[28]

Indications

Lifitegrast is approved for the treatment of signs and symptoms of dry eye disease.[28]

Dosing

Place one drop twice daily (approximately 12 hours apart) into each eye. Remove contact lenses prior to the use of lifitegrast. The contact lenses may be reinserted 15 minutes following administration.[28]

Efficacy

Although the initial clinical trials with lifitegrast showed inconsistent results, OPUS-3 did demonstrate safety and efficacy of the product in the management of DED. The OPUS-3 trial included 355 patients receiving lifitegrast and 356 patients receiving placebo. Patients were asked to assess their eye dryness symptoms on day 84. The patients who received lifitegrast had a statistically significant improvement in their symptoms ($p<0.0007$) at day 84 and showed significant improvement at 2 weeks after starting therapy ($p<0.0001$). The patients tolerated the drug and the most common side effects reported were dysguesia and burning at the application site. These side effects were determined to be of mild to moderate severity.[29]

Contraindications/Warnings

There are no contraindications or warnings to the use of lifitegrast.[28]

Drug Interactions

Since lifitegrast is applied locally to the surface of the eye, there are no specific drug interactions reported. As described above, contact lenses should be removed prior to the use of lifitegrast.[28]

Adverse Effects

The most common side effects seen with lifitegrast are local eye irritation, dysgeusia and reduced visual acuity. These have been reported in up to 25% of patients taking lifitegrast. Less common side effects (1 to 5%) include blurred vision, conjunctival hyperemia, headache, eye discharge, eye pruritus and sinusitis.[28]

Pregnancy and Lactation

There is no data on the use of lifitegrast in pregnant or lactating women. Systemic absorption of lifitegrast is low and the risk for use in pregnancy and lactation are expected to be low. Individuals should consult their physician and weigh the risks and benefits before use.[28]

Counseling the patient

Patients should be instructed to wash their hands before using lifitegrast. Lifitegrast comes in single use containers sealed in a foil pouch.[28] The pharmacist should instruct the patient to open the foil pouch immediately before using it. The patient should place one drop in each eye. Instruct the patient to avoid touching their eye with the container. There is enough medication in each single use container for both eyes. There is extra medicine in the container in case the patient misses the eye, they can try again. If the patient wears contact lenses, the pharmacist should explain that they need to take out their lenses and wait for 15 minutes after the drug is used before placing the lenses back in their eyes.

Explain to the patient that they may experience some eye discomfort or blurred vision. This is a common side effect. If they develop more serious side effects such as headache or an eye discharge they should talk to their doctor.

Role in therapy

Lifitegrast is only the second prescription drug approved in the United States for the treatment of DED. Cyclosporine ophthalmic solution (Restatis) was approved ten years ago

to increase tear production in DED associated with inflammation. Lifitegrast can be used regardless of the cause of DED. Patients who were unable to tolerate the side effects of cyclosporine ophthalmic solution may be candidates for a course of lifitegrast.

DACLIZUMAB (ZINBRYTA)

Multiple sclerosis (MS) is an immune-mediated disease that attacks and destroys myelin in the brain, spinal cord and optic nerve. MS affects approximately 400,000 people in the United States. This condition appears to be most common in white females between the ages of 20 and 40 years. A number of medications are available to treat MS, and the FDA approved daclizumab in May, 2016. Daclizumab is a monoclonal antibody directed at CD25 that can be administered once a month to patients with the relapsing form of MS. Daclizumab is only available through a restricted access program due to the risks of hepatic injury associated with its use. Pharmacies need to be certified with the program in order to dispense daclizumab to patients with MS.[30,31]

Pharmacology/Pharmacokinetics

Daclizumab is a monoclonal antibody directed at CD25. Daclizumab is well absorbed following subcutaneous administration (>90%). This drug has a small volume of distribution of 6.34 L and has a long elimination half-life of approximately 3 weeks. Since daclizumab is a protein it is catabolized to peptides and amino acids without renal clearance. Because daclizumab is not metabolized by cytochrome isoenzymes, significant drug interactions are not anticipated.[32]

Indications

Daclizumab is indicated for the treatment of adults with relapsing multiple sclerosis. Because of the risk of liver injury, daclizumab should be used only in patients who have had a poor response to two or more drugs indicated for MS.[5,32]

Dosing

The recommended dose of daclizumab is 150 mg administered subcutaneously once monthly. The drug should be administered into the thigh, abdomen, and back of the upper arm. If a patient misses a dose and it is less than two weeks late, the patient can take the dose. If it is more than two weeks late, skip the dose and take the next dose on schedule.[32]

Prior to administration of a dose of daclizumab, the syringe should be removed from the refrigerator to be allowed to warm to room temperature. Do not use hot water or other heat sources to warm the drug.[32]

Efficacy

Two clinical trials were submitted to the FDA to support the safety and efficacy of daclizumab. One trial compared daclizumab to placebo and the second trial compared it to interferon. In the SELECT trial, daclizumab 150 mg once a month reduced the annualized relapse rate (ARR) by 54% compared to placebo. In the DECIDE trial where daclizumab was compared to beta interferon, there was a 44% reduction in ARR with daclizumab. Both clinical trials showed that daclizumab had a significant improvement in ARR.[32]

Contraindications/Warnings

Daclizumab is contraindicated in patients with established liver impairment (AST or ALT > 2 times the upper limit of normal). It should not be given to patients with a history of autoimmune hepatitis or other autoimmune conditions. It is also contraindicated in patients who are allergic

to daclizumab or any of the components of the product. Do not administer live vaccines during treatment with daclizumab and for four months after discontinuation.[32]

Drug Interactions

Since daclizumab is not metabolized by the CYP450 system, no specific drug interactions have been identified. Drugs that increase the risk for liver damage should be avoided when taking daclizumab. This would include any dietary supplements or herbal products.[32]

Adverse Effects

The most common side effects reported with daclizumab include upper respiratory tract infection, nasopharyngitis, rash, dermatitis, eczema, infections, influenza, lymphadenopathy and depression. More serious side effects reported include celiac disease, autoimmune thyroiditis, immune hemolytic anemia, thrombocytopenia, pancreatitis, and rheumatoid arthritis.[32]

Pregnancy and Lactation

There are no studies evaluating the safety of daclizumab in pregnancy. There is no information on the fetal risk associated with its use during pregnancy. Studies in monkeys have shown reduced fetal growth and fetal death at doses 30 times that expected in humans. In addition, there is no data on the presence of daclizumab in human breast milk, however it has been detected in lactating monkeys. Patients are encouraged to weigh the risk and benefits of daclizumab use in pregnant and lactating women.[32]

Counseling the patient

The pharmacist should explain how daclizumab is administered and have the patient or caregiver demonstrate their ability to administer the injection. The pharmacist should remind the patient to avoid any live vaccines while taking this drug. Patients should understand the importance of having their transaminase and bilirubin levels monitored monthly during treatment and for up to 6 months after the last dose of the drug.[31] The pharmacist should encourage the patient to carry the daclizumab wallet alert card so healthcare workers are aware of the medication and side effects. The patient should be counseled on the signs and symptoms of liver injury, including unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice or dark urine. Patients should be aware of the risk for skin rash and understand that they need to report this information to their physician prior to their next dose. Patients may develop lymphadenopathy that requires invasive treatment. Patients should be aware of the symptoms such as infections, salivary neoplasm, skin reactions, thrombocytopenia, and interstitial lung changes. Patients may also develop gastrointestinal problems that need to be assessed by a specialist.

Role in therapy

Daclizumab appears to be more effective than intramuscular interferon beta-1a at reducing relapse rates in patients with relapsing-remitting multiple sclerosis (MS). It can cause hepatotoxicity and immune-mediated disorders. There are no direct comparisons with other agents used to treat MS. However, because of the risk of liver injury, daclizumab is not considered a first line therapy. It should be reserved for use only in patients who have had a poor response to two or more drugs indicated for MS.

PIMAVANSERIN (NUPLAZID)

Pimavanserin is an atypical antipsychotic that was approved by the FDA on April 29, 2016 for the treatment of hallucinations and delusions associated with Parkinson's Disease Psychosis (PDP). This drug was given breakthrough status because it may offer substantial improvement over currently available therapy. The drug was also granted a priority review. Parkinson's disease is reported to occur in almost 1 million Americans. Approximately 30-40% of patients treated with medications for Parkinson's disease may develop PDP.[33,34]

Pharmacology/Pharmacokinetics

The exact mechanism of action of pimavanserin is not known but it is postulated that the effect could be due to its effects on serotonin. Pimavanserin is well absorbed after oral administration and is not affected by the intake of food. The drug is >95% plasma protein bound and has a volume of distribution of 2173 L. Pimavanserin is metabolized by cytochrome P450 enzymes. The elimination half-life of primavanserin is 57 hours and the active metabolite (AC-279) has a half-life of 200 hours. The majority of pimavanserin is excreted in the feces as metabolites. Less than 1% of the drug is excreted in the urine.[35]

Indications

Pimavanserin is approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.[5,35]

Dosing

The dose of pimavanserin is 34 mg given as two 17 mg tablets once a day. This drug can be taken without regard to meals. Pimavanserin does not need to be titrated. In patients taking strong CYP3A4 inhibitors such as ketoconazole, the dose should be reduced to 17 mg once a day. Patients taking a strong CYP3A4 inducer (rifampin) should be monitored for a reduction in efficacy of pimvanserin. An increase in dose may be needed. Pimavanserin should not be used in patients with severe renal impairment (CrCl < 30 mL/min) or in patients with hepatic impairment.[35]

Efficacy

Pimavanserin was compared to placebo in patients with symptomatic Parkinson's disease psychosis for 6 weeks. Efficacy was determined based on the Parkinson's disease (PD) adapted Scale for Assessment of Positive Symptoms (SAPS-PD). Patients receiving pimavanserin had a statistically significant reduction in the frequency and/or severity of hallucinations and delusions compared to the placebo group. The mean difference from baseline in the SAPS-PD score was 3.1 points better in the pimavanserin group (p= 0.001). Although this is a statistically significant difference, it did not translate into clinical improvement. The most common adverse events (> 5% and at least twice the rate of placebo) reported included peripheral edema and confusional state. Serious adverse events that led to discontinuation of pimavanserin during the studies were hallucinations, urinary tract infection and fatigue.[36]

Contraindications/Warnings

There are no contraindications to the use of pimavanserin. Like other atypical antipsychotics, pimavanserin has a black box warning regarding an increased risk of mortality in patients with dementia-related psychosis. Atypical antipsychotic agents have demonstrated an increased risk of death in patients with dementia-related psychosis. Pimavanserin is not approved for dementia-related psychosis and should be avoided in this population.[35]

Pimavanserin does prolong the QT interval and should be avoided in patients who have a known QT prolongation. It should not be given in combination with any other drugs that can prolong the QT interval such as Class 1A or 3 antiarrhythmics, some antipsychotic medications, and some antibiotics. It should also be avoided in patients who have a history of cardiac arrhythmias, hypokalemia, or symptomatic bradycardia.[35]

Drug Interactions

There are some significant drug-drug interactions with pimavanserin.[35]

- ***CYP3A4 Inhibitors***
  When combined with strong CYP3A4 inhibitors (ketoconazole, nefazodone), there can be an increase in the serum level of pimavanserin. Physicians should decrease the dose of pimavanserin by 50% when combined with CYP3A4 inhibitors.
- ***CYP3A4 Inducers***
  In cases where strong CYP3A4 inducers are combined with pimavanserin, there can be a reduction in the serum level of pimavanserin. Physicians may need to increase the dose of pimavanserin if combined with strong CYP3A4 inducers (rifampin, carbamazepine).
- ***QT prolongation***
  The other major drug interaction with pimavanserin is the concomitant use of drugs that can prolong the QT interval. This includes Class 1A antiarrhythmic agents such as procainamide and disopyramide and Class 3 antiarrhythmics such as amiodarone. Other drugs that can prolong the QT interval include some antipsychotic agents such as ziprasidone and some quinolone antibiotics.

Adverse Effects

The most common adverse effects reported with pimavanserin include peripheral edema, nausea, constipation, weight loss, hallucinations and confusion. More serious side effects that have been reported with pimavanserin include prolonged QT interval, cardiac arrhythmia and death (dementia-related psychosis).[35]

Pregnancy and Lactation

There is no clinical data on the use of pimavanserin in pregnant or lactating women. Animal studies with rats indicated that there was significant maternal toxicity including death, dehydration, or weight loss. The effect on the pups included reduced body weight, reduced litter size and lower pup survival. Similar maternal toxicity was reported in pregnant rabbits given pimavanserin.[35]

Counseling the patient

The pharmacist should discuss the risks and benefits of pimavanserin with the patient and/or the caregiver. Discuss the potential drug interactions with pimavanserin. All medication changes should be discussed with the doctor or pharmacist to be sure the dose of pimavanserin does not need to be changed.

Role in therapy

Currently there is no other FDA-approved therapy for Parkinson's disease psychosis. There is only one controlled phase 3 trial that was submitted to the FDA for the approval of the product. The study failed to show clinically meaningful differences, although there was statistical significance. The study was only conducted for a 6 week period so additional longer term trials are needed. One benefit of pimavanserin is that it does not appear to

worsen the motor symptoms of Parkinson's disease.

CONCLUSION

This past year, 2016 was a much slower year for drug approvals than the previous ten years. There were 22 new drug approvals, the fewest since 2001. Sixteen of the 22 drugs were approved through one of the expedited categories of FDA approval. It is important for the pharmacist to understand these new drugs and how these medications fit into the current standards of care.

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August 2017 "Part 1: New Drugs Approved in 2016" Volume 39 #8

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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?
   - List the new drugs approved by the FDA in 2016 — YES NO
   - Discuss the role of these agents in therapy — YES NO
   - Summarize the adverse effects & potential drug interactions with these agents — YES NO
   - Recommend counseling points when dispensing these drugs — YES NO

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

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

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. **The dose of eteplirsen is:**
   A. 30 mg/kg of body weight once a week infused over 35 to 60 minutes.
   B. 35 mg/kg of body weight once a week infused over 2 hours.
   C. 50 mg/kg of body weight twice a week.
   D. 75 mg/kg of body weight twice a week

2. **Ixekizumab is a recombinant monoclonal antibody that binds & neutralizes:**
   A. IL-5 B. IL-17A
   C. IL-3 D. IL-14B

3. **Which of the following drugs is approved for use in moderate psoriasis?**
   A. Bezlotoxumab
   B. Daclizumab
   C. Ixekizumab
   D. Atezolizumab

4. **Lifitegrast blocks the interaction of _____ with intercellular adhesion molecule-1 (ICAM-1).**
   A. LFA-1 B. LFA-2
   C. IL-2 D. IL3

5. **A patient presents a prescription for lifitegrast. After it is filled, what counseling points should you mention to the patient?**
   A. Open the outer pouch of the container immediately before using the eye drop.
   B. Remove contacts before using eye drops & do not place back in eyes for 15 minutes.
   C. There is enough extra medication in case you miss your eye, you can try again.
   D. All of the above are correct.

6. **A physician prescribes pimavanserin. The patient has been taking nefazodone for 6 months, and is continuing with its use. What dose of pimavanserin is suggested?**
   A. 34 mg once daily. B. 21 mg once daily.
   C. 17 mg once daily. D.17 mg twice daily.

7. **Which of these statements is true about Duchene Muscular Dystrophy?**
   A. DMD is a genetic disorder that results in progressive muscle degeneration & weakness.
   B. DMD primarily affects females.
   C. Symptoms of DMD start in the heart and Respiratory muscles.
   D. All of the above are true.

8. **A doctor starts a patient on pimavanserin. The patient has been stable on carbamazepine for 2 years. What dose of pimavanserin is suggested?**
   A. Increase dose of pimavanserin.
   B. Decrease dose of pimavanserin by 50%.
   C. Decrease dose of pimavanserin by 25%.
   D. None of the answers is correct.

9. **Which of the following drugs was approved by the FDA in 2016 for the treatment of relapsing Multiple Sclerosis?**
   A. Pimavanserin. B. Lifitegrast.
   C. Daclizumab. D. Velpatasvir.

10. **Daclizumab is contraindicated with:**
    A. Pulmonary fibrosis.
    B. Cardiac arrhythmias.
    C. CrCl < 30 mL/min.
    D. Established liver impairment.