NWX HHS FDA CDER

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Catherine Chew: Hello. My name is Captain Catherine Chew, Acting Director of the Division of Drug Information within the US Food & Drug Administration. I would like to welcome you to the Global Alliance of Drug Information Specialist Webinar Series 2015 Novel Drugs Approved in 2014.

The objectives for today's program are to, number one, explain the methods used by FDA to expedite approval of novel drugs and, two, discuss indications, identify the appropriate patient populations, and discuss the contraindications, warnings and precautions for the novel drugs approved by FDA in 2014.

I would like to introduce our speaker today from FDA's Division of Drug Information Holli Tierno. Holli Tierno graduated with her Pharm.D. from Arnold and Marie Schwartz College of Pharmacy in 2005. She has been with the FDA for one year.

Prior to joining the Division of Drug Information Holli was an associate director with Boehringer Ingelheim Pharmaceuticals for seven years. Holli

also completed an ASHP Drug Information Residency at MedAssets Supply Chain Solutions. Holli?

Holli Tierno: Thank you Cat. The introduction of new drugs into the marketplace is one of the most important topics for us as pharmacists. It is equally important to understand the warnings and correct patient populations for these drugs.

Innovation drives progress. Each year the Center for Drug Evaluation and Research, CDER for short, approved a wide range of new drugs and biologic products. Some of these products are innovative new products that never before have been used in clinical practice.

Others are the same as or related to previously approved products and they will compete with these products in the marketplace. Each year since 2011 we have developed a novel new drugs report that highlights the new products. Many of these products offer new hope for patients suffering from the condition these products are intended to treat.

In 2014 the Center for Drug Evaluation and Research approved 41 novel new drugs approved as new molecular entities, NMEs, under new drug applications, NDAs, or as new therapeutic biologics under biologic license applications, BLAs.

The top numbers of this chart show the new molecular entity, new biological approvals and the bars underneath show the new filings. Looking at this chart we can see that from 2005 through 2013 CDER has averaged 25 novel new drug approvals per year.

As I mentioned in 2014 CDER approved 41 novel new drugs. CDER used a number of regulatory methods to expedite the approval of novel new drugs in

2014. These involve the following four expedited development and review pathways: fast track, breakthrough, priority review and accelerated approval.

Seventeen or 41% of the 2014 novel new drugs were designated by CDER as fast track, meaning drugs with the potential to address unmet medical needs. Fast track speeds new drug development and review. For instance by increasing the level of communications FDA allocates to drug developers and by enabling CDER to review portions of a drug application ahead of the submission of the complete application.

CDER designated nine of the 2014 novel new drugs, 22% as breakthrough therapies meaning drugs with preliminary clinical evidence demonstrating that the drug may result in substantial improvement on at least one clinically significant endpoint over other available therapies.

For purposes of breakthrough therapy designations, clinically significant end points generally refers to an end point that measures an effect of irreversible morbidity or mortality or symptoms that represent serious consequences of the disease.

A breakthrough therapy designation includes all of the fast track program features as well as more intensive FDA guidance on an efficient drug development program. Breakthrough status is designed to help shorten the development time of a promising new therapy.

Twenty-five of the 2014 novel new drugs, 61%, were designated priority review in which CDER determined the drug to potentially provide a significance advance in medical care and sets a target to review the drug within six months instead of the standard ten months.

CDER approved eight of the 2014 novel new drugs, 20%, under FDA's accelerated approval program which allows early approval of the drug for a serious or life threatening illness that offers a benefit over current treatment.

This approval is based on a surrogate end point. For example laboratory measure or other clinical measure that we consider reasonably likely to predict the clinical benefit of the drug. This speeds the availability of the drug to patients who need it.

Once accelerated approval is granted the drug must undergo additional testing to confirm that benefit. In many cases more than one expedited development and review tool was used to speed drug approval.

More than half of the 2014 novel new drugs, 66% were designated in one or more of these four categories. Each of these designations helps expedite the speed of the development and/or approval process and is designed to help bring important medications to the market as quickly as possible.

First in class and rare diseases is another important aspect when looking at the potential positive public health impact and unique contributions of these drugs. Many of the 41 novel new drugs CDER approved in 2014 are notable for their potential positive impact and unique contributions to quality medical care and public health.

CDER identified more than one third of the novel new drugs approved in 2014, about 41% as first in class, one indicator of the innovative nature of a drug. For example these drugs might use new or unique mechanisms of action for treating medical conditions than existing therapies.

These are five drugs that may potentially have a strong clinical impact. I will review 5 of these noteworthy first in class products. Belsomra, Harvoni, Viekira, Keytruda, and Zontivity in more detail.

Belsomra is an orexin receptor antagonist approved to treat difficulty in falling and staying asleep. It is contraindicated in narcolepsy. Exposure to Belsomra is increased in obese compared to non-obese patients and in women compared to men.

Particularly in obese women the increased risk of exposure related adverse effects should be considered before increasing the dose. Belsomra can cause daytime somnolence including risk of impaired alertness and motor coordination including impaired driving.

This risk increases with dose. Caution patients taking 20 milligrams against next day driving and other activities requiring complete mental alertness. The risk of next day impairment is increased if Belsomra is taken with less than a full night of sleep remaining, if a higher dose is taken, if co-administered with other CNS depressants like benzodiazepines, opioids, tricyclic antidepressants or any other drugs that increase blood levels of Belsomra.

Sleep disturbances may be manifestations of other physical or psychiatric disorders and failure of insomnia to remit, worsen or emergence of new cognitive or behavioral abnormalities after seven to ten days of treatment would indicate the presence of a primary illness that should be evaluated.

Nighttime sleep driving and other behaviors like eating or making phone calls with amnesia of the event have been reported with the use of hypnotics like Belsomra. A dose dependent increase in suicidal ideation was observed in patients taking Belsomra during clinical studies.

So counseling, taking a patient's history and dispensing the least number of pills is advisable. Belsomra has not been studied in sleep apnea or COPD patients. Thus the drug should be used with caution in patients with compromised respiratory function.

Patients should be counseled regarding sleep paralysis, cataplexy and hallucinations that can occur with the drug. The hallucinations may be while falling asleep or while transitioning to wakefulness. Hallucinations can be visual, auditory or other sensory events.

Harvoni is a two drug fixed dose combination product that contains 90 milligrams of ledipasvir and 400 milligrams of sofosbuvir in a single tablet. Harvoni is approved to treat chronic Hep C genotype 1infections in adults.

The concomitant use of Harvoni and P-gp inducers for example, rifampin or St. John's Wort, is not recommended as it may significantly decrease both ledipasvir and sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of Harvoni.

The table provides the recommended Harvoni treatment duration for treatment naïve and treatment experienced patients and those with and without cirrhosis. It is important to also note that Harvoni for eight weeks can be considered in treatment naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million international units per mL.

Treatment experienced patients are those who are defined as failing treatment with either peginterferon alfa plus ribavirin or an HCV protease inhibitor plus peginterferon alfa plus ribavirin.

Thus the duration of treatment in these patient populations will vary from eight to twenty-four weeks. Keep this in mind when filling refills and checking their previous disease and medication history.

Viekira Pak is four drugs in one, dasabuvir sodium, ombitasvir, paritaprevir and ritonavir. It is approved to treat genotype 1 chronic Hepatitis C including those with compensated cirrhosis.

Viekira Pak is contraindicated in patients with decompensated liver disease or severe hepatic impairment. In the prescribing information there's a table of drugs that are contraindicated due to the high dependence of CYP3A clearance.

Drugs that are strong inducers of CYP3A and CYP2C8 may lead to decreased efficacy of Viekira Pak and strong inhibitors of CYP2C8 may increase dasabuvir concentrations and increase the risk of QT prolongation.

It is also contraindicated in patients that are hypersensitive to ritonavir or have any contraindications to ribavirin. During clinical trials with Viekira Pak, with or without ribavirin, elevations of ALT to greater than five times the upper limit of normal occurred in approximately 1% of all subjects.

These elevations were typically asymptomatic occurring within the first four weeks of treatment and declining within two to eight weeks of onset. These elevations were significantly more frequent in females who were using ethinyl estradiol medications. These medications must be discontinued prior to starting therapy and can be restarted approximately two weeks following completion of treatment.

Hepatic testing is recommended during the first four weeks of starting treatment and is clinically indicated thereafter.

Other warnings or precautions include, of course, any warnings with ribavirin treatment, risk of reduced effect due to drug interactions and a risk of HIV protease inhibitor drug resistance if a co-infected patient is not on an antiretroviral drug regimen due to the ability of ritonavir to select for HIV 1 protease substitutions.

As you can see in the table here the treatment regimen and duration varies by genotype and cirrhosis. Ribavirin is given in all of the patient populations except patients with genotype 1B without cirrhosis.

Treatment is typically 12 weeks in duration but may be 24 weeks in patients with genotype 1A with cirrhosis. A difference here though is that the treatment is the same whether treatment experienced or treatment naïve.

Keytruda is approved for patients with unresectable or metastatic melanoma and disease progression following ipilimumab and if BRAF V600 mutation positive, a BRAF inhibitor. This drug was approved on a surrogate end point.

We will now do a question and answer. Based on this information would this be considered fast track, accelerated approval, priority review or breakthrough. The poll is now open.

It looks like most people have voted. And, yes, you are correct. The answer is B. The indication is approved under accelerated approval based on a surrogate end point of tumor response rate and their ability of response.

An improvement in survival or disease related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. If you wanted to find what those trials would be you can go to drugs@fda and look at the approval letter. We can go there right now.

So we will go ahead and type in Keytruda and we will hit submit. And then we will go to approval history, letters, reviews and related documents here. And then here we're going to look at the letter.

This is the approval letter for Keytruda. And if we scroll down - we're looking at from the top here. If we scroll down in the letter you will find the requirement for accelerated approval as well as the time frame of when this is expected to be completed.

Now going back to the other choices in the poll if you chose C or D you would have also been correct. This drug was also approved under priority review which has a set target to review within six months. And breakthrough was also correct which provides intensive FDA guidance on an efficient drug development program to help shorten the development time for drugs that are intended to treat a serious condition.

Be aware that for Keytruda there are a number of immune mediated adverse reactions that depending on the severity of the reaction may precipitate administering steroids, withholding a dose or permanently discontinuing therapy.

The main ones are listed here on this slide. For suspected immune mediated adverse reactions ensure adequate evaluation to confirm etiology or exclude other causes.

Based on its mechanism of action Keytruda may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use highly effective contraception during treatment with Keytruda and for four months after the last dose of Keytruda.

Zontivity is a proteus activated receptor 1 antagonist approved to reduce thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease.

It has been shown to reduce the rate of a combined end point of cardiovascular death, MI, stroke and urgent coronary revascularization. Zontivity is contraindicated in patients with a history of stroke, TIA or ICH because of an increased risk of ICH in this population.

Zontivity can also increase the risk of bleeding including ICH and fatal bleeding. Avoid use with strong CYP3A inhibitors or inducers as they will decrease Zontivity exposure. Zontivity has been studied only as an addition to aspirin and/or clopidogrel and thus is not recommended to be used alone.

It is important to note that significant inhibition of platelet aggregation remains four weeks after discontinuation and there is no known treatment to reverse the anti-platelet effects of Zontivity.

Those five drugs were noteworthy examples of first in class. About 43% of the novel new drugs approved in 2014, 17 of 41, were approved to treat rare or orphan diseases that affect 200,000 or fewer Americans.

This is significant because patients with rare diseases often have few or no drugs available to treat their conditions. I will review these noteworthy examples listed below starting with Vimizim.

Vimizim was approved to treat mucopolysaccharidosis type IVA a rare genetic disorder resulting in skeletal deformities, gross retardation and heart problems.

The boxed warning for Vimizim warns about the risk of anaphylaxis. Life threatening anaphylactic reactions have occurred in some patients during Vimizim infusions regardless of duration of the course of treatment. Closely observe patients during and after all Vimizim administration and be prepared to manage the anaphylaxis. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should any symptoms occur.

Because of the anaphylaxis, patients with acute respiratory illness may be at risk of serious acute exacerbations of their respiratory compromise due to hypersensitivity reactions and require additional monitoring.

Careful consideration should be given to the patient's clinical status prior to administration of Vimizim and consider delaying the Vimizim infusion. Spinal or cervical cord compression, SCC, is a known and serious complication of MPS IVA and may occur as part of the natural history of the disease.

In clinical trials SCC was observed both in patients receiving Vimizim and patients receiving placebo and thus patients should be monitored for signs and symptoms of SCC including back pain, paralysis of limbs below the level of compression and urinary and fecal incontinence.

Impavido is an antileishmanial drug indicated in adults and adolescents greater or equal to 12 years of age weighing greater than or equal to 66 pounds for treatment of visceral, cutaneous and mucosal leishmaniasis.

Leishmaniasis is transmitted by bites of infected sand flies. It is important to note that leishmania species evaluated in clinical trials were based on epidemiologic data and there may be geographic variations in the response of the same species to Impavido.

Impavido approval was based on studies conducted in India, Columbia and Guatemala. The effect of Impavido in the treatment of other species that I have not mentioned has not been evaluated.

Impavido has a boxed warning for use in pregnancies because it may cause fetal harm. Fetal death, teratogenicity as well as impaired fertility occurred in animals administered Impavido at doses lower than the recommended human dose.

So doses lower than the recommended human dose in animals they found fetal death and teratogenicity. Obtain a serum or urine pregnancy test in females of reproductive potential prior to prescribing Impavido. Advise females of reproductive potential to use effective contraception during therapy and for five months after therapy discontinuation.

Impavido is also contraindicated in Sjogren-Larsson Syndrome because patients aren’t able to metabolize Impavido correctly. There are a number of warnings and precautions with Impavido.

Elevations of serum creatinine, ALT, AST and bilirubin were noted during clinical trials so kidneys and liver function should be monitored throughout therapy. Because vomiting and diarrhea often occur during Impavido therapy dehydration is an ongoing concern. Patients should be counseled regarding fluid intake. Platelet count should be monitored due to the concern of thrombocytopenia which occurred during clinical trials.

As I mentioned vomiting and diarrhea are of concern, so oral contraceptives may not be adequate protection against pregnancy. Stevens-Johnson Syndrome has been reported during therapy. Discontinue if an exfoliative or bullous rash is observed.

Sylvant is an interleukin-6 antagonist approved to treat Multicentric Castleman's Disease. Patients with MCD have an abnormal overgrowth of lymph cells that is similar in many ways to lymphoma.

People with MCD also have problems such as serious infections, fevers, weight loss, fatigue, night sweats and nerve damage and cause weakness and numbness. Blood tests often show too few red blood cells and high levels of antibodies in the blood.

An important limitation of use is that Sylvant was not studied in patients with MCD who are HIV positive or HHV-8 positive because Sylvant did not bind to virally produced IL-6 in a nonclinical study.

This was important because Sylvant - because Multicentric Castleman's Disease is often found in HIV patients. Do not administer Sylvant to patients with severe infection until the infection resolves.

Hematology laboratory tests must be performed prior to each dose of Sylvant therapy for the first twelve months and every three dosing cycles thereafter as prior to each dose of Sylvant therapy for the first twelve months and every three dosing cycles thereafter.

If treatment criteria are not met consider delaying treatment with Sylvant but do not reduce dose. Do not administer live vaccines because IL-6 inhibition may interfere with the normal immune response to new antigens.

You should administer Sylvant in a setting that provides resuscitation equipment, medication and personnel trained to provide resuscitation due to infusion related reactions. Do not reinstitute treatment in patients with severe infusion related reactions and if there is severe allergic reactions or cytokine release syndrome.

Use with caution in patients who may be at an increased risk of gastrointestinal perforations. Gastrointestinal perforation is basically a hole that develops to the wall of the esophagus, stomach, small intestines, large bowel, rectum or gall bladder. Gastrointestinal perforation has been reported in clinical trials with Sylvant, although not in MCD trials. Promptly evaluate patients presenting with symptoms that may be associated or suggestive of GI perforation.

Cerdelga is indicated for the long-term treatment of adult patients with Gaucher's disease Type I who are CYP2D6 extensive metabolizers, intermediate metabolizers, or poor metabolizers as detected by an FDA-cleared test.

Gaucher's disease is a rare genetic disorder resulting in an enlargement of the liver and spleen, a low number of red blood cells, easy bruising caused by a

decrease in blood platelets, lung disease and lung problems. Contraindications are in regards to important drug interactions.

In addition, CYP2D6 ultra-rapid metabolizers may not achieve adequate concentration of Cerdelga to achieve a therapeutic effect. A specific dosage cannot be recommended for CPY2D6 indeterminate metabolizers.

Cerdelga is not recommended in patients with pre-existing cardiac disease, long QT syndrome, or in concomitant use of Class IA and Class III antiarrhythmics due to the potential for ECG changes in cardiac arrhythmia. Dosing will be impacted based on the type of metabolizer the patient is as well as other drugs the patient is taking.

These next two drugs Esbriet and Ofev are both indicated for the treatment of idiopathic pulmonary fibrosis or IPF. They have different mechanisms of action. IPF results in decreased lung function and breathing failure. Dosage is titrated over three weeks to help minimize the adverse effects.

You should consider temporary dosage reduction, treatment interruption or discontinuation for management of adverse reactions. Prior to treatment, conduct the liver function test as elevated liver enzymes ALT, AST and bilirubin have occurred with both therapies.

Gastrointestinal disorders such as nausea, vomiting, diarrhea, dyspepsia, GERD and abdominal pain have occurred with both therapies. Temporary dosage reductions or discontinuation may be required.

Photo sensitivity and rash have been noted with Esbriet. Tell patients to avoid exposure to sunlight and sunlamps and wear sunscreen and protective clothing daily. Temporary dosage reductions or discontinuation may also be required.

Women of childbearing potential should be advised to avoid becoming pregnant or receiving treatment with Ofev and to use adequate contraception during treatment and then at least three months after the last dose. Ofev was found to be teratogenic to animals.

Arterial thromboembolic events have been reported in 2.5% of patients treated with Ofev and 0.8% of placebo treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of Ofev treated patients compared to 0.4% of placebo treated patients.

Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. Based on the mechanism of action of VEGFR inhibition, Ofev may increase the risk of bleeding.

In clinical trials, bleeding events were reported in 10% of patients treated with Ofev and in 7% of patients treated with placebo. Use Ofev in patients with known risk of bleeding only if the anticipated benefits outweigh the potential risks. Also based on the mechanism of action, Ofev may increase the risk of gastrointestinal perforation.

In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with Ofev compared to zero cases in the placebo treated patients. Use caution when treating patients who have had recent abdominal surgery and discontinue therapy in patients who develop gastrointestinal perforation.

Only use Ofev in patients with known risk of gastrointestinal perforation if the anticipated benefits outweigh the potential risks. Time for another poll question. Which two drugs have an adverse effect of an increased risk of bleeding? Choose your response in the polls on the screen.

It looks like most people have voted and you are correct. It is D, Zontivity for reducing thrombo thrombotic cardiovascular events in patients with a history of myocardial infarction and Ofev for idiopathic pulmonary fibrosis. Make sure a history of patient's disease and risk factors is evaluated and patients are counseled about the signs and symptoms of bleeding.

Myalept is a leptin analogue indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

The safety and effectiveness of Myalept for the treatment of complications of partial lipodystrophy and for the treatment of liver disease including non-alcoholic steatohepatitis have not been established.

Myalept is also not indicated to be used in patients with HIV-related lipodystrophy or in patients with metabolic disease without concurrent evidence of generalized lipodystrophy. To reiterate, it is approved to treat complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

Myalept has a box warning. You should test for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of Myalept efficacy during treatment. Anti-metreleptin antibodies with neutralizing activity could inhibit endogenous leptin action and/or result in loss of Myalept efficacy.

These antibodies were identified in two patients with generalized lipodystrophy treated with Myalept resulting in severe infections, increases in HbA1c and triglycerides, and in three patients without lipodystrophy showing as excessive weight gain, development of glucose intolerance or diabetes. The consequences, however, are not well-characterized as this has occurred in so few patients.

T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with Myalept. Carefully consider the benefits and risks of treatment with Myalept in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy.

Myalept is available only through a restrictive program called the Myalept REMS Program. Both prescribers and pharmacies must be certified.

Closely monitor blood glucose in patients on concomitant insulin or insulin secretagogue such as sulfonylurea therapy as hypoglycemia may occur. A dose adjustment including possible large reductions of insulin or insulin secretagogue may be necessary.

Carefully consider benefits and risks of Myalept treatment in patients with autoimmune disease as autoimmune disorder progression has been observed in patients treated with Myalept. Hypersensitivity reactions such as urticaria or generalized rash have been reported. Advise patients to promptly seek medical advice regarding suspected reactions.

Benzyl alcoholic toxicity can occur. Reconstitute with preservative-free sterile water for injection for neonates and infants.

Additional drugs that were approved in 2014 include four new antibiotics as qualified infectious disease products. These were the first four QIDP, for short, designated novel new drugs approved by FDA.

In Generating Antibiotics Incentives Now Act, which we also call the GAIN Act, provides incentives to help bring new antibiotics and other antimicrobials to market. A drug with particular promise can be designated as a QIDP qualified infectious disease product by authority of the GAIN Act.

Additional products included four diabetes products, Entyvio to treat moderately to severely active ulcerative colitis and Crohn's disease and some drugs for ovarian cancer, acute lymphoblastic leukemia, and melanoma. 63% of novel new drugs approved in 2014 were approved in the United States before receiving approval in any other country.

Our professions require us to always know what medications are new, what they are for, who should receive them and any safety concerns. As you can see, there are many first in-class, orphan, and other drugs made a strong impact in 2014, focusing on quality and getting drugs to patients who may have little or no options.

You can follow the 2015 new molecular entities and biologic product approvals at this link. As you can see here, there's six listed so far for 2015. You can also find archived new molecular entity approvals for previous years on the side here. Here are the references which were also included in the GADIS invite.

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