The Advancement of Pipeline Drugs in 2012

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There are no financial relationships that could be perceived as real or apparent conflicts of interest.

Universal Activity # 0143-0000-12-009-H04-P&T
1 Contact Hour (0.1 CEUs)

OBJECTIVES:
At the conclusion of this lesson, the reader should be able to:

- Outline the process for FDA new drug approvals.
- List both trade and generic names for New Molecular Entities (NMEs) approved from January 2012 thru April 2012.
- Name the indication, administration route, dosage form, dosage and side effects of each NME.
- State significant black box warnings, contraindications, necessary dosing adjustments and drug interactions for each NME.

BACKGROUND
The Food and Drug Administration (FDA) released a statement in November 2011 that over the past 12 months the U.S. FDA had approved 35 new medications.\(^1\) The approval rate was among the highest on record, exceeded only by 37 approvals in 2009. The 35 approved medications have studies indicating increased survival and quality of life for disease states such as hepatitis C, lupus, Hodgkin’s lymphoma and late-stage prostate cancer. The FDA has attempted to expedite such new drug approvals by creating more flexible clinical trial requirements, while maintaining safety standards. Industries are working feverishly to market drugs for oncology, rare disease states and second-line therapies for chronic disease states.

Industries who wish to market a new drug for U.S. consumption have to prove the drug’s efficacy and safety to the FDA. New Drug Applications (NDAs) are completed by the applicant and include drug name, indication, ingredients, strength, dosage form and route of administration.\(^2\) The application also should contain clinical trial information, stability testing, pharmacokinetic studies, side effects, toxicology and labeling information. The application provides comprehensive drug information with the goal of showing that the drug’s benefits outweigh its risks. The FDA aims to reduce the time it takes for drugs to be approved to less than six months in order to more efficiently provide the best possible treatment options to individuals who suffer from acute or chronic diseases.\(^1\)

The collaborated effort of the FDA and pharmaceutical manufacturers has increased new drug approvals over the past few years. New drug products are marketed through commercial advertising and drug representatives. It is important for physicians, practitioners and pharmacists in particular to become familiar with these newly approved drugs in order to provide the best, most current treatment options to patients.

Since January 2012, 11 New Molecular Entities (NMEs) have been approved with indications spanning from an erythropoiesis-stimulating agent (ESA) to a drug used for erectile dysfunction.\(^3\)

NEWLY APPROVED DRUGS FOR 2012 (Jan. 1 – May 1, 2012)\(^3\)

VORAXAZE\(^\circledR\) (glucarpidase)

Glucarpidase is a carboxypeptidase enzyme FDA approved Jan. 17, 2012 that is used to treat toxic methotrexate levels (>1µmol/L).\(^4\) Patients receiving a methotrexate chemotherapy regimen with renal impairment have difficulty clearing the drug which can result in extensive stomatitis, kidney/liver damage, intestinal destruction, skin rashes and reduced blood cell counts. The drug lowers methotrexate levels by converting the entity to glutamate and 4-deoxy-4-amino-N 10-methylpteroid acid (DAMPA) which can
be eliminated hepatically.\textsuperscript{5} It should be given at a
dose of 50 units/kg reconstituted in 1mL normal saline
and administered intravenously over five minutes; the
line should be flushed before and after administration.
Leucovorin rescue treatment should be continued but
should not be given within two hours of glucarpidase
administration.\textsuperscript{5} Hypotension, flushing, headache,
nausea and vomiting were reported side effects of
glucarpidase. DAMPA levels can cause falsely high
readings of methotrexate levels within 48 hours of ad-
ministration; therefore, use DNA chromatographic
method for accurate readings.\textsuperscript{5}

\textbf{PICATO\textsuperscript{®} (ingenol mebutate)}

Ingenol mebutate gel was approved Jan. 23, 2012 for
actinic keratosis as the first topical that can be used
for as little as two to three consecutive days.\textsuperscript{6} Actinic
keratosis is a precancerous condition caused by on-
going sun exposure that has potential to progress to
squamous cell carcinoma.\textsuperscript{7} The mechanism of which
the gel induces cell death is unknown. The 0.015 per-
cent strength is approved for use once daily on the
face and scalp for three consecutive days, and the
0.05 percent strength is approved for use once daily
on the trunk and extremities for two consecutive days.
The drug is not systemically absorbed, but patients
with pre-existing eye/skin disorders should take extra
precaution. The lesion site may crust, become red,
flake, form a pustule or become painful throughout the
days of administration. Pharmacists should counsel
patients to apply gel from the single-use tube to af-
fected area and allow drying for 15 minutes. Patients
should wash their hands immediately after administra-
tion, avoiding any ophthalmic contact. The gel can be
washed off six hours after administration with mild
soap.\textsuperscript{6}

\textbf{INLYTA\textsuperscript{®} (axtinib)}

The tyrosine kinase-inhibitor, axtinib, was approved
Jan. 27, 2012 for the treatment of advanced renal cell
carcinoma for patients who have not responded to
other types of therapy.\textsuperscript{8} Axtinib is available in a 1 mg
and 5 mg tablet with a recommended initial dose of 5
mg every 12 hours.\textsuperscript{8} The dose can be increased to 7
mg twice daily then 10 mg twice daily if previous dose
was well-tolerated by patient in previous two weeks.
Dose interruptions or decreases are necessary with
hypertensive crisis, uncontrolled or worsening hyper-
tension, hemorrhage, proteinuria or concomitant use
with CYP3A4/5 inhibitors. Axtinib must be adjusted
with hepatic impairment and discontinued 24 hours
before surgery. Liver function testing, INR, clotting
signs, blood pressure and urinalyses should be con-
ducted to monitor side effects. Trademark chemother-
apy side effects of nausea, vomiting, hypothyroidism,
redness on hands and feet, diarrhea, fatigue and stom-
atitis have been frequently reported.\textsuperscript{9} Close moni-
toring of blood cell counts and patient counseling on
side effects are essential for patients receiving this
drug.

\textbf{ERIVEDGE\textsuperscript{®} (vismodegib)}

Vismodegib, manufactured by Genentech, was ap-
proved Jan. 30, 2012 for the treatment of adults with
metastatic basal cell carcinoma, locally advanced ba-
asal cell carcinoma that has recurred following surgery
or who are not candidates for surgery or radiation.\textsuperscript{10,11}
This is the first FDA-approved drug for advanced
stages of the most common skin cancer.\textsuperscript{10} Vismo-
degib is an oral capsule designed to selectively inhibit
abnormal signaling of the Hedgehog pathway. This
pathway is a molecular driver of basal cell carcinoma
by increasing cell growth and decreasing cell repair.
The capsule is available in 150 mg strength dosed
once daily with or without food. Safety and efficacy in
renal/hepatic impaired patients havenot been estab-
lished, nor has safety in adults over 65 years of age.
The drug has few interactions but does carry a black
box warning for embryo-fetal death and severe birth
defects. Due to its high teratogenicity, monitoring for
pregnancy and using additional anti-contraceptives
are important. Pharmacists should counsel patients to
take a pregnancy test seven days before initiation of
therapy and use extra birth control precautions for
seven months after therapy discontinuation. There
has been greater than 10 percent incidence of side
effects reported including muscle spasms, alopecia,
weight loss, nausea, vomiting, diarrhea, dysgeusia
and fatigue. The drug has a similar side effect profile
to other antineoplastics, but it is important for pharma-
cists to counsel on its teratogenic black box warning.

\textbf{KALYDECO\textsuperscript{®} (ivacaftor)}

Ivacaftor was approved Jan. 31, 2012 for cystic fibro-
sis (CF) patients ages 6 and older with the G551D mutation.\textsuperscript{12,13} Approximately four percent of CF patients have the G551D mutation which causes an increased blockage of salt and fluid flow.\textsuperscript{12} Ivacaftor helps to unlock this block and restore function of the defective protein to improve lung function. The 150 mg tablet is to be taken with a high fat meal every 12 hours. The drug has been associated with serious drug interactions with CYP3A inhibitors and inducers; therefore, dose adjustments with drugs such as St. John’s Wort, rifampin and phenytoin will be necessary. Headache, nasal congestion, oropharyngeal pain and abdominal pain are among this drug’s side effect profile. Monitoring for elevated transaminases before treatment, three months after initiation, then annually thereafter are important considerations for physicians.\textsuperscript{12} Pharmacists should screen patients for drug interactions while using this drug.

**ZIOPTAN\textsuperscript{®} (tafluprost ophthalmic solution)**

Tafluprost’s approval was announced Feb. 13, 2012 by the FDA to be the first preservative-free prostaglandin analog for open-angle glaucoma (OAG) or ocular hypertension.\textsuperscript{14,15} Tafluprost was shown to have powerful intraocular pressure (IOP) lowering effects. In clinical studies of up to two years in length, tafluprost, dosed once-daily in the night lowered IOP at three and six months by 6-8 mmHg and 5-8 mmHg respectively, from a baseline pressure of 23-26 mmHg (mmHg = millimeters of mercury, a measurement of fluid pressure in the eye).\textsuperscript{15} The prostaglandin analog is thought to increase uveoscleral outflow. The product is available in 0.0015 percent solution single-use packs to be instilled into the conjunctival sac once daily in the evening. Dosing should not occur more than once daily as the IOP effects could be lessened over time. Changes in length, thickness and number of lashes were observed in clinical trials in addition to pigmentation changes of the iris.\textsuperscript{14} Patients with active macular edema should not use this product.

**SURFAXIN\textsuperscript{®} (lucinactant)**

Lucinactant is a liquid medication approved by the FDA on March 6, 2012 for the prevention of Respiratory Distress Syndrome (RDS) within 24 hours of infant birth.\textsuperscript{16} Premature infants’ lungs do not contain enough surfactant. Without surfactant, infants have difficulty breathing and can experience low oxygen saturation. The drug works to supply surfactant and reduce pulmonary surface tension during respiration.

<table>
<thead>
<tr>
<th>Trade Name\textsuperscript{®}</th>
<th>Generic Name</th>
<th>Manufacturer</th>
<th>Drug Class</th>
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<tbody>
<tr>
<td>Voraxaze</td>
<td>glucarpidase</td>
<td>BTG International, Inc</td>
<td>Hematologic Antidote</td>
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<td>Picato</td>
<td>ingenol mebutate</td>
<td>LEO, Inc</td>
<td>Dermatologics</td>
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<td>Inlyta</td>
<td>axtinib</td>
<td>Pfizer, Inc</td>
<td>Antineoplastics</td>
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<td>Erivedge</td>
<td>vismodegib</td>
<td>Genentech, Inc</td>
<td>Antineoplastics</td>
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<td>Kalydeco</td>
<td>ivacaftor</td>
<td>Vertex Pharmaceuticals, Inc</td>
<td>Pulmonary</td>
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<td>Zioptan</td>
<td>tafluprost</td>
<td>Merck, Inc</td>
<td>Antiglaucoma, Prostaglandin Agonist</td>
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<tr>
<td>Surfaxin</td>
<td>lucinactant</td>
<td>Discovery Laboratories</td>
<td>Lung Surfactant</td>
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<td>AMYViD</td>
<td>florbetapir F 18</td>
<td>Eli Lilly, Inc</td>
<td>Diagnostic Imaging Agent</td>
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<td>Omontys</td>
<td>peginestanide</td>
<td>Affymax</td>
<td>Hematopoietic Growth Factor</td>
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<td>Stendra</td>
<td>avanafil</td>
<td>Vivus, Inc</td>
<td>Phosphodiesterase-5 Enzyme Inhibitors</td>
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<td>Elelyso</td>
<td>taliglucerase alfa</td>
<td>Protalix/Pfizer, Inc</td>
<td>Enzyme Replacement Therapy</td>
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</table>
Lucinactant is provided as an 8.5 mL suspension that is to be administered intratracheally. The suggested dosing is 5.8 mL/ kg birth weight into four aliquoted doses, with up to four doses in 48 hours, but not to exceed more than one dose in six hours. The doses will need to be warmed for 15 minutes on a warming block at 44°C and shaken vigorously before given as a free-flowing suspension: the suspension should appear opaque white to clear. The drug is contraindicated in adults and its side effects include endotracheal tube reflux or airway obstruction.

**AMYVID® (Florbetapir F 18 Injection)**

The FDA approved Amyvid on April 10, 2012 for Positron Emission Tomography (PET) viewing of the brain in patients suspected of Alzheimer’s Disease (AD). The florbetapir F 18 isotope binds to the beta-amyloid plaque and can be detected by the PET scanner. Inject 370 MBq (10 mCi) as a single IV bolus injection in a total volume of 10 mL or less and perform the PET starting 30-50 minutes after injection. A positive scan is indicated when there is little white to gray contrast in the cerebral cortex or higher gray content in one or more areas. Positive scans are not a gold standard for diagnosis of AD but can be used to aid diagnosis and treatment approaches. There are minimal side effects of florbetapir F 18 except for headaches, reported in one to 10 percent of patients. PET scans with florbetapir F 18 will be able to show evidence of cognitive decline in patients over time.

**OMONTYS® (peginesatide)**

Peginesatide was approved by the FDA on March 27, 2012 to treat anemia in adult dialysis patients who have chronic kidney disease (CKD). This erythropoiesis-stimulating agent (ESA) is used to promote red blood cell production to increase hemoglobin and reticulocyte counts. Peginesatide is available in various strengths within single-use vials, pre-filled syringes and multiple-dose vials. Therapy should be initiated at hemoglobin levels less than 10 g/dL at the initial treatment dose of 0.04-0.08mg/kg subcutaneously once monthly. There are dose conversions for patients previously receiving Aranesp and Epogen. Peginesatide offers the advantage of once monthly dosing as opposed to other agents that have weekly dosing. If hemoglobin rises rapidly (>1 g/dL in the two weeks or >2 g/dL in four weeks), reduce peginesatide dose by 25 percent. Peginesatide has a black box warning for increased risk of stroke and cardiovascular risk and should not be given when hemoglobin levels are greater than 11 g/dL. Diarrhea, dyspnea, nausea, cough, injection site reaction, headache, muscle spasms and changes in blood pressure have been observed. In addition to checking blood pressure, hemoglobin levels should be monitored every two weeks and therapy should be discontinued if there is no response.

**STENDRA® (avanafil)**

Avanafil was approved for erectile dysfunction on April 27, 2012, expanding available treatment options for the 30 million men in the United States that suffer from this condition. The drug is a phosphodiesterase type 5 inhibitor that enhances the effects of nitrous oxide. Avanafil is available in 50 mg, 100 mg, and 200 mg tablets to be taken 30 minutes before intercourse. Therapy may be initiated with the 100 mg tablet and titrated to 200 mg or decreased to 50 mg depending on tolerability. Avanafil safety and efficacy in severe hepatic or renal impairment has not been established. Do not exceed 50 mg/ 24 hours if using alpha blockers; organic nitrates or CYP3A4 inhibitor concomitant use is contraindicated. The drug has minimal side effects, including headaches, flushing and nasal congestion, but hypertensive patients should be counseled on risks.

**ELELYSO® (taliglucerase alfa)**

Taliglucerase alfa was approved May 1, 2012 by the FDA as an orphan drug for the rare Gaucher’s disease. Gaucher’s disease is found in approximately 6,000 Americans who have the genetic defect for the glucocerebrosidase enzyme used to breakdown harmful substances in the liver, spleen, bones and bone marrow. Patients would most likely resort to a bone marrow transplant in severe cases, but this enzyme replacement drug offers a less invasive treatment approach. Taliglucerase alfa catalyzes the hydrolysis of glucocerebroside to glucose and ceramide which results in reduced spleen and liver enlargement and increased RBCs and platelets. The drug is dosed as 60 units/kg IV every two weeks infused over one to two hours. There are no dose conversions that
need to be made when switching from Cerezyme (imiglucerase), another medication currently available for the rare disease. Healthcare professionals should observe for allergic type reactions upon intravenous administration.

CONCLUSION

The FDA has remained true to its promise to expedite drug approvals as evident by 11 drugs already approved in the first four months of 2012. With 35 approvals in 2011, the pipeline looks promising for 2012. The 2012 approvals are on the market and available to consumers ahead of their deadlines, allowing patients to have the best available options for treatment sooner.

Drugs have been developed for rare and incurable diseases such as Gaucher’s Disease (Elelyso) and cystic fibrosis (Kalydeco) giving hope to patients who otherwise had fewer therapeutic options. With cancer rates soaring, manufacturers are pushing oncologic and hematologic drugs to increase survival rates for cancer patients refractory to first-line treatments. Drugs have been currently approved as second-line therapies for renal cell carcinoma (Inlyta) and basal cell carcinoma (Erivedge) but could have indications expanded to first-line therapies as more trial data are available. Manufacturers are pushing to produce drugs specific to patients with renal impairment to increase survival rates in CKD patients with multiple disease states.

Manufacturers have shifted focus from marketing chronic maintenance drugs to rarer, more plaguing conditions. While these drugs may have more convenient dosing and offer promise to minority diseases, they come with a hefty price tag. Drug manufacturers are working with insurance agencies and local governments to promote coverage of these newly approved drugs. The FDA pushing for faster drug approvals in addition to drug marketing possible at earlier dates will give consumers more choices and prevent clogs within the drug pipeline.

REFERENCES

14. FDA Approves Zioptan (tafluprost ophthalmic solution),
1. In order for the FDA to approve a drug _______.
   A. Safety and efficacy must be proved
   B. The drug must be cost effective
   C. The benefits of the drug must outweigh the risks
   D. A and C

2. Patients taking Picato® most likely have which of the following conditions?
   A. Acitinic keratosis
   B. Hyperuremia
   C. Steven Johnson’s Syndrome
   D. Cystic Fibrosis

3. Which of the following drugs is indicated for advanced renal cell carcinoma?
   A. Elelyso®
   B. Inlyta®
   C. Stendra®
   D. Amyvid®

4. Which of the following drugs should be administered with a high fat meal and requires close monitoring of liver transaminases?
   A. Picato®
   B. Erivedge®
   C. Elelyso®
   D. Kalydeco®

5. AMYViD® binds to _____________ in PET scans to show evidence of cognitive decline.
   A. α- amyloid
   B. GABA receptors
   C. β-amyloid
   D. cerebral axons

6. When is Omontys® contraindicated?
   A. History of breast cancer
   B. Chronic kidney disease
   C. Hg> 11g/dL
   D. Folic acid deficient anemia

7. Voraxaze® is used to decrease levels of _______ to prevent organ damage and bone marrow suppression.
   A. Cyclophosphamide
   B. Etoposide
   C. Leucovorin
   D. Methotrexate

8. Elelyso® is used to treat which rare condition?
   A. Gaucher’s Disease
   B. Turner’s syndrome
   C. Addison’s Disease
   D. Cushing’s Syndrome