TRENDS-in-MEDICINE

January 23, 2011

by Lynne Peterson

Quick Takes

…Highlights from this week's news affecting drugs and devices in development…

SHORT TAKES

- **ALEXZA PHARMACEUTICALS' Adusuve Staccato (loxapine, AZ-004)** – The company plans to refile an NDA for this inhaled treatment for agitation caused by bipolar disorder and schizophrenia with the FDA in July 2011. The FDA rejected it last year due to safety and manufacturing concerns.
- **BAYER's Gadovist (gadobutrol)** – The FDA's Peripheral and Central Nervous System Drugs Advisory Committee unanimously recommended approval of this gadolinium-based contrast agent for contrast-enhanced MRI of the central nervous system.
- **BOSTON SCIENTIFIC** is buying privately held **Atritech**, developer of the Watchman, a device to occlude the left atrial appendage in patients with atrial fibrillation at risk for ischemic stroke.
- **FRESENIUS MEDICAL CARE's CombiSet True Flow Series Hemodialysis Blood Tubing Set** – Several lots were recalled because they may develop kinking of the arterial line, which can cause the destruction of red blood cells, leading to serious injury and/or death. The company first sent a notice to customers in November 2010, instructing them to immediately discontinue use and replace the affected items. Now, the FDA has upgraded the notice to a Class I recall, the most serious form of recall, involving situations where there is a reasonable probability that use of a product will cause serious adverse health consequences or death.
- **Implantable cardioverter defibrillators (ICDs)** – The U.S. Department of Justice has begun a civil investigation of ICD implants, and the Heart Rhythm Society (HRS) will assist in an advisory role, providing expertise on electrophysiology and on proper guidelines for clinical decision making. HRS is reviewing only information that does not include identifiable patient or facility-level data. *This could lead to at least a temporary slowdown in ICD implants.*
- **NOVARTIS's Gilenya (fingolimod)** – The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) gave a thumbs up to this oral drug for patients with highly active relapsing-remitting multiple sclerosis (MS) despite treatment with beta interferon or in patients with rapidly evolving, severe relapsing-remitting MS.
- **ONCOLYTICS BIOTECH's Reolysin** – The National Cancer Institute (NCI) will sponsor a Phase II trial of this treatment for metastatic pancreatic cancer testing paclitaxel/carboplatin ± Reolysin.

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- **OSIRIS THERAPEUTICS' Prochymal (remestemcel-L) –** Canadian regulators requested additional information before approving this stem cell therapy for graft vs. host disease, which is a side effect of organ or bone marrow transplants. Health Canada said the application is "not in full compliance of current regulations."

- **PFIZER** is collaborating with **Theraclone Sciences** on antibody drugs for two cancer targets and two infectious disease goals. Pfizer is responsible for preclinical and clinical development. In July 2010, ***Quick Takes*** reported that Theraclone and University of Wisconsin researchers had identified rare antibodies effective against flu viruses, but this deal does not appear related to that.

- **ROCHE/PLEXXIKON's PLX-4032 (RG-7204) –** In the Phase III BRIM3 trial, PLX-4032 met its coprimary endpoints, significantly extending overall survival and progression-free survival in patients with the genetic mutation BRAF V600 who had previously untreated malignant melanoma that had metastasized.

- **TARGACEPT's TC-5619 –** A Phase II study showed improved cognition with TC-5619 vs. placebo in schizophrenics with stable psychotic symptoms who were taking other anti-psychotic medications. The primary endpoint was met – an improvement in the Groton Maze Learning Task of the CogState Schizophrenia Battery. The drug also showed "positive signals" on several secondary endpoints and was well tolerated.

- **VERTEX PHARMACEUTICALS' telaprevir**, a treatment for hepatitis C, was granted priority review by both the FDA and Health Canada. The FDA PDUFA date is May 23, 2011.

- **ZIOPHARM ONCOLOGY's Zinapar (darinaparsin) –** An EMA committee recommended orphan drug status for this IV drug for peripheral T-cell lymphoma, which already has FDA designation as an orphan drug. Ziopharm aims to start clinical trials by the end of 2011.

NEWS IN BRIEF

ARIAD PHARMACEUTICALS/MERCK's ridaforolimus – positive Phase III results

The 711-patient SUCCEED trial met the primary endpoint in patients with metastatic soft tissue and bone sarcomas who had previously responded to chemotherapy, showing a statistically significant 28% improvement in progression-free survival (PFS) vs. placebo. Median PFS was 17.7 weeks vs. 14.6 weeks with placebo. The most common side effects were stomatitis, fatigue, diarrhea, and thrombocytopenia. Oral ridaforolimus is being developed under a Special Protocol Agreement with the FDA, and Ariad plans to submit it to the FDA later this year.

ASCO Gastrointestinal Cancers Symposium

- **Bayer's Nexavar (sorafenib) – effective when Gleevec and Sutent fail in GIST.** The final results of a Phase II trial found that Nexavar has activity in GIST that is resistant to both Novartis's Gleevec (imatinib) and Pfizer's Sutent (sunitinib). The most common Grade 3 toxicities were hand-foot syndrome (45%) and hypertension (21%).

Nexavar Phase II Results in Treatment-Resistant GIST

Measurement	Gleevec resistant	Gleevec/Sutent resistant	All
PR	17%	13%	13%
Stable disease	50%	56%	55%
Disease control	67%	69%	68%
Median PFS	3.4 months	5.2 months	5.2 months
Overall survival	13.6 months	10.5 months	11.6 months
Dose reductions	83%	56%	61%

- **Dose-painted IMRT – reduces dermatologic and GI toxicity.** A researcher said the two-year outcomes of the 63-patient Phase II RTOG-0529 study of dose-painted IMRT (intensity-modulated radiation therapy) in combination with 5FU/mitomycin-C in anal carcinoma will be the new platform in the future in RTOG anal cancer trials that incorporate novel agents and may allow further dose escalation in advanced stage disease even though the primary endpoint was not met (reducing Grade 2+ toxicity by ≥15% vs. conventional radiotherapy + 5FU/mitomycin-C).

- **Agendia's ColoPrint – a prognostic genomic profile for Stage 2 CRC.** German researchers reported on the second validation study of this test, claiming that this is the first prognostic genomic test to be submitted to a second independent validation. The 18-gene test, which was developed to determine low- vs. high-risk patients. In Stage 2, 74% of colorectal cancer patients were identified by ColoPrint as low-risk patients.

  The five-year distant metastasis-free survival was 95% for low-risk patients and 79.9% for high-risk patients. It was the only significant parameter to predict the development of distant mets. The researchers concluded that ColoPrint is able to predict development of distant mets and facilitate the identification of patients who might not need additional chemotherapy.

  A third validation study is getting underway in collaboration with MD Anderson Cancer Center.

How does ColoPrint compare to Genomic Health's Oncotype DX? A researcher said, "The intention of both tests is the same…to identify high-/low-risk patients. But the tests are completely different. The ColoPrint signature was purely data driven and not biologically driven…I think Onco*type* DX was developed with a candidate-gene approach…And ColoPrint is a binary test, so we have low or high results, and with Onco*type* DX, there is a distinction of low, intermediate, and high risk, and not all distinctions are really significant… ColoPrint is a fresh tissue [test], and Onco*type* DX is archival, from frozen tissue…which makes a logistical difference."

ColoPrint is not yet commercially available.

DELTEX PHARMACEUTICALS – shut down by FDA

At the request of the FDA, the U.S. District Court for the Southern District of Texas issued a permanent injunction against this company, which manufactured and distributed both prescription and over-the-counter drugs. The FDA said Deltex sold unapproved prescription drugs, failed to comply with FDA regulations on OTC products, and did not have good manufacturing practices. Despite multiple notifications by the Agency, Deltex continued to manufacture and distribute unapproved, adulterated, and misbranded drugs. Deltex also must recall and destroy all products manufactured and distributed since October 31, 2008.

EPO for kidney transplant patients – not enough info on benefits

A CMS Medicare Evidence Development and Coverage Advisory Committee (MedCAC) advisory panel overwhelmingly agreed that there are not enough data – and existing data are poor – to show that erythropoiesis stimulating agents (ESAs) improve outcomes for kidney transplant patients.

The panel could not dismiss a technical assessment done by the University of Connecticut/Hartford Hospital EPC for CMS which showed low or insufficient confidence in the existing ESA data. The panel agreed (with an average vote of 1.33 out of a possible 5) that there is ***inadequate evidence*** to determine if ESA use for anemia/blood loss management improves renal transplant graft survival.

CMS is expected to make a preliminary decision on how to cover ESAs for kidney disease patients by March 16, 2011, with a final decision due by June 16, 2011.

JOHNSON & JOHNSON

- **Recalls continue** – J&J most recently pulled 3.9 million packages of antacid Rolaids as well as 42.9 million bottles of Sudafed, Tylenol, Benadryl, and Sinutab products. The new recalls, which come after a company record review, only affect wholesalers, not individual consumers.
- **McNeil plant** – The company blames the massive recalls at its McNeil manufacturing plant in Fort Washington PA on lax cleaning procedures and poor documentation. The company also found one product with an incorrect label.
- **Ortho-McNeil-Janssen Pharmaceuticals**, a J&J subsidiary, and Sanford-Burnham Medical Research Institute are collaborating to search for new drugs to treat Alzheimer's disease and psychiatric disorders.

LILLY's Amyvid (florbetapir) – gets FDA panel backing

The FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted 16-0 that this injectable positron emission tomography (PET) imaging agent designed to screen for Alzheimer's disease should be approved, provided the company (1) develops a training program to ensure that physicians can consistently interpret the images and (2) conducts another clinical trial showing that the training helps physicians accurately and consistently interpret the scans. Without the training and the new trial, the panel voted 13-3 against approval.

Panel members agreed Amyvid improves the visibility of the plaque in the brain, but they were concerned that doctors had widely different interpretations of the scans and worried that it would lead to misdiagnoses. Lilly obtained Amyvid with its acquisition of Avid Radiopharmaceuticals.

MANNKIND's Afrezza (inhaled insulin) – rejected by FDA

The FDA declined to approve this product, asking for more information on its redesign. The pivotal clinical data were obtained with an older device, MedTone, not the next-generation device, Afrezza, for which MannKind sought approval, and the FDA did not believe the *in vitro* and pharmacology bridging data were sufficient.

The FDA is asking for more information on the performance characteristics, usage, handling, shipment, and storage of Afrezza as well as updated information on safety, proposed user training, and changes to the proposed labeling. The FDA also wants two more trials: one in Type 1 diabetics and another in Type 2 diabetics. At least one of these trials must include an arm using the MedTone inhaler to compare it head-to-head

with Afrezza, and both trials must show 12 weeks of stable dosing after titration. However, the ongoing AFFINITY-1 and AFFINITY-2 trials may be sufficient.

MEDTRONIC's CoreValve – changes in pivotal trial

The FDA gave Medtronic permission to change the comparator in the pivotal trial. Originally, in inoperable patients CoreValve was to be compared to medical management, and now it will be compared only to patients in contemporary TAVI studies (probably Edwards PARTNER Cohort B data). Furthermore, the FDA is allowing some patients to be implanted using the subclavian approach, not just the transfemoral approach. The FDA decisions do not affect the high-risk surgical patient arm, which is ongoing, randomizing CoreValve vs. surgical valves.

RESVERLOGIX's RVX-208 – disappointing results

This oral agent to raise HDL missed the primary endpoint in the 299-patient ASSERT trial, increasing apoA-1 but not significantly. The 12-week results, published in the ***Journal of the American College of Cardiology***, showed that RVX-208 dose-dependently increased apoA-1, but none of the tests was statistically significant. The increases in HDL and apoA-1 at the highest dose were only modest and were associated with an "unacceptable" 10% rate of transaminase elevation. The additional problem for this drug is that it still has not been proven that raising HDL is beneficial.

SANOFI-AVENTIS

- **Fluzone –** The FDA and the Centers for Disease Control and Prevention (CDC) are working together to investigate a possible correlation between this flu vaccine and febrile seizures, primarily in children ages 6 months to 2 years. As of December 13, 2010, the FDA had received reports of 42 cases of the adverse reaction, with 38 occurring within one day of receiving the vaccine. All the children recovered, with no lasting effects.
- **Multaq (dronedarone) –** The company expects the EMA to follow the FDA and warn doctors and patients about the risk of liver damage with this cardiac drug.

REGULATORY NEWS

FDA – record number of device complaints in 2010

In 2010, the FDA's Center for Devices and Radiological Health received:

- 171 complaints, a record number and an increase of 29% from 2009. Many of these focused on the Office of Device Evaluation, with the compliance office a distant second.
- 414 contacts (defined as complaints, disputes, and inquiries), a 45% increase. Of these, 65% came from the medical device industry, with the other 35% from consumers, healthcare providers, etc. But contacts involving the 510(k) process were down.
- 26 disputes, down from 53 in 2009.

U.K.'s NICE – finally approves 3 drugs for early Alzheimer's

The U.K.'s National Institute for Health and Clinical Excellence (NICE) gave its stamp of approval to the use of Pfizer/Eisai's Aricept (donepezil hydrochloride), Shire's Reminyl (galantamine), and Novartis's Exelon (rivastigmine) for patients with mild or moderate Alzheimer's disease.

USP – urges overhaul of prescription labels

The U.S. Pharmacopeial Convention (USP) said prescription drug labels are not clear enough or easy enough to read, recommending:

- Simple language be used to convey explicit instructions as well as the medication's purpose.
- Using larger typefaces and running text only horizontally.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	January 2011	
January 25	Consideration of reclassification of **automated external defibrillators** from PMA to 510(k) products	FDA's Circulatory System Devices Advisory Committee
January 26	**Abbott's RX Acculink** carotid stent system	FDA's Circulatory System Devices Advisory Committee
January 27-28	Discussion of **possible reclassification of electroconvulsive therapy devices**	FDA's Neurological Devices Advisory Committee
January 31	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
	February 2011	
February 8	Review of **postmarketing studies for cancer drugs** receiving accelerated approval prior to January 1, 2009	FDA's Oncologic Drugs Advisory Committee (ODAC)
February 9	Public workshop on expanding ***in vivo* biomarker detection devices**, focusing on research opportunities and technical challenges	FDA and the Defense Advanced Research Projects Agency (DARPA)
	Other future 2011 meetings	
March 2	Discussion of **innovative approaches to the development of drugs for orphan and rare disease**, including how to utilize biomarkers and pharmacogenetics	FDA Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee meeting ***in Dallas, Texas***
March 5 (approx.)	**Merck KGaA's cladribine** for multiple sclerosis	PDUFA date
March 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 8	**Novartis's Arcapta Neohaler** (indacaterol maleate), a QD bronchodilator for long-term use in COPD	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 10	Risk of **neurodegeneration in pediatric patients** from anesthetic drugs	FDA's Anesthetic and Life Support Drugs Advisory Committee
March 10	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	PDUFA date
March 16	Preliminary decision due on **how to cover ESAs** for kidney disease patients	CMS decision
March 26	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date
April 7	**AstraZeneca's Zactima** (vandetanib) for inoperable medullary thyroid cancer	PDUFA date
April 7-8	**510(k) reform**	FDA public meeting
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency Forum
April 13	**KV Pharmaceutical/Hologic's Gestiva** (17-alpha hydroxyprogesterone) to prevent premature birth	PDUFA date
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
June	**King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	Approximate PDUFA date
June 16	Final decision expected on **coverage of ESAs** for kidney disease patients	CMS decision
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date