Trends-in-Medicine

Quick Takes

by Maude Campbell

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Check out the new *Trends-in-Medicine* blog on our website (www.trends-in-medicine.com). The latest entry is about patients who are litigious, and some who are not.

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

SHORT TAKES

- **ASTRAZENECA/POZEN's Vimovo (naproxen + esomeprazole magnesium) –** The FDA approved this combination pain reliever and proton pump inhibitor (PPI) for use in arthritis patients at risk of developing gastric ulcers.
- **C. R. BARD** is buying SenoRx for $213 million and will make it part of its peripheral vascular unit. SenoRx's products include the EnCor breast biopsy system, Gel Mark breast tissue markers, and the Contura balloon catheter.
- **ENDO PHARMACEUTICALS** is expanding into the technology arena with the acquisition of HealthTronics, a manufacturer of urology technology equipment.
- **KING PHARMACEUTICALS' Acurox (oxycodone immediate-release + niacin) –** After failing to convince an FDA advisory committee that adding niacin to oxycodone was either appropriate or made the opioid less abusable, King announced that it would resubmit Acurox ***without*** niacin.
- **LILLY/AMYLIN/ALKERMES' Bydureon (long-acting exenatide) –** The new FDA decision (PDUFA) date is October 22, 2010. The companies responded in March 2010 to an FDA request for more information on manufacturing and on the proposed Risk Evaluation and Mitigation Strategy (REMS).
- **MERRION PHARMACEUTICALS** is developing Orazol, an oral zoledronic acid tablet (which would compete with Novartis's intravenous bisphosphonate Zometa), using its proprietary GIPET technology.
- **OSIRIS's Prochymal (mesenchymal stem cells) –** The FDA has granted orphan-drug status to this stem cell treatment for Type 1 diabetes. The FDA previously granted orphan-drug status for Prochymal in the treatment of graft vs. host disease.
- **SEPRACOR/DAINIPPON SUMITOMO's Stedesa (eslicarbazepine),** a once-daily antiseizure medication, was rejected by the FDA for use in epilepsy. The company said it will meet with the FDA to better understand the Complete Response letter

and to determine whether additional clinical studies are needed.

- **SHIRE PHARMACEUTICALS' Lialda (mesalamine) and Pentasa (mesalamine) –** The FDA sent a warning letter to Shire ordering it to stop the use of promotional materials that reportedly exaggerate the effectiveness of these drugs for ulcerative colitis. Shire responded that it will comply with both the letter and spirit of the law and will respond to the Agency by May 11, 2010.
- **VASCULAR SOLUTIONS** will pay $5.75 million to acquire the Smartneedle and pdAccess Doppler-guided needle access products from Escalon Vascular Access. Vascular Solutions will also acquire Escalon's VascuView TAP visual ultrasound system.

NEWS IN BRIEF

ALLERGAN's Latisse (topical bimatoprost) – prescribing questions

Latisse, a topical form of the glaucoma drug Lumigan, is used to grow longer, fuller eyelashes. Allergan renamed bimatoprost and repackaged it to avoid impacting its glaucoma franchise. The ***New York Times*** reported that consumers are getting Latisse online with "few questions asked." The concern is that consumers are not getting warned about the possible side effects – discoloration of the eyelid or change in iris color. Internet prescribing is against Allergan's policy, and the company said it will cut off supplies to doctors who provide it over the internet.

BOSTON SCIENTIFIC – ICD reimbursement practices under investigation

The Department of Justice (DOJ) is investigating reimbursement for Boston Scientific's implantable cardioverter defibrillators (ICDs). St. Jude earlier revealed that the Justice Department had requested documents in a similar investigation.

When DOJ requests documents from multiple companies in one field, it can be investigating both companies, or it can be targeting just one company but looking for comparison data from the others. The order in which the requests are made does not indicate who the target or targets are, so in this case it could be all the heart rhythm companies, or just one of them. And if it is just one, it could be any one of the three major companies (Boston Scientific, St. Jude, or even Medtronic). However, Boston Scientific's heart rhythm business also is being investigated by the U.S. Attorney's Office for the District of Massachusetts (which is known for its Medicare fraud investigations).

BRISTOL-MYERS SQUIBB's belatacept – FDA wants more data

The FDA wants more long-term data before approving belatacept. The Agency asked for 36-month data from the Phase III trials "to further evaluate the long-term effect" of the drug in patients who have received kidney transplants. And the FDA wants a REMS. However, the FDA did not request new clinical studies.

CVRx's Rheos – hypertension trial likely to fail

The Data Safety Monitoring Board (DSMB) told the company that a review of the data to date indicate the trial is unlikely to meet its primary efficacy endpoint. CVRx then told the FDA, and the Agency did its own analysis and came to the same conclusion. The trial is fully enrolled, with the device implanted in 332 patients, so the company said it will continue the trial, though the company is in discussions with the FDA about the next steps. The Rheos device involves a generator implanted in the chest, with leads running to the baroreceptors on both sides of the neck by the carotid bulb. When the baroreceptors are stimulated, that sends a message to the brain to lower blood pressure.

ELLEX MEDICAL LASERS' 2RT – showed efficacy in AMD and diabetic retinopathy trials

Initial 6-month results of a trial using the Ellex 2RT to treat early age-related macular degeneration (AMD) in 14 patients showed that drusen decreased in 70% of treated eyes vs. 56% of untreated eyes and that central visual function improved in 50% of treated eyes vs. 36% of untreated eyes. There was no evidence of laser damage on retinal imaging. Completed 6-month results using the laser in 48 patients with diabetic macular edema showed that it produced similar reductions in macular edema compared with conventional retinal photocoagulation treatment but used 500 times less laser energy. Results of both trials were presented at the Association for Research in Vision and Ophthalmology (ARVO) 2010 annual meeting.

GENENTECH's Avastin (bevacizumab) – U.K. may cover for AMD

In an unusual move, the U.K.'s National Health Service (NHS) is considering recommending Avastin, approved for colon cancer, as a treatment for wet AMD, even though it is unlikely that clinical trials of the drug for AMD will be performed. Currently, Genentech's Lucentis (ranibizumab) is the preferred AMD treatment in the U.K., but treatment is expensive, at £10,000 per patient. The ***Telegraph*** reported that the Department of Health has asked the National Institute for Health and Clinical Excellence (NICE) to advise NHS on whether it can recommend Avastin for use in AMD and expects a report this summer. Genentech has not applied to have Avastin licensed for wet AMD.

GLAXOSMITHKLINE's SRT-501 – red wine drug trial halted for safety

Enrollment of patients in a trial of SRT-501 in multiple myeloma has been halted because of cases of kidney damage appearing in patients receiving the resveratrol formulation. This may be a setback for other research using the red wine derivative to treat a variety of diseases, including diabetes and cancer. In the clinical trial SRT-501 was used alone and in combination with Takeda's Velcade (bortezomib). Researchers reported that 5 of 24 multiple myeloma patients taking SRT-501 developed cast nephropathy, which can be caused by multiple myeloma and can lead to kidney failure. However, two previous trials of SRT-501 in diabetes did not have any cases of cast nephropathy.

INTERMUNE's Esbriet (pirfenidone) – FDA wants more clinical data

The FDA denied approval of Esbriet, which would have been the first treatment for idiopathic pulmonary fibrosis (IPF), a fatal lung disease. The Agency requested additional clinical data to show efficacy. One clinical trial using Esbriet showed efficacy, but a second clinical trial did not, and the FDA questioned whether the benefit from the treatment was meaningful since treatment cannot repair damage already done to the lungs. An FDA advisory committee had voted that pirfenidone was safe and should be approved, but it was split on the question of efficacy. InterMune said it will meet with the FDA to discuss the additional data needed.

JOHNSON & JOHNSON – now Congress investigating the pediatric drug recalls

The recall of J&J's pediatric Tylenol and other over-the-counter medications due to contamination has drawn the attention of the House Committee on Oversight and Government Reform, which plans to investigate not only J&J but also the FDA's inspection procedures. J&J claims the recall was prompted by an internal investigation initiated because of customer complaints, but the FDA indicated that it was due to problems discovered during one of its routine inspections. *The question is how this recall and investigation will affect prescription medications that J&J has in development.*

MERCK/ARIAD's ridaforolimus – restructuring their deal

The companies are restructuring their agreement to develop ridaforolimus as a potential treatment for metastatic soft-tissue and bone sarcoma. Ridaforolimus is also being investigated as a potential treatment for prostate and endometrial cancer.

MS drug development funding

Merck KGaA and Fast Forward, a not-for-profit organization established by the National Multiple Sclerosis Society, have awarded nearly $1.5 million for MS research, and the projects chosen are very interesting:

- **INNATE THERAPEUTICS' MIS-416 –** for a Phase IIa clinical trial of this naturally occurring agent derived from bacteria.
- **COGNOSCI's COG-112 –** to test the efficacy in laboratory models in repairing myelin in the CNS of this molecule that mimics actions of the cholesterol transporting protein.
- **CENTRION THERAPEUTICS –** for safety and efficacy studies in laboratory models of MS of its proprietary neuroprotective compounds related to lamotrigine (which some studies have suggested can protect nerve cells from damage).
- **Oregon Health & Science University –** for the screening and efficacy of small molecule inhibitors of hyaluronidase, an enzyme that dissolves hyaluronic acid – a complex sugar molecule that accumulates in MS lesions. By-products resulting from breakdown of hyaluronic acid have been shown to prevent myelin repair. This project will assess whether myelin repair blockage can be overcome by inhibiting the activity of hyaluronidase.

NOVARTIS's Exelon Patch (rivastigmine transdermal system) – Health Canada issues misuse warning

Health Canada is warning consumers and health professionals against applying more than one Exelon Patch at a time in order to prevent possible side effects. There have been 129 reported cases of misuse of the patch worldwide, including three reported in Canada. Two deaths have been attributed to misuse. The Exelon Patch is used to treat symptoms of mild-to-moderate Alzheimer's disease dementia. Side effects of cholinesterase inhibitors, including the Exelon Patch, include bradycardia, nausea, hallucinations, vomiting, and high blood pressure.

SIEMENS/OLYMPUS – testing capsule endoscope system

Siemens is collaborating with Olympus in testing a prototype of a magnetically-guided intragastric capsule endoscope that would allow physicians to move the endoscope using a joystick-type device. Traditional capsule endoscopes can only be moved through peristaltic motion of the gastrointestinal tract which limits the areas that can be viewed. The prototype endoscope is 31 mm long and 11 mm in diameter and when used, patients' stomachs will be filled with water to enable the navigation.

SUCAMPO's Amitiza (lubiprostone) – may reduce amount of liquid colonoscopy prep needed

Oral Amitiza, which is approved to treat for constipation and irritable bowel syndrome with constipation (IBS-C), appears to reduce the need for ingesting large quantities of liquid prior

to a colonoscopy by 50% or more, according to results of a study presented during Digestive Disease Week. A small study of 126 patients given liquid GoLytely (Braintree Laboratories, polyethylene glycol + electrolytes) plus either an Amitiza tablet or placebo showed that most patients receiving Amitiza were able to achieve a clear bowel movement by drinking half as much GoLytely as those taking placebo. Some Amitiza patients needed only 8 ounces of the unpalatable liquid instead of the gallon of GoLytely patients typically are instructed to consume before a colonoscopy. Researchers said that preparation quality and the detection of colon polyps was the same among patients taking Amitiza and those only using GoLytely.

VIVUS' Qnexa (phentermine + topiramate) – produces weight loss *and* lowers blood pressure

This combination of a very low dose of an appetite suppressant (phentermine) and an antiseizure drug (topiramate) produced a substantial weight loss of up to 10% at 1 year and significantly reduced systolic blood pressure (SBP), according to a pooled analysis of three trials presented at the American Society of Hypertension 2010 meeting. The trials evaluated three different dosages of Qnexa for 28 or 56 weeks in obese and overweight patients with a body mass index (BMI) of 27-45 and who had at least two weight-related comorbidities, such as hypertension or dyslipidemia.

The 56-week results showed a mean weight loss of 10.4% among the 1,479 patients taking the highest dose, a weight loss of 8.2% in the 488 patients taking a middle dose, and 4.7% for the 234 patients taking the lowest dose. The 1,477 placebo patients lost a mean 1.5% of body weight. Systolic blood pressure decreased by 6.5 mmHg with the highest dose of Qnexa and 6.8 mmHg with the lowest Qnexa dose vs. 3.1 mmHg with placebo. An FDA advisory committee is expected to review the trial results in summer 2010.

FDA NEWS

➢ FDA conducts safety review of GnRH agonists for prostate cancer

The FDA's preliminary safety review of gonadotropin-releasing hormone (GnRH) agonists showed an increased risk of diabetes and cardiovascular disease in men taking the drugs for prostate cancer. Dr. Robert Justice, director of the FDA's Division of Drug Oncology Products in the Center for Drug Evaluation and Research (CDER), said, "While our review of these prostate cancer treatments is ongoing, and there are some limitations to the data, FDA believes it is important to tell patients and healthcare professionals that there may be an increased risk of serious side effects." The FDA has not come to any conclusions about whether GnRH agonists cause an increase in the development of diabetes or heart disease.

The medications in question include Abbott's Lupron Depot (leuprolide acetate for suspension), AstraZeneca's Zoladex (goserelin acetate implant), Bayer's Viadur (leuprolide acetate implant), Endo Pharmaceuticals' Vantas (histrelin acetate implant), Pfizer's Synarel (nafarelin acetate), Sanofi-Aventis's Eligard (leuprolide acetate), and Watson's Trelstar (triptorelin pamoate).

Based on initial safety review findings the FDA advises:

- Healthcare professionals should be aware of potential risks and carefully weigh the benefits and risks of GnRH agonists when determining a treatment for patients with prostate cancer.
- Patients receiving a GnRH agonist should be monitored for the development of diabetes and cardiovascular disease.
- Cardiovascular risk factors such as smoking, hypertension, dyslipidemia, increased blood glucose, and excess weight should be managed according to current clinical practice guidelines.
- Patients should not discontinue treatment with a GnRH agonist unless instructed to do so by a healthcare professional.

➢ FDA expands infusion pump safety initiative

The FDA has received more than 56,000 reports of adverse events associated with infusion pumps including more than 500 deaths, and 87 infusion pump recalls were conducted between 2005 and 2009.

- **BAXTER's Colleague –** On April 30, 2010, the FDA ordered Baxter to recall and destroy all Colleague Volumetric Infusion Pumps in use in the U.S. because the company failed to correct many longstanding, serious problems with the pumps. The FDA also ordered the company to provide refunds or to replace pumps in use at no cost to customers and to assist in finding replacement pumps. The action follows a June 2006 consent decree obtained by the FDA in which Baxter agreed to stop manufacturing and distributing all models of the Colleague pump until manufacturing deficiencies were corrected and the pumps were in compliance. Although Baxter made numerous changes to the infusion pump line, on April 8, 2010, the company submitted a proposed schedule of additional corrections to the FDA indicating the next round of corrections would not begin until May 2012 and would not be completed until 2013. The FDA said, "On that schedule, a device with known safety concerns would remain in use on patients needing specialized care until 2013. FDA found this proposal unacceptable."

The FDA believes there may be as many as 200,000 Colleague pumps currently in use. "Baxter intends to work with FDA to minimize disruption to healthcare facilities using Colleague pumps," the company said. "Baxter anticipates that, among alternatives to be provided to customers, the company will offer to exchange Baxter's Sigma Spectrum infusion pumps for Colleague infusion pumps without charge to customers."

When asked if there are sufficient pumps on the market to handle the replacement of Baxter's Colleague pumps, because Baxter reportedly has only 50,000 of the Sigma pumps to replace the 200,000 Colleague pumps, an FDA official said, "We believe there are sufficient pumps available to meet the demand caused by the withdrawal of Baxter's Colleague pump."

Asked if there are similar issues with other infusion pumps that could affect the ability of industry to supply the market with replacement infusion pumps, the FDA official said, "We believe that there are many problems with infusion pumps, and those problems are not limited to a single device or single manufacturer."

- **CAREFUSION's Alaris SE –** CareFusion is operating under an amended consent decree as of January 2010 with its Alaris SE pumps, Alaris System, and all other infusion pumps manufactured by or for its CareFusion 303 subsidiary. The consent decree does not affect intravenous administration sets and accessories. In January 2010 the FDA gave CareFusion permission to resume manufacturing and marketing of the Alaris SE pumps after those that had been seized by the FDA were reconditioned and an independent inspection of Alaris SE pump facilities certified to the FDA that they were in compliance.

CareFusion also reported it is implementing corrective action for the Alaris System and all its other infusion pumps in use in the U.S. CareFusion said, "We continue to remain subject to the other aspects of the amended consent decree…We cannot currently predict the outcome of this matter, whether additional amounts will be incurred to resolve this matter, if any, or the matter's ultimate impact on our business. We may be obligated to pay more or less than the amount that we reserved in connection with the amended consent decree and our corrective action plan because, among other things, the cost of implementing the corrective action plan may be different than our current expectations." Under the consent decree CareFusion could be required to pay $15,000 per day per violation for failure to comply.

➢ More FDA Safety Investigations

The FDA is investigating several additional safety issues including:

- **ABBOTT's Kaletra (lopinavir + ritonavir) –** reports of liver toxicity in patients given Kaletra for prevention of HIV infection after exposure to the AIDS virus.
- **GLAXOSMITHKLINE's Avodart (dutasteride) and MERCK's Proscar (finasteride) –** cases of male breast cancer in patients taking Avodart and Proscar for treatment of benign prostatic hyperplasia (BPH).
- **MERCK's Propecia (finasteride) –** cases of male breast cancer in patients with male-pattern baldness treated with Propecia.

➢ FDA Town Hall meetings on devices

The FDA announced two Town Hall meetings with Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiologic Health (CDRH) for 2010:

1. Bloomington, Minnesota: May 18, 2010.
2. Los Angeles, California: October 2010.

The meetings will ***not*** be videotaped or webcast. Dr. Shuren will discuss CDRH's FY2010 priorities, and device industry officials can tell him their concerns about medical device oversight.

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