Trends-in-Medicine

Quick Takes

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

SHORT TAKES

- **ABBOTT LABORATORIES** received FDA clearance for its Tecnis multifocal, one-piece intraocular lens for cataract patients with or without presbyopia.
- **BOSTON SCIENTIFIC** will launch its Express LD Iliac Premounted Stent System for iliac artery disease treatment in the U.S. now that it has FDA approval.

NEWS IN BRIEF

ABBOTT – buys FACET BIOTECH

Abbott Laboratories agreed to buy Facet Biotech for $450 million ($27 per share), giving Abbott half the rights to Zenapax (daclizumab), a monoclonal antibody in Phase II trials in multiple sclerosis. Facet had partnered with Biogen Idec on the development of daclizumab and last year turned down Biogen's much lower, unsolicited takeover bid of $17.50 per share. Another Facet monoclonal antibody, volociximab, is also in Phase II development in advanced solid tumors. Facet has two interesting Phase I drugs – elotuzumab for multiple myeloma and PDL-192 for solid tumors – as well as PDL-241 in preclinical development for immunologic diseases. *The question is whether the FDA's refusal to accept Merck's filing for its oral MS therapy, cladribine, made Abbott more anxious to get Zenapax.*

INTERMUNE's Esbriet (pirfenidone) – FDA advisory panel recommends approval

The FDA's Pulmonary-Allergy Drugs Advisory Committee voted 9 to 3 to recommend approval of Esbriet, an oral antifibrotic agent, to treat idiopathic pulmonary fibrosis (IPF). However, the panel voted 7 to 5 that Esbriet provides a "clinically meaningful benefit" to IPF patients, and the FDA generally views that as a mixed, inconclusive vote. The results of Phase III clinical trials, including 779 IPF patients, showed that Esbriet significantly improved lung function after 72 weeks of treatment ($p<0.001$), improved vital capacity by 4.4%, and resulted in numerically fewer deaths vs. placebo. Patients taking Esbriet had higher rates of gastrointestinal side effects, photosensitivity, liver enzyme abnormalities, and rash vs. those taking placebo. *With these kinds of votes, the final FDA decision is likely to be in favor of approval, but it is far from assured.*

JOHNSON & JOHNSON/DUPUY – withdraws its ASR artificial hip

Device failures within a few years after implantation have been reported for more than two years with J&J's metal-on-metal ASR artificial hip, and late last year the company announced that it planned to phase out worldwide sales of the ASR by the end of 2010. On March 6th J&J announced the withdrawal of the implant and warned physicians that the device has a high rate of early failure, particularly in patients with weaker bones or those with small stature. The alert specifies failures when the ASR is used in traditional hip replacements. The ASR is also used in hip resurfacing procedures.

MEDTRONIC/COREVALVE – government probe of cardiologist relationships

In a recent filing with the Securities and Exchange Commission (SEC), Medtronic revealed that federal prosecutors are investigating the company's CoreValve division and its relationship with cardiologists at the Lahey Clinic, a teaching hospital affiliated with Tufts University School of Medicine. Medtronic said it will cooperate with a request to turn documents over to the U.S. Attorney's Office for the District of Massachusetts, one of the most – if not ***the*** most – aggressive Medicare fraud investigation offices in the country.

It appears that the investigation came about as the result of a whistleblower. It is a little unusual for a U.S. Attorney's office to move this quickly on a whistleblower suit, which could suggest that the investigators believe it has strong merit.

The charge apparently is that Medtronic/CoreValve has been extremely aggressive in its negotiations with potential U.S. trial sites for CoreValve's ReValving System percutaneous valve, tying participation to use of its Endeavor drug-eluting stent.

Could the investigation spread to Edwards Lifesciences? In any of these investigations, other firms in the field remain at risk of similar scrutiny. Remember what happened with orthopedic device companies.

Don't expect a quick resolution of this investigation; they tend to take a long time to play out. And no news does not mean good news. However, *it does not seem likely that the investigation will impede the FDA status of either company's percutaneous valves since the investigation does not appear to focus on any data fraud.*

Oral bisphosphonates – FDA continues to investigate long-term bone safety

The FDA is recommending that physicians be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking an oral bisphosphonate. Although news reports and previously published case reports indicate that patients taking oral bisphosphonates may have an increased risk of this type of fracture, "FDA's review of these data did ***not*** show an increase in this risk in women using these medications," the safety announcement said. In related news, study results reported at the recent American Academy of Orthopaedic Surgeons (AAOS) meeting showed that improvements in the femur buckling ratio seen among women taking bisphosphonates for 4-5 years declined among those taking the drugs for more than 5 years. The FDA has been conducting a review of bisphosphonates since 2008 and will continue to gather and evaluate additional data in collaboration with outside experts, including the recently convened American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force.

SANOFI-AVENTIS/BRISTOL-MYERS SQUIBB's Plavix (clopidogrel) – boxed warning on "poor metabolizers"

The FDA has added a boxed warning – often mistakenly referred to as a "black box" – to the antiplatelet drug Plavix. The Agency wants doctors and patients to be aware – and to remember – that Plavix can be less effective in people whose liver cannot metabolize the drug to convert it to its active form. These people, known as "poor metabolizers," have reduced functioning of their CYP2C19 liver enzyme. The result is that these poor metabolizers may not get sufficient protection against MI, unstable angina, stroke, and cardiovascular death.

The only way to know if a patient is a poor metabolizer is to do genetic testing, and there are tests available to assess CYP2C19 genotype and determine a patient's ability to metabolize Plavix. However, the FDA stopped short of recommending that all Plavix patients be tested for Plavix resistance, leaving the decision on when testing is appropriate to physicians but emphasizing the importance of knowing a patient's resistance status. Thus, there was an implied suggestion that at least some patients should be tested.

In May 2009 the FDA put a warning about CYP2C19 metabolism in the Plavix label, but the decision to upgrade the warning to a boxed warning came after Sanofi completed an FDA-requested postmarketing study. In that study, Sanofi examined the effect of Plavix in four groups of patients (10 patients to a group): poor metabolizers, intermediate metabolizers, good metabolizers, and ultra rapid metabolizers.

The incidence of poor metabolizers varies by race. The FDA estimates that, in the U.S., 2% of Caucasians and 14% of Asians are poor metabolizers.

What should be done with poor metabolizers? Mary Ross Southworth, PharmD, a clinical analyst in the FDA's Division of Cardiovascular and Renal Products, Center for Drug Evaluation and Research (CDER), said the FDA is recommending that prescribers "consider alternative dosing of Plavix for these patients or consider using other antiplatelet medications." In short – use a higher dose of Plavix or switch

to ticlopidine (Roche's Ticlid, which is now generic) or Lilly's Effient (prasugrel).

In a briefing with reporters, FDA officials carefully avoided saying patients should be switched to these drugs, noting that higher doses of Plavix are also an alternative. Southworth commented, "Plavix and Effient share some indications, but not all the same indications." Dr. Robert Temple, deputy director for clinical science, CDER, added, "Ticlid is the first member of the class, and it has a fairly high level of hematologic problems, so it has lost considerable popularity." That means Effient is really the only alternative drug.

Which patients should be tested or should all patients be tested? The FDA offered no guidance. Dr. Temple pointed out that there are situations, like percutaneous coronary interventions (PCI), where there may not be time to test patients before prescribing Plavix, but he also didn't recommend that all patients being prescribed Plavix long-term (e.g., a patient getting a drug-eluting stent) should be tested after starting Plavix. He commented, "Unfortunately, this drug is to keep you from having a heart attack or dying, so waiting is not an option. Often, the drug is used acutely in association with an angioplasty, and you really can't wait for the test results in that case…The drug is also approved for people who had an MI some time ago, and you might be able to wait for the test then. That is up to the doctor to figure out."

Rather, FDA officials simply said genetic factors are one thing to consider when prescribing Plavix. The FDA's Southworth said, "That is a decision best left to the prescriber of Plavix and the patient…A patient's CYP2C19 status is one thing to consider…[But] you have to consider the patient as a whole – what the patient is taking, the dose, and some of their risk for ischemic events or bleeding. The point of the [label] information is to share it with prescribers, so they can make a decision based on specific factors."

Part of the FDA's problem is that there are no outcome data saying (1) that boosting the dose in poor metabolizers improves outcomes even if platelet aggregation decreases. Dr. Temple explained, "There is some evidence...that people who are very poor metabolizers [have worse outcomes]…It is not the kind of data you wish you had, but there is some evidence …There is no evidence that if you take a poor metabolizer and double the dose, that they do just as well…We know that double dose gets you closer, but not necessarily where you want to be…and that gives us some optimism, but it is too much to say that."

There are tests of higher dose Plavix ongoing that the FDA hopes will answer this question. Dr. Temple said, "There is considerable interest in increasing the dose…We are hoping to get more information [on that]."

The interesting twist in all of this is that the only FDA-cleared test for CYP2C19 function is Roche's AmpliChip test, but that test is not FDA-approved for making Plavix treatment decisions. The Roche test is FDA-validated for genotyping CYP2C19 genes, specifically the *1, *2, and *3 alleles, but not for guiding therapy. FDA officials admitted that this means doctors will have to use the test off-label. Courtney Harper, PhD, director of the Division of Chemistry and Toxicology Devices in the FDA's Center for Devices and Radiological Health (CDRH) noted that tests are often used off-label, but she said the FDA does not intend to loosen its ban on off-label promotion to let Roche talk to doctors about the test more broadly, "It is up to physicians if they want to use it (the Roche test). If Roche wants to get a claim – [and submitted an application]…maybe we would grant that type of approval."

Some laboratories may offer their own home-grown genetic test, but there is no FDA quality control over those, and prices may vary widely. CDRH's Dr. Harper said that providers should ask whether those tests are "at least 98% accurate in making calls." Southworth added, "The tests are relatively widely available. The larger labs probably do have access to testing, but we don't have information on the quality of tests run at other labs."

The new Plavix label mentions more alleles than the Roche test checks – *4, *5, *6, *7, and *8 – but Southworth says those are very rare. And some local labs may test for those rare alleles.

The FDA estimates that one genetic test will cost about $500, though that will vary by laboratory. The time to get the results also will vary – anywhere from a few hours to a couple of weeks, depending on the laboratory. Dr. Harper urged people ordering a test to check the pricing first.

Is this the first boxed warning advising genetic testing? No, FDA officials said genetic testing is also advised for carbamazepine (Novartis's Tegretol for epilepsy) and abacavir (GlaxoSmithKline's Ziagen for HIV).

Does the new genetic test advice affect the FDA's warning about using Plavix in combination with a proton pump inhibitor? Not yet – but stay tuned. Southworth said, "[These] label changes didn't change the recommendation around using Plavix with PPIs as currently labeled, but we are currently looking at further data on interactions that will be forthcoming and that will hopefully provide more information on that interaction as well."

In the meantime, the FDA also cautioned that patients should not stop taking Plavix unless told to do so by their doctor.

STEM CELL THERAPEUTICS – stroke treatment advances

Stem Cell Therapeutics' sequential growth factor treatment, designed to encourage neuron creation in stroke-damaged areas of the brain, has entered Phase IIb trials after no safety concerns were observed during a Phase IIa trial. The two deaths in the 15-patient Phase IIa trial were not deemed

related to the study treatment. The investigators reported that the majority of patients treated exhibited minimal or no disability at 3 months after stroke occurrence. In the Phase IIb studies, patients undergo three QD injections of beta-human chorionic gonadotropin (β-hCG) followed by three QD injections of erythropoietin during a 9-day period, with treatment beginning between 24 and 48 hours of ischemic stroke.

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