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

- **BIOGEN IDEC/ELAN's Tysabri (natalizumab) –** The FDA issued a warning letter about misleading advertising. The FDA found a promotional webcast misleading, saying it minimized the risks of progressive multifocal leukoencephalopathy (PML), a serious brain infection that occurs (but rarely) with this multiple sclerosis drug. The Agency also said Biogen failed to submit the webcast for review 30 days before using it.
- **EDWARDS LIFESCIENCES** received an FDA warning letter for failing to report complaints of adverse events associated with three of its annuloplasty rings and its Perimount pericardial heart valve device within the required 30 days.
- **GILEAD SCIENCES' Truvada (emtricitabine + tenofovir) –** The FDA sent a warning letter stating that a multi-page, direct-to-consumer print ad was misleading because it suggested the HIV treatment is more effective than it is.
- **LENSTEC's Softec HD –** The FDA approved this intraocular lens for use in cataract patients. Softec HD is already available in Europe, China, and Australia.
- **NOVARTIS's Gilenia (fingolimod, FTY-720) –** The FDA's Peripheral and Central Nervous System Drugs Advisory Committee will review Gilenia 0.5 mg capsules for the treatment of relapsing-remitting multiple sclerosis on June 10, 2010.
- **ORAYA's IRay system**, a low-energy X-ray system for the treatment of wet age-related macular degeneration (ARMD), received a C.E. Mark. The company has not announced a launch date, and European clinical trials are underway.

NEWS IN BRIEF

CELGENE's apremilast – oral psoriasis therapy could be marketed by 2014

Celgene announced that it will begin Phase III trials this year for apremilast in psoriasis and psoriatic arthritis. If approved, the agent could be on the market by 2014, and the company expects it could reach between $2 and $3 billion in sales annually. A key advantage of apremilast would be oral administration since currently available biologic agents for these disorders require subcutaneous injections or infusion. In Phase II

clinical trials, apremilast was effective and was associated with fewer side effects than Amgen's Enbrel (etanercept).

COVIDIEN/COMBINATORX's Exalgo (extended-release hydromorphone) – FDA approves with interim REMS

The FDA approved Exalgo for the treatment of moderate-to-severe pain relief in opioid tolerant patients requiring continuous treatment but imposed an interim Risk Evaluation and Mitigation Strategy (REMS) until the class-wide opioid REMS is finalized. The REMS requires the company to distribute a patient medication guide, send a letter to health-care providers most likely to prescribe the drug, and provide prescriber training addressing appropriate patient selection, dosing, and misuse information.

FATE THERAPEUTICS – boosting stem cell research with acquisition of Verio Therapeutics

Fate Therapeutics announced a "definitive agreement" to acquire privately-held Verio Therapeutics, a move aimed at strengthening its approach to stem cell therapeutics by using small molecule agents and biologics to stimulate the body's natural stem cell production to promote tissue regeneration and to treat disease. Fate has a stem cell modulator, FT-1050, in Phase Ib development, and Verio's pipeline includes agents to promote insulin-producing β-cells for diabetes treatment and for regenerating cardiomyocytes after a myocardial infarction (MI).

FDA revises radiotherapy equipment approval process – no more third-party reviewers

The FDA will no longer permit third-party reviewers in the approval process for radiotherapy equipment. In 2009, 40% of new equipment was approved through the third-party review process. The Agency said in a letter to manufacturers that the revisions are part of an effort to reduce reported overdoses, underdoses, and other errors found in an analysis of 1,000 error reports filed during the past decade. A majority of the reported errors concerned linear accelerators used in radio-therapy for cancer treatment, and faulty software was the most frequent cause for these errors, the FDA said. In some cases, the nature of the equipment problem was unidentified.

MEDTRONIC/COREVALVE – loses patent suit to Edwards Lifesciences, future of its percutaneous aortic valve in the U.S. now in question

A federal court ordered Medtronic to pay at least $73.5 million to Edwards Lifesciences for "willfully" infringing a Sapien XT percutaneous heart valve patent. Edwards said it will seek a permanent injunction that would prevent Medtronic from selling the CoreValve device in the U.S. Medtronic said it plans to appeal the ruling and oppose the injunction.

Medtronic also said it will be able to conduct CoreValve clinical trials in the U.S. despite the ruling. The Edwards patent is scheduled to expire before Medtronic expects a final FDA decision on the CoreValve device.

Courts in the U.K. and Germany have found the CoreValve device does not infringe the same patent, and the U.S. ruling will not prevent Medtronic from selling CoreValve products in other countries.

PURDUE PHARMA's OxyContin (oxycodone) – FDA approves new formulation

The FDA approved a reformulated version of this pain drug aimed at reducing the risk of misuse and overdose due to tampering. The FDA is imposing the same REMS as for Exalgo plus postmarket surveillance to gather information on the efficacy of the formulation in terms of reducing abuse and misuse.

The original controlled-release OxyContin formula contains high levels of oxycodone intended to be released over time for patients requiring continuous relief of moderate-to-severe pain, but abusers have found methods to release the drug from the tablets all at once, an issue thought to contribute to high rates of abuse and overdose. The new formulation will have the exact same label and indication, though it is designed to discourage patients from cutting, breaking, chewing, crushing, or dissolving the medication in liquid in order to increase oxycodone release. While the new formulation may still be abused or misused by ingesting doses larger than recommended, it may help reduce misuse through snorting or injection.

Dr. Bob Rappaport, director of the FDA's Division of Anesthesia and Analgesia Products in the Center for Drug Evaluation and Research (CDER), said, "Although this new formulation of OxyContin may provide only an incremental advantage over the current version of the drug, it is still a step in the right direction…Prescribers and patients need to know that its tamper-resistant properties are limited and need to carefully weigh the benefits and risks of using this medication to treat pain."

In a teleconference with patient advocates and other stake-holders about the new OxyContin formulation, Dr. Rappaport offered some additional details:

- "Approximately half a million people used OxyContin non-medically for the first time in 2008.
- The new formulation "cannot be crushed or chopped into small pieces by the methods most commonly used by abusers…as such it is also less likely to be abused by snorting…Also, individual intent on preparing this for injection will find that it…will form a gummy substance that can't be drawn up through most standard-gauge needles and cannot be injected through many of the needles acceptable to users."

- "The new formulation may provide an incremental reduction in abuse. However, this new formulation can still be abused or misused."
- "Both the Agency review team and the experts at the September 2009 advisory committee supported approval of this application. This is because we believe even an incremental change that results in a reduction in abuse and misuse is a step in the right direction."
- **The new formulation is a switch out for the old formulation; both will not be sold.** "This new formulation will not result in any additional OxyContin available on the street…It is intended to replace the original."
- **Purdue cannot market the new formulation as tamper-resistant.** "Labeling has not changed substantially, and ***no marketing claims*** are allowed that would state this product is abuse deterrent or safer [such as the claims made with the original OxyContin that led to 'widespread over-prescribing of the original formulation']."
- **The details of the Medication Guide are not finalized.** "It will be more proactive than just a medication Guide in requiring prescribers to appropriately educate their patients as well as themselves. The details of that are still somewhat under discussion but we have a very good plan outlined."
- **There is no label change, no mention of tamper-resistance in the label.** "The product indication has not changed at all…It is still the treatment of moderate-to-severe pain around the clock when an opioid analgesic is needed…It has not changed at all. The features of the product that we hope will provide abuse deterrence are changes of its formulation, and that is the only change to the product. And it has not changed the indication."
- **There will be an FDA advisory committee meeting on Purdue's postmarketing study.** Dr. Rappaport did not say when this will be, but it will be an opportunity for public comment, "We will be taking the protocol that Purdue submits to us, after adequate discussions with us about our internal concerns about their protocol, and after we've done our usual negotiation on what it should look like, and then we will take it to an Advisory Committee for public discussion on the topic, with epidemiologists."
- **Purdue can launch the new formulation whenever it wants.** Purdue does not have to wait for the Advisory Committee meeting or the finalized REMS. The launch timing is up to Purdue.
- **The REMS for the new formulation is the same as for Covidien's Exalgo (hydromorphone ER).** In fact, it is a standard "interim" REMS that will be used for all long-acting/extended-release opioids until the class-wide REMS is finalized. "What we are calling an interim REMS has been approved. The Agency is still working on the class-wide REMS…**That we will be discussing publicly later in the summer**. But in the meantime, we approved an interim REMS for this and other opioid class products, so the (class) REMS is not going to hold up marketing of the product." There is no registry in the interim REMS for either drug, but another FDA official explained that the sponsor is supposed to keep a list of doctors who have been trained to help "assess if the REMS is working, how it is working, and if it is effective in reducing the risk." Dr. Rappaport added, "It will be the same as for Exalgo, which is our interim REMS for all of the long-acting opioid products. It will not have a registry, and neither does Exalgo at this point…It is not a registry. [But] they are supposed to report to us the percentage of the prescriber population they have educated appropriately…It is not a traditional registry."
- **Purdue does not get 3-5 year exclusivity for the new formulation.** "Exclusivity is not determined by the Division [of Anesthesia and Analgesia Products], but it is not likely to get exclusivity because no clinical studies were required. It was approved on bioequivalence."

Asked how the FDA can trust the postmarketing trial data submitted by Purdue, Dr. Rappaport said, "Once the study has been completed, we will review in detail, as we always do, the data that come in from the company. We generally have the clinical sites evaluated by our scientific investigation unit, and if we feel there are any concerns, we would further investigate, so we will be keeping a very close eye on the data, and hopefully we won't see any problems with it."

Purdue later said that it would stop selling the old formulation and ship only the new formulation starting some time in the third quarter of 2010.

SANOFI-AVENTIS's Multaq (dronedarone) – no more effective than amiodarone

A review of Multaq clinical trials published in the ***Journal of the American College of Cardiology*** concluded that this anti-atrial fibrillation agent should be used only as a second- or third-line agent. In an accompanying editorial, Dr. Christian Torp-Pedersen of Denmark and colleagues said Multaq should still be considered as a first-line agent because the safety of most antiarrhythmic drugs for intermediate-risk patients is uncertain. Multaq was approved in July 2009 for patients with atrial fibrillation or atrial flutter. Last week, ***Quick Takes*** reported that the U.K.'s National Institute for Health and Clinical Excellence (NICE) recommended dronedarone as a second-line agent, having overturned a previous decision not to endorse its use at all.

SANOFI-AVENTIS's Rilutek (riluzole) – ALS study with lithium halted

A randomized clinical trial using a combination of Rilutek and lithium in amyotrophic lateral sclerosis (ALS) was halted after 5.4 months because the combination was no more effective than Rilutek alone, according to a report in ***Lancet Neurology***.

An earlier pilot study indicated that the combination may slow ALS progression, but in this trial, 22 patients receiving Rilutek plus lithium doses titrated to achieve serum levels of 0.4 - 0.8 mEq/L failed to show a significantly decreased time to death or a greater incidence in decrease of at least six points on the ALS Functional Rating Scale vs. 20 patients randomized to receive Rilutek + placebo. In 2007, the addition of minocycline to a Rilutek regimen failed to improve outcomes over Rilutek alone, even though studies in animal models of ALS suggested the combination was promising.

Silicone breast implants – concerns escalate

Last week ***Quick Takes*** reported concerns about three brands of silicone breast implants manufactured by the French company Poly Implant Prothèse (PIP). Now, the situation has escalated. France and Sweden have banned implants made by this manufacturer, and Italian regulators are calling for initiation of an implant registry because of the "impossibility" of tracing all the women who may have received one. An estimated 35,000 - 45,000 European women have a PIP breast implant. While officials would like to warn them of the possibility of breakage and silicone leakage, there is no way to determine who to warn.

UCB's Vimpat (lacosamide) – no better than placebo in diabetic neuropathy

In clinical trial results reported in ***Diabetes Care***, both doses of Vimpat that were tested (400 mg and 600 mg) missed the primary endpoint, failing to show a significant change in average daily pain score from baseline to the average obtained during the last 4 weeks of the study. The 18-week trial, which enrolled 246 patients with diabetes and moderate-to-severe neuropathic pain, did show that drug was well tolerated and numerically superior to placebo. The investigators called the placebo rate very high, saying that is "not unusual in neuropathic pain studies" and might explain the non-significant response to Vimpat treatment. Vimpat is currently approved to prevent seizures in epilepsy.

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