

NEWS FROM THE FDA

First Device Is Approved to Treat Brain Tumors

Portable, battery-powered device delivers electrical fields to treat recurrent glioblastoma multiforme.

BY ELIZABETH MEHCATIE

The Food and Drug Administration has approved a portable, battery-powered device that delivers electrical fields to the brain for treating recurrent glioblastoma multiforme, despite its failure to meet a primary end point in a pivotal phase III trial.

The NovoTTF-100A system is indicated for treating adult patients who have tumor recurrence or progression after receiving chemotherapy and radiation therapy. The device is not intended to be used in combination with other cancer treatment, and it should only be used after other treatments have failed, according to the agency.

In March, the FDA's Neurological Devices Advisory Panel voted 7-3 with 2 abstentions that the benefits of the device exceed its risks when used as monotherapy in adults who have exhausted surgical and radiation treatment options for histologically or radiologically confirmed recurrent glioblastoma multiforme (GBM).

The device's manufacturer, Israel-based Novocure, sought an indication in that population based on the results of a company-sponsored prospective randomized trial that compared treatment with the device to best standard of care (BSC) chemotherapy in 237 patients with recurrent GBM.

At the meeting, panelists emphasized that the indication should reflect that patients have also failed chemotherapy options, and that while the treatment appears to be safe in the short term, the potential for chronic adverse effects should be monitored closely.

The device weighs about 6 pounds and is intended to be worn about 20 hours per day. It delivers "tumor-treating fields" (TTF) via four electrodes placed

on the scalp. This creates "a low intensity, alternating electric field within the tumor that exerts physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death prior to division," according to the company. Normal cells are not affected, it said.

Scattered throughout the audience at the panel meeting were about 20 people undergoing treatment with the device, which was evident from the partially exposed electrodes under their hats and the attached leads that were visible.

Several testified about their positive experiences with TTF therapy, including reports of tumor shrinkage and good quality of life. They described their ability to participate in activities such as coaching a child's sports team and playing with their children during treatment, in contrast to how they felt during chemotherapy, when their quality of life was poor. They described the sensation of the device as negligible, with a slightly warm or itchy feeling at the most.

In the pivotal study, median overall survival, the primary end point, was 6.3 months among those treated with the device and 6.4 months among those treated with the best available chemotherapy.

The most common treatment-associated adverse event reported was mild to moderate skin irritation under the electrodes, which was easily treated, the company reported.

Central nervous system (43% vs. 36%) and neuropsychiatric (10% vs. 8%) adverse events were higher among those in the TTF group than among those on BSC, but the differences were not significant.

The study was designed to show that TTF therapy is superior to BSC chemotherapy, but it failed to do so. The com-



The NovoTTF-100A's low-intensity electric field kills the cancer cells before cell division.

surgery department at Temple University, Philadelphia, said that while he agreed there were serious questions about the methodology used in the trial, "considering the compelling nature of the clinical problem, I could not see that with an excellent safety profile, it should be denied to the patient."

He urged Novocure "to behave responsibly, to promote this device and promulgate it as part of a continuum of effective therapies," and not as if patients "no longer need any other therapy."

The concept behind TTF "is a good idea. I like the idea, I like the basic science, and I wish we had clear evidence of effectiveness," said Dr. Stephen

Haines, chair and head of the neurosurgery department at the University of Minnesota, Minneapolis, one of the three panelists who voted no on the risk-benefit question.

He said he would have preferred a noninferiority study that "clearly showed" the device could replace salvage chemotherapy in patients with recurrent GBM.

NovoCure is conducting a phase III study of the device in patients with newly diagnosed GBM, in combination with temozolomide.

The device has been approved in the European Union as a treatment for newly diagnosed and recurrent GBM and for the treatment of non-small cell lung cancer.

Median survival of patients diagnosed with GBM is 15 months, and the 5-year overall survival rate is less than 10%, according to data cited by the company and the FDA.

Dr. Donald Richardson, professor and chair of the department of neurological surgery at Tulane University, New Orleans, said that despite concerns about the data, the device should be made available because of its safety profile and because of "clear evidence ... of obvious benefit" in some patients.

Dr. Christopher Loftus, professor of neurosurgery and chair of the neuro-

FDA Approved Gabapentin Prodrug for Treating RLS

BY ALICIA AULT

The Food and Drug Administration announced the approval of an extended-release form of gabapentin for moderate to severe restless legs syndrome.

The drug, known as Horizant (gabapentin enacarbil), is a prodrug of gabapentin. It was developed by XenoPort Inc. of Santa Clara, Calif., and GlaxoSmithKline.

"People with restless legs syndrome can experience considerable distress from their symptoms," said Dr. Russell Katz, director of the FDA's

Division of Neurology Products at the agency's Center for Drug Evaluation and Research, in a statement. "Horizant provides significant help in treating these symptoms."

According to the National Institute of Neurological Disorders and Stroke, restless legs syndrome (RLS) is a neurologic disorder that is "characterized by unpleasant sensations in the legs and an uncontrollable, and sometimes overwhelming, urge to move them for relief." Mild to moderate cases are treated with lifestyle and behavioral changes. More severe cases warrant

therapies such as dopaminergics, benzodiazepines, opioids, and anticonvulsants.

Two other drugs were approved for the condition for moderate to severe RLS: Requip (ropinirole) in 2005 and Mirapex (pramipexole) in 2006.

The prevalence and incidence rates of RLS are currently not well known, according to the Restless Legs Syndrome Foundation. There is no cure and symptoms can worsen with age. The manufacturers estimate that 1%-3% of the U.S. population is symptomatic.

RLS remains underrecog-

nized, "and many patients go untreated as a result," said Dr. Atul Pande, senior vice president at GlaxoSmithKline Neurosciences Medicine Development Center. "GSK has been committed to helping patients and healthcare professionals better understand and treat this condition. We are pleased to provide a new treatment" for moderate to severe primary RLS, he said in a statement.

XenoPort CEO Ronald W. Barrett said that Horizant was the "culmination of XenoPort's efforts to develop a non-dopaminergic therapy" for

patients with RLS.

Horizant carries a number of risks and contraindications. Even at the once-daily dose of 600 mg, it can cause somnolence and "significant driving impairment," according to GSK and XenoPort.

It is an antiepileptic, and that class of drugs has been shown to increase the risk of suicidal thoughts or behaviors. Horizant also increases this risk, and will carry such a warning, said the companies and the FDA.

The dosage also needs to be adjusted for patients with renal impairment.