US FDA approves higher-dose donepezil for the treatment of Alzheimer's disease

The US FDA has approved a once-daily higher-dose donepezil HCl (Aricept®, Eisai Inc. and Pfizer Inc.) tablet for the treatment of moderate-to-severe Alzheimer's disease. The drug was previously available as a 5- or 10-mg tablet, with a maximum daily dose of 10 mg, but the new approval allows for a daily dose of 23 mg for patients who have been established on the 10-mg daily dose for at least 3 months.

The approval of donepezil 23 mg was based on results from a large head-to-head comparison trial with the original 10-mg formulation in 1467 patients with moderate-to-severe Alzheimer's disease. The results showed that patients receiving the 23-mg donepezil dose had a statistically significant improvement in cognition at 24 weeks, compared with those on the 10-mg dose. Statistically significant improvement in global function, however, was not achieved in the patients receiving the higher-dose tablet.

Lead author of the trial publication, Martin Farlow, Indiana University School of Medicine (IN, USA), commented "slowing the decline of cognitive symptoms is important at all stages of Alzheimer's disease. Throughout the course of Alzheimer's disease, caregivers are usually the first to notice changes in cognition. It's important for families to talk with their doctor when they notice a worsening in cognitive function in their loved ones to reevaluate therapeutic needs."

On the basis of the new approval, the recommended dosing of donepezil is 5 mg once daily, which can be increased to 10 mg once daily after 4–6 weeks. For patients with moderate-to-severe Alzheimer's disease, the dose can then be increased to 23 mg once daily after a further 3 months.

Alzheimer's disease affects over 26 million people worldwide, with age being the biggest risk factor. The approval of Donezepil 23 mg is an important addition in improving the treatments available for this disease in an increasingly aging population.

Source: Eisai press release: www.eisai.com/view_press_release.asp?ID=147&press=280

Oncologic Drugs Advisory Committee recommends withdrawing approval for bevacizumab use in breast cancer

The Oncologic Drugs Advisory Committee, a US FDA advisory panel, voted overwhelmingly to recommend withdrawing the marketing authorization for bevacizumab (Avastin®; Genentech, Inc., CA, USA) for first-line use in metastatic breast cancer.

The original approval for bevacizumab was controversial as it was based on a single trial (E2100), which demonstrated that progression-free survival was increased by 5.5 months in patients treated with bevacizumab and paclitaxel compared with paclitaxel alone, although no statistically significant overall survival advantage was observed.

The Oncologic Drugs Advisory Committee's decision to recommend removing approval of the drug for this indication follows two further trials (AVADO and RIBBON 1), which demonstrated considerably shorter progression-free survival advantage for the addition of bevacizumab (0.9 and 1.2 months, respectively) and no overall survival advantage. Given the known toxicity of bevacizumab, including the potential for cardiovascular side effects, bleeding and gastrointestinal perforation, the panel felt that the risk:benefit ratio was not sufficiently favorable to recommend continued approval for this indication.

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The chair of the panel, Wyndham Wilson of the National Cancer Institute (Bethesda, MD, USA), stated "we have to take into account risks, and there are definite risks." Pointing out that some of the side effects of bevacizumab can be fatal.

Gabriel Hortobagyi, Professor of breast medical oncology at the MD Anderson Cancer Center (TX, USA), who attended the Oncologic Drugs Advisory Committee meeting as a consultant to Genentech was disappointed with the decision. "Bevacizumab is clearly active in breast cancer, and there is more experience with this agent in metastatic breast cancer than with many, if not most, other agents evaluated for the metastatic breast cancer indication," he stated. "Anecdotally, bevacizumab combinations can produce dramatic responses in individual patients, and it is my clinical impression that responses of such quality are seldom seen with the same chemotherapy programs without bevacizumab. As a frequent user of this agent, I have also found that it is very well tolerated by the great majority of patients; in very few do I need to modify dose or schedule, and in even fewer do I need to discontinue treatment because of toxicities."

He concluded, "I am concerned, in part, because this recommendation might remove an important treatment option from patients with metastatic breast cancer. I am also concerned because 'clinical benefit' remains poorly defined. This precedent will set many drugs currently under development up for failure."

Source: Medscape Medical News: Will the FDA revoke bevacizumab's approval for breast cancer? www.medscape.com/viewarticle/725509

Promising findings in the development of a universal influenza vaccine

In a recent paper published online ahead of print in *Science,* researchers from the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, outline their recent progress in the development of a new universal influenza vaccine.

Owing to antigenic shift and drift, influenza vaccines are annually reforumulated to correspond to strains most prevalent in circulation. A universal flu vaccine would aim to elicit broadly neutralizing antibodies, capable of binding to a diverse range of influenza stains.

Gary J Nabel and his team from the NIAID used experiments in a range of models, including mice, ferrets and monkeys, to determine the impact of a two-step immunization approach. This involved priming the animal's immune system with plasmid DNA that encoded for the hemagglutinin (HA) surface protein of influenza. Postpriming, the murine and ferret models received a booster dose of either the seasonal influenza vaccine for 2006–2007 or a replication-deficient adenovirus 5 vector encoding HA (monkeys received only a boost of the seasonal vaccine).

The prime-boost regimen was demonstrated to stimulate the production of broadly neutralizing influenza antibodies capable of binding to and neutralizing H1N1 strains from 1934 to 2007 more effectively than either component of the regimen alone. The antibodies were capable of conferring protection against levels of the viruses in mice and ferrets that were seen to be deadly if only one component of the regimen had been administered. Interestingly, tests with H5N1 demonstrated the ability of the antibodies to neutralize subtypes of influenza. The researchers demonstrated the ability of the regimen to elicit the antibodies in nonhuman primates and determined that the antibodies were directed against a conserved stem region of HA. Unlike the spherical head of the influenza glycoprotein, the stem region of HA – consisting of three identical monomers in an α-helix coil – is not subject to frequent mutations. Consequently, the group from NIAID note that, "cross-neutralization of H1N1 subtypes elicited by this approach provides a basis for development of a universal influenza vaccine for humans."

Anthony S Fauci, director of the NIAID elaborates on this, "generating broadly neutralizing antibodies to multiple strains of influenza in animals through vaccination is an important milestone in the quest for a universal influenza vaccine. This significant advance lays the groundwork for the development of a vaccine to provide long-lasting protection against any strain of influenza. A durable and effective universal influenza vaccine would have enormous ramifications for the control of influenza, a disease that claims an estimated 250,000 to 500,000 lives annually, including an average of 36,000 in the United States."

The group believes they may be able to begin efficacy trials for the vaccine in the next 3–5 years, and have already begun trials into the safety and immunogenicity of the prime-boost influenza vaccines in humans.

Sources: NIH news: NIH scientists advance universal flu vaccine: www.niaid.nih.gov/news/newsreleases/2010/Pages/UniversalFluVax.aspx; Wei C-J, Boyington JC, McTamney PM et al.: *Induction of broadly neutralizing H1N1 influenza antibodies by vaccination.* Science *doi: 10.1126/science.1192517 (2010) (Epub ahead of print).*

New vaccine for preventing recurrent sarcoma enters Phase II clinical trial

MabVax Therapeutics Inc. (CA, USA) has announced the enrolment of the first patients to a Phase II clinical trial of its vaccine to prevent or delay the recurrence of sarcoma.

Approximately 13,200 cases of sarcoma are diagnosed and more than 5200 sarcoma patients die of the disease each year in the USA. As with most cancers, recurrence and metastases are common in sarcoma patients. Despite surgical interventions and combination therapy, most patients die following further recurrences. Thus, treatments are limited to expectant management once the disease becomes metastatic.

The current clinical trial is a randomized, multicenter, double-blind Phase II study involving 126 metastatic sarcoma patients aged 16 years or older. Patients will receive a series of ten subcutaneous injections of a trivalent vaccine over an 84-week period. The vaccine is an adjuvanted, trivalent ganglioside vaccine that is designed to target and destroy residual circulating cancer cells and micrometastases believed to cause recurrent sarcoma.

The vaccine aims to induce the patient's immune system to produce antibodies against the three ganglioside antigens present on the surface of sarcoma cells. The antibodies will seek out residual circulating cancer cells and micrometastases and assist the immune system to kill these cells, thus preventing cancer recurrences. The vaccine was developed at Memorial Sloan-Kettering Cancer Center (NY, USA) where preclinical and early clinical development work was completed in 2009. The vaccine was licensed exclusively to MabVax in 2008, along with additional vaccines targeting other neuroectodermal and epithelial cancers.

The enrolment process for this clinical trial is expected to take 15 months at 12 leading academic medical centers across the USA. The primary objective is to determine the 1-year progression-free survival rate, and secondary objectives are overall survival, disease-free survival and disease-specific survival, along with 3-year progression-free survival rates.

Source: MabVax Therapeutics, Inc., CA, USA: www.mabvax.com/news4.html

US FDA approves Tribenzor™ for the treatment of hypertension

The US FDA has recently approved Daiichi Sankyo Inc.'s (Munich, Germany) Tribenzor™ (olmesartan medoxomil, amlodipine and hydrochlorothiazide) once-daily three-in-one combination pill for the treatment of hypertension.

The new combination, the second three-in-one antihypertensive to be approved by the FDA (after Exforge HCT® from Novartis, NJ, USA), is not indicated for initial therapy, but for patients not adequately controlled on any two of the following treatments: angiotensin receptor blockers, calcium channel blockers and diuretics.

More than two-thirds of hypertension patients require two or more antihypertensive medications in order to achieve their target blood pressure level, and the new three-in-one combination will help simplify dosing regimens and improve adherence to treatment.

Joseph Izzo, Chief of Medicine, Erie Council Medical Center (NY, USA), comments "generally speaking, it can be a struggle for some patients who need to take multi-pill regimens to take their medications as prescribed. Tribenzor is a three-in-one pill that offers a simple, convenient and consistently effective therapy for patients, and may be just what some patients need to help bring their blood pressure to goal."

Olmesartan medoxomil functions by blocking angiotensin II receptors; amlodipine inhibits the entry of calcium into blood vessel walls and hydrochlorothiazide acts as a diuretic to reduce water volume in the blood, enabling Tribenzor to combat hypertension from a range of angles, relaxing the blood vessels and reducing blood pressure.

The pivotal, Phase III TRINITY trial, involved a total of 2492 patients, and statistically significant greater reductions in both systolic and diastolic blood pressure were observed after 8 weeks of treatment with Tribenzor, compared with each of the three dual combination treatments (amlodipine/hydrochlorothiazide, olmesartan/hydrochlorothiazide and olmesartan/amlodipine).

Hypertension affects approximately 600 million people worldwide and is responsible for 5 million premature deaths each year. It is hoped that the approval of Tribenzor will help combat this silent killer by improving both the adherence and effectiveness of antihypertensive treatment for patients on this regimen.

Source: Daiichi-Sankyo: FDA approves Tribenzor™, a new three-in-one combination product for the treatment of high blood pressure: www.daiichisankyo.com/news/20100727_TRIBENZOR%20FDA%20Approval%20Press%20Release%20FINAL.pdf

Drug Approvals June to August 2010.

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Cardiology					
Tribenzor™	Olmesartan medoxomil/amlodipine/ hydrochlorothiazide	Hypertension	USA	Daiichi Sankyo	July 2010
Neurology					
Aricept®	Donepezil hydrochloride once-daily, higher-dose formulation	Moderate-to-severe dementia of the Alzheimer's type	USA	Eisai/Pfizer	July 2010
Namenda XR™	Memantine hydrochloride once-daily, extended-release formulation	Moderate-to-severe dementia of the Alzheimer's type	USA	Forest Laboratories	June 2010
Xeomin®	Incobotulinumtoxin A	Cervical dystonia and blepharospasm	USA	Merz Pharmaceuticals	July 2010
Oncology					
Abraxane® IV infusion	Paclitaxel injection (suspension with albumin)	Breast cancer	Japan	Abraxis BioScience	July 2010
Jevtana®	Cabazitaxel	To be used in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen	USA	Sanofi-aventis	June 2010
Respiratory					
Dulera®	Mometasone furoate and formoterol fumarate	Asthma, in adults and children 12 years of age and older	USA	Merck	June 2010
Daxas®	Roflumilast	Maintenance treatment of severe chronic obstructive pulmonary syndrome (forced expiratory volume in 1 s postbronchodilator <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as an add-on to bronchodilator treatment	EU	Nycomed/Forest Laboratories	July 2010
Rheumatology					
Orencia®	Abatacept and methotrexate	Moderate-to-severe active rheumatoid arthritis in adult patients who have responded inadequately to previous therapy with one or more disease-modifying antirheumatic drugs	EU	Bristol-Myers Squibb	July 2010
Other					
Butrans™	Buprenorphine transdermal system	For transdermal administration for the management of persistent, moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time	USA	Purdue Pharma	June 2010
Jalyn™	Dutasteride/tamsulosin hydrochloride	Symptomatic benign prostatic hyperplasia in men with an enlarged prostate	USA	GlaxoSmithKline	June 2010
Staxyn™	Vardenafil hydrochloride orally disintegrating tablets	Erectile dysfunction	USA	Bayer Healthcare/ GlaxoSmithKline and Merck	June 2010