Regulatory Action and News

Recommended influenza virus vaccine composition: 2013–2014 Northern hemisphere season

Wold Health Organization — It is recommended that vaccines for use in the 2013–2014 influenza season (Northern hemisphere Winter) contain the following:

- An A/California/7/2009 (H1N1)pdm09-like virus (A/Christchurch/16/2010 is an A/California/7/2009-like virus).

- An A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011 (A/Texas/50/2012 is an A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011). It is recommended that A/Texas/50/2012 is used as the A(H3N2) vaccine component because of antigenic changes in earlier A/Victoria/361/2011-like vaccine viruses (such as IVR-165) resulting from adaptation to propagation in eggs.

- A B/Massachusetts/2/2012-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus (B/Brisbane/33/2008 is a B/Brisbane/60/2008-like virus).

As in previous years, national or regional authorities approve the composition and formulation of vaccines used in each country. National public health authorities are responsible for making recommendations regarding use of the vaccine.

Reference: Weekly Epidemiological Record, 8 March 2013, vol. 88, 10 (pp. 101–116) at http://www.who.int/wer

Counterfeit antimalarial medicines: detection tool

United States of America — The Food and Drug Administration (FDA) has announced a public-private partnership to identify counterfeit or substandard antimalarial medicines, including falsified products, with the deployment of the FDA-developed Counterfeit Detection Device, called CD-3.

Globally, malaria kills more than 660,000 people annually, mostly children. The threat of drug resistance, limited availability of medication and increased presence of counterfeit or substandard antimalarial medicines pose significant challenges to treating this disease. Compromised antimalarials often have too little or no active ingredients, preventing adequate and timely treatment. Antimalarial medicines made with reduced dosages of active ingredients will not cure patients, and they can lead to resistant strains of the parasite, making it tougher to treat, even with authentic medicines.

The FDA has established a partnership with the Skoll Global Threats Fund, the U.S. Pharmacopeia (USP), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the multi-agency President’s Malaria Initiative (PMI), led by the U.S. Agency for International Development (USAID).

The partnership will focus on testing and optimizing the use of the handheld CD-3 to identify counterfeit or substandard antimalarial medicines, including falsified products, in Africa and parts of Southeast Asia where the rates of malaria infection are high and where counterfeit antimalarial medicines are prevalent.
The effectiveness of the tool in detecting counterfeit or substandard versions of two common antimalarial therapies will be tested in Ghana in 2013 and 2014. Making detection technology more accessible to low and middle income countries would be invaluable in controlling the trade in counterfeit, falsified, or substandard medicines.


Black triangle for medicines subject to additional monitoring

European Union — The European Medicines Agency (EMA) has published an initial list of medicines that are subject to additional monitoring. This represents a deliverable of the new European pharmacovigilance legislation. These medicines will have to display an inverted back triangle in their package leaflet and in the summary of product characteristics (SmPC), together with a short sentence explaining what the triangle means.

All medicines on the European Union market are carefully monitored. If a medicine is labelled with the inverted black triangle, it does not mean that it is unsafe; the purpose of the symbol is to actively encourage healthcare professionals and patients to report any suspected adverse reactions observed with the medicine, either because the medicine is new to the market or because there is a limitation to the data available on its safety. Medicines subject to additional monitoring are:

• Medicines authorized after 1 January 2011 that contain a new active substance.

• Biological medicines for which there is limited post-marketing experience.

• Medicines with a conditional approval or approved under exceptional circumstances.

• Medicines for which the marketing-authorization holder is required to carry out a post-authorization safety study (PASS).

Other medicines can also be placed under additional monitoring, based on a recommendation from the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC). A medicine can be included on this list when it is approved for the first time or at any time during its lifecycle. It remains under additional monitoring for five years or until the PRAC decides to remove it from the list usually because studies have further established the safety profile of the product concerned. The complete additional-monitoring list will be reviewed every month by the PRAC and published on the EMA web site, where additional information on monitoring can also be found in all EU languages.

The inverted black triangle will start appearing in the package leaflet and SmPC of the medicines concerned from the autumn of 2013.


Levothyroxine: licence suspension

United Kingdom — The Medicines and Healthcare Products Regulatory Agency (MHRA) has suspended the licence for levothyroxine 100 microgram tablets for patients with hypothyroidism. This follows manufacturing difficulties and concerns that the product might not be interchangeable with other available levothyroxine 100 mcg tablets.

The decision to suspend follows a review by the Commission on Human Medicines (CHM), the MHRA’s independent advisory body, of manufacturing issues and sporadic reports of loss of control of hypothyroidism when switching between products.
Pregnant women, those with heart disease and those under treatment with levothyroxine following treatment for thyroid cancer may be particularly susceptible to changes in thyroid stimulating hormone and may require close monitoring by their doctor.


Strontium ranelate: restricted use

European Union — The Committee for Medicinal Products for Human Use (CHMP) has recommended a restriction in the use of the osteoporosis medicine strontium ranelate (Proteolos/Osseor®), following an assessment of data showing an increased risk of serious heart problems. The CHMP recommended that Proteolos/Osseor® should only be used to treat severe osteoporosis in postmenopausal women at high risk of fracture and severe osteoporosis in men at increased risk of fracture. Additional measures, including restrictions in patients with heart or circulatory problems, were also recommended to minimize the heart risks of these medicines. Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease or cerebrovascular disease or if hypertension becomes uncontrolled.

The CHMP recommendation is based on the advice of the Pharmacovigilance Risk Assessment Committee (PRAC).


Tetrazepam-containing medicines: suspension

European Union — The Coordination Group for Mutual Recognition and

Decentralized Procedures: Human (CMDh) has endorsed the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation to suspend the marketing authorizations of tetrazepeam-containing medicines across the European Union (EU). The CMDh, a body representing Member States, is responsible for ensuring harmonized safety standards for medicines authorized via national marketing authorization procedures.

Tetrazepeam, a medicine of the benzodiazepine class, is used in several Member States to treat painful contractures and spasticity. The review of tetrazepeam was triggered by the French National Agency for the Safety of Medicine and Health Products (ANSM), following reports of serious skin reactions with this medicine in France.

Having assessed all available data on the risk of skin reactions, the PRAC concluded that tetrazepeam is associated with a low but increased risk of serious skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS syndrome) compared with other benzodiazepines. The Committee also noted that the available data on the effectiveness of tetrazepeam were not sufficiently robust to support its use for the authorized indications.


Dabigatran etexilate: updated contraindications

European Union — On 25 April 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the contraindication for dabigatran etexilate (Pradaxa®).
Contraindications for Pradaxa® are now:

- Hypersensitivity to the active substance or to any of the excipients.
- Severe renal impairment (CrCL < 30 mL/min).
- Active clinically-significant bleeding.
- Lesion or condition, if considered a significant risk factor for major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthamlic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa® (or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Hepatic impairment or liver disease expected to have any impact on survival.
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone.
- Prosthetic heart valves requiring anticoagulant treatment.


Idebenone: voluntary withdrawal

Canada — Health Canada has informed healthcare professionals of the manufacturer’s decision to voluntarily withdraw idebenone (Catena®) from the Canadian market, as of 30 April 2013.

The withdrawal is based on the negative outcome of additional confirmatory efficacy studies required by Health Canada and is not the result of a specific safety concern. Prescribers are advised to discuss alternative treatment options with their patients.

Idebenone was authorized with conditions in Canada in July 2008 on the basis of promising evidence of clinical safety and efficacy in the symptomatic management of patients with Friedreich Ataxia. One of the conditions of authorization was to provide confirmatory evidence of efficacy in further clinical studies. However, the additional studies completed to date failed to meet their primary efficacy endpoint. The manufacturer will not recall Catena® currently prescribed.


Autologous chondrocyte implantation approved for cartilage defects

European Union — The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended marketing authorization for Maci® (matrix-induced autologous chondrocyte implantation), an advanced-therapy medicinal product (ATMP), for the repair of symptomatic, full-thickness cartilage defects of the knee in skeletally mature adult patients.

Cartilage has a poor ability to repair itself when injured. Injuries to the smooth cartilage surface of the knee joint increase rubbing and friction in the knee and predispose the knee to
differentiation of cells. The benefits with Erivedge® are its ability to reduce lesion size or sum of the longest diameter of lesions more than 30% or to provide complete resolution of ulceration in all target lesions in 48% of the patients with locally advanced BCC and in 33% of the patients with metastatic BCC. The most common side effects are muscle spasms, alopecia, dysgeusia, weight decreased, fatigue and nausea. There is a high risk that vismodegib can cause embryo-foetal death or severe birth defects.


Lenalidomide: approved for myelodysplastic syndromes

European Union — The Committee for Medicinal Products for Human Use (CHMP) has recommended a variation to the terms of the marketing authorization for lenalidomide (Revlimid®).

The CHMP adopted a new indication for myelodysplastic syndromes. Revlimid® is now also indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.


Nimodipine oral solution approved for subarachnoid haemorrhage

United States of America — The Food and Drug Administration (FDA) has approved Nymalize®, a new nimodipine oral solution to treat patients with further cartilage wear and erosion, which can eventually lead to osteoarthritis if untreated.

A number of surgical procedures aiming to repair cartilage have been developed to treat patients with articular cartilage defect of the knee. One of them is autologous chondrocyte implantation (ACI), a therapy based on tissue engineering, which was first described in 1994. It uses chondrocytes, or cartilage cells, which are derived from the patient’s own cartilage, grown outside the patient’s body and then transplanted into the patient’s lesions after several weeks. The benefit of ACI over other restoration techniques is that larger lesions can be treated.

Maci® is a third-generation ACI product which uses a scaffold formed of porcine collagen on which autologous chondrocytes are seeded. At implantation, the scaffold is trimmed to the size and shape of the cartilage defect. The cells/collagen structure is held in place in the lesion with fibrin glue.


Vismodegib approved for basal cell carcinoma

European Union — The Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a conditional marketing authorization for vismodegib (Erivedge®) 150 mg, hard capsule, intended for the treatment of adult patients with symptomatic metastatic basal cell carcinoma (BCC) or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

Vismodegib, an antineoplastic agent, is an orally available small-molecule which acts by blocking specific genes involved in proliferation, survival, and
Symptoms resulting from subarachnoid haemorrhage. Nimodipine was previously available only as a liquid-filled gel capsule.

The FDA has received reports of serious and sometimes fatal consequences from intravenous (IV) injection of the liquid contents of oral nimodipine capsules. IV administration of nimodipine meant for oral use can result in death, cardiac arrest, severe decreases in blood pressure and other heart-related complications.

The approval of Nymalize® is based on clinical studies evaluating the use of nimodipine oral capsules in patients with subarachnoid haemorrhage. The most common adverse event observed in the studies was decreased blood pressure.

**Reference:** FDA News Release, 14 May 2013 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements

**Golimumab approved for ulcerative colitis**

**United States of America** — The Food and Drug Administration (FDA) has approved a new use for golimumab (Simponi®) injection to treat adults with moderate to severe ulcerative colitis.

Golimumab works by blocking tumour necrosis factor (TNF). Previously approved to treat rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, Simponi® is now approved to treat adults with moderate to severe ulcerative colitis that is refractory to prior treatment or requires continuous corticosteroid therapy.

The most common side effects in patients treated with Simponi® are upper respiratory infection and redness at the site of injection. Patients treated with Simponi® are at increased risk of developing serious infections, invasive fungal infections, reactivation of Hepatitis B infection, lymphoma, heart failure, nervous system disorders and allergic reactions.


**Radium dichloride approved for advanced prostate cancer**

**United States of America** — The Food and Drug Administration (FDA) has approved radium $^{223}$Ra dichloride (Xofigo®) to treat men with symptomatic metastatic castration-resistant prostate cancer that has spread to bones but not to other organs. It is intended for men whose cancer has spread after receiving medical or surgical therapy to lower testosterone.

The most common side effects reported during clinical trials in men receiving Xofigo® were nausea, diarrhoea, vomiting and swelling of the leg, ankle or foot. The most common abnormalities detected during blood testing included anemia, lymphocytopenia, leukopenia, thrombocytopenia, neutropenia.


**Erlotinib and diagnostic test approved for non-small cell lung cancer**

**United States of America** — The Food and Drug Administration (FDA) has approved the cobas EGFR Mutation Test, a companion diagnostic for the cancer drug erlotinib (Tarceva®). This is the first FDA-approved companion diagnostic that detects epidermal growth factor receptor (EGFR) gene mutations, which are present in approximately 10 percent of non-small cell lung cancers (NSCLC).

The test is being approved with an expanded use for erlotinib as a first-line treatment for patients with NSCLC that
has metastasized and who have certain mutations in the EGFR gene.

The FDA approved Tarceva® on 16 April 2010 for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.


**Dabrafenib, trametinib and companion diagnostic test for advanced skin cancer**

**United States of America** — The Food and Drug Administration (FDA) has approved two drugs, dabrafenib (Tafinlar®) and trametinib (Mekinist®), for patients with metastatic or unresectable melanoma.

Tafinlar®, a BRAF inhibitor, is approved to treat patients with melanoma whose tumours express the BRAF V600E gene mutation. Mekinist®, a MEK inhibitor, is approved to treat patients whose tumors express the BRAF V600E or V600K gene mutations. Approximately half of melanomas arising in the skin have a BRAF gene mutation. They are being approved as single agents, not as a combination treatment.

The FDA has approved Tafinlar® and Mekinist® with a genetic test called the THxID BRAF test®, a companion diagnostic that will help determine if a patient’s melanoma cells have the V600E or V600K mutation in the BRAF gene.

The most common side effects reported in patients receiving Tafinlar® included hyperkeratosis, headache, fever, joint pain, non-cancerous skin tumors, hair loss and hand-foot syndrome.

The most serious side effects reported in patients receiving Mekinist® included heart failure, lung inflammation, skin infections and loss of vision. Common side effects included rash, diarrhea, peripheral edema and skin breakouts that resemble acne.

Women of child bearing years should be advised that Tafinlar® and Mekinist® carry the potential to cause foetal harm. Men and women should also be advised that these products carry the potential to cause infertility.


**Cysteamine bitartrate approved for rare genetic condition**

**United States of America** — The Food and Drug Administration (FDA) has approved cysteamine bitartrate (Procysbi®) for the management of nephropathic cystinosis in children and adults.

Cystinosis is a rare genetic condition that affects an estimated 500 patients in the United States and about 3000 patients worldwide. Cystinosis may lead to slow body growth and small stature, weak bones and developing and worsening kidney failure.

The most common side effects include nausea, bad breath, abdominal pain, constipation, indigestion or upset stomach, headache, drowsiness and dizziness. Other uncommon but serious side effects include ulcers or bleeding of the stomach or intestine, altered mental state, seizures, severe skin rashes and allergic reactions.
Fluticasone furoate and vilanterol approved for chronic obstructive pulmonary disease

United States of America — The Food and Drug Administration (FDA) has approved fluticasone furoate and vilanterol inhalation powder (Breo Ellipta®) for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations.

The drug carries a boxed warning that long-acting beta2-adrenergic agonists (LABAs) increase the risk of asthma-related death. The safety and efficacy of Breo Ellipta® in patients with asthma have not been established, and it is not approved for the treatment of asthma.

Breo Ellipta® may cause serious side effects, including increased risks of pneumonia and bone fractures. The most common side effects reported included nasopharyngitis, upper respiratory tract infection, headache, and oral candidiasis.

Oxycodone with abuse-deterrent properties approved

United States of America — The Food and Drug Administration (FDA) has approved updated labelling for reformulated oxycodone hydrochloride controlled-release tablets (OxyContin®). The new labelling indicates that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route.

Additionally, because original OxyContin® provides the same therapeutic benefits as reformulated OxyContin®, but poses an increased potential for certain types of abuse, the FDA has determined that the benefits of original OxyContin® no longer outweigh its risks and has been withdrawn from sale. Accordingly, the agency will not accept or approve any abbreviated new drug applications (generics) that rely upon the approval of original OxyContin®.

The reformulated tablet is more difficult to crush, break, or dissolve. It also forms a viscous hydrogel and cannot be easily prepared for injection.

Imatinib approved for leukaemia

European Union — The Committee for Medicinal Products for Human Use (CHMP) has recommended granting of a marketing authorization for imatinib (Imatinib Accord®), film-coated tablet 100 mg and 400 mg intended for the treatment of leukaemia.

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs. Imatinib Accord® is indicated for the treatment of:

- Paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
- Paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
- Adult patients with Ph+ CML in blast crisis.
First A1c test labelled for diagnosing diabetes

United States of America — The Food and Drug Administration (FDA) has announced that it is allowing marketing of the Tina-quant HbA1cDx assay (Cobas Integra 800 Tina-quant HbA1cDx assay®) for the diagnosis of diabetes by healthcare professionals.

The HbA1c tests, or A1c tests, currently on the market are FDA-cleared for monitoring a patient’s blood glucose control, but not for diagnosing diabetes. A1c tests measure the percentage of hemoglobin A1c that is bound to glucose, giving a patient’s average glucose level over a three-month period.

The diagnostic criteria for diabetes have changed over time. Based on the research and recommendations of international diabetes experts, many health care providers have already been using some A1c tests to diagnose diabetes, in addition to the established diagnostic procedures of a fasting blood glucose test and an oral glucose tolerance test to diagnose diabetes.

However, before now, A1c tests were not specifically designed or granted permission by FDA to be marketed for diabetes diagnosis, making it difficult to know which A1c tests were accurate enough for this purpose. The Tina-quant HbA1cDx assay, a laboratory-based test, can be used to both accurately diagnose diabetes and monitor blood glucose control.

Over-the-counter HbA1c tests should not be used by patients to diagnose diabetes, and only a qualified health care professional should make a diagnosis of diabetes. Individuals who receive a diabetes diagnosis should discuss with their physician what they need to do to manage their diabetes.

Hemoglobin A1c tests, including the Tina-quant HbA1cDx assay, should not be used to diagnose diabetes during pregnancy and should not be used to monitor diabetes in patients with hemoglobinopathy, hereditary spherocytosis, malignancies, or severe chronic, hepatic and renal disease. This test should not be used to diagnose or monitor diabetes in patients with the hemoglobin variant hemoglobin F.