WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request.

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NEWS & ISSUES:

As usual, the WHO Pharmaceuticals Newsletter provides you with the latest safety reports, advice, warnings and other updates from regulatory authorities across the world.

In adverse events reporting, Malaysia releases record collection figures for the past year even as the WHO database, Vigibase, announces that it has surpassed 4 million case reports. To mark 50 years since the thalidomide crisis, we reprint one of the very first reports in a medical journal to raise questions about possible teratogenic adverse effects of the drug.

The Annual Meeting of National Pharmacovigilance Centres was held this year in Uppsala, Sweden. This meeting celebrated 30 years of the Uppsala Monitoring Centre, 40 years of the WHO Programme for International Drug Monitoring and 60 years of WHO. The discussions from the Working Groups at this meeting are published under Feature. A short abstract of some of the safety issues reviewed by the eighteenth meeting of the Global Advisory Committee on Vaccine Safety is also included.

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Regulatory Matters

Safety of Medicines

Feature

Counterfeit medicines

Regulator tackles incident of fake Vicks Kingo

Tanzania. The Tanzania Food and Drugs Authority (TFDA) has released a statement about counterfeit cough medicine, Vicks Kingo, circulating in the market. The Agency is taking a tough line on the matter and has threatened legal action against traders.

TFDA described the counterfeit Vicks Kingo tablets as being white instead of cream coloured and said that they do not have the menthol smell of the genuine tablets. Anyone in possession of the counterfeit product is urged to return it to the suppliers and report to the nearest district or Regional Health Offices or to TFDA Zonal Offices. The statement said that "the TFDA is making a close follow-up through inspection to identify any counterfeit Vicks Kingo circulating in the market and persons proved to be dealing in supply or manufacture of the same shall be taken to court and in addition will be liable to any action for compensation if so filed by the subject".
The TFDA recently celebrated its fifth anniversary and its web site states that it aims to be Africa's best regulatory authority by 2015.

Reference:
TFDA Public announcement, 12 October 2008 (www.tfda.or.tz).

Efalizumab

Labelling changes to highlight risks of PML

USA. The United States Food and Drug Administration (US FDA) announced labelling changes, including a Boxed Warning, to highlight the risks of life-threatening infections, including progressive multifocal leukoencephalopathy, with the use of efalizumab (Raptiva).

The labelling changes are based on the US FDA's postmarketing surveillance. The Agency is also requiring the submission of a Risk Evaluation and Mitigation Strategy (REMS), which will include a Medication Guide for patients and a timetable for assessment of the REMS.
Efalizumab, approved in 2003, is a once-weekly injection approved for adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy to control their psoriasis. The drug works by suppressing the immune system to reduce psoriasis flare-ups, however by suppressing the body's immune system, it can also increase the risk of serious infections and malignancies.

Reference:
News Release, US FDA, 16 October 2008 (www.fda.gov).

Ephedrine and kava kava products

Warning against unauthorized use

Canada. Health Canada has advised consumers against using natural health products Life Choice ephedrine hydrochloride 30 mg capsules and Life Choice kava kava (kavain) 150 mg capsules. The advice came as the agency took steps to prevent these products, which have not been approved, from entering the Canadian market.

According to Health Canada, Life Choice ephedrine contains an excessive amount of ephedrine and, when taken alone or in combination with caffeine or other stimulants may lead to serious, potentially life-threatening adverse events. Furthermore, the Agency has found this product to be contaminated with bacteria, which could cause irreversible and serious adverse events, including death.

Health Canada says that kava kava-containing products have been linked to liver dysfunction. Kava kava is also associated with coordination disorders, muscle weakness and kava dermopathy (a peculiar scaly eruption on the skin).

Reference:
Media Release, Health Canada, 21 August 2008 (www.hc-sc.gc.ca).

Ergot-derived dopamine agonists

New warning on fibrosis

Europe. The European Medicines Agency (EMEA) has recommended revising the product information for ergot-derived dopamine agonists with new warnings and contraindications relating to the risk of fibrosis.

The Agency explained that although the development of fibrosis symptoms is a known adverse effect of ergot-derived dopamine agonists, new data have suggested that fibrosis may start long before the onset of symptoms. The EMEA affirmed that marketing authorizations should be maintained, but that new warnings and contraindications should be added to the relevant product information.

Ergot-derived dopamine agonists are a group of medicines that have been on the market for many years and are used to treat Parkinson's disease, either on their own or in combination with other medicines. They are also used to treat other conditions including hyperprolactinaemia, prolactinoma and to prevent lactation and migraine.

Reference:
Media Release, EMEA, 26 June 2008 (www.emea.europa.eu).

Erythropoiesis-stimulating agents

Labelling changes to clarify use / directions

USA. The US FDA has informed health-care professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the US FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the haemoglobin level at which treatment with an ESA should be initiated. Additional revisions to prescribing information that ESAs are not intended for use in patients receiving myelosuppressive therapy when the expected outcome is cure and when to initiate and discontinue ESA dosing will be forthcoming.
The US FDA approved epoetin-α in 1989 and darbepoetin-α in 2001 to treat anaemia associated with chronic renal failure. Since then the indications have been expanded to include anaemia that occurs in some types of cancers.

Reference:
Follow up to the 3 January 2008 communication, US FDA (www.fda.gov).

Ezetimibe / simvastatin

Association with increased cancer risk being investigated

USA. The US FDA is reviewing the safety of the anti-cholesterol drug combination ezetimibe/simvastatin (Vytorin), after receiving a report about a possible connection between the drug and an increased cancer risk.

Preliminary results from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial revealed that a larger percentage of ezetimibe/simvastatin (Vytorin) recipients were diagnosed with and died from cancer compared with placebo recipients, during the five year study. However, interim data from two other large ongoing trials - Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) - did not show increased cancer risk with simvastatin and ezetimibe combination.
The US FDA says that it will fully evaluate the SEAS trial data and other relevant information, and has advised patients not to stop taking ezetimibe/simvastatin (Vytorin) or any other cholesterol lowering drugs until further information is available.

Reference:
US FDA, August 2008 (www.fda.gov).

Illegal medicines

Erectile stimulant Powertabs "potentially dangerous"

Switzerland. Swissmedic has announced that the erectile stimulant Powertabs, which is being sold illegally in Switzerland, contains a potentially dangerous active substance. The Agency has therefore issued an urgent warning against taking this product.

Powertabs is advertised as being a natural, purely herbal erectile stimulant. Swissmedic has analysed samples of the product, and the results have revealed that the capsules contain an active substance related to sildenafil but which has not been investigated. (Sildenafil is the active ingredient in Viagra.)

Swissmedic has already seized stocks of Powertabs from illegal sources and instigated criminal proceedings. Anyone in possession of the product is advised to destroy them or to take them to a pharmacy for destruction.

Reference:
Swissmedic, 13 August 2008 (www.swissmedic.ch).

Malaysia ADR reporting

Record figures for 2007

Malaysia. The Malaysian National Centre for Adverse Drug Reactions Monitoring has released its collection figures for 2007. The Agency had received a total of 3068 local spontaneous reports of ADRs, an increase of 20.6 per cent over the previous year.

Disorders associated with skin and appendages were the most commonly reported ADRs. The highest number of suspected cases were attributed to anti-infectives (700), followed by cardiovascular drugs (400) and analgesics (300). Perindopril, with 97 cases, was at the top of drugs with most cases, followed by allopurinol (75), cloxacillin (71), diclofenac (71), metformin (69), aspirin (67), ticlopidine (50), rifampicin (46), phenytoin (44) and amoxicillin (43).

Pharmacists and dentists sent in 1283 reports representing over 40 per cent of the total, followed by government doctors (1075), companies (409), universities (240) and general practitioners/private specialists (61).

The reporting of ADRs in Malaysia has increased steadily over the past two decades. To encourage this trend, the authorities have released results by State and a list of the top ten best reporting hospitals.

Reference:
Reactions 1121:3, 19 July 2008 (www.adisoline.com).

Vigibase

WHO adverse events database tops four million mark

Worldwide. The WHO's Individual Case Safety Reports (ICSR) database, Vigibase, has now received over four million case reports, according to the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring. These reports represent the concerns of health professionals around the world about possible harm caused to their patients by medicines. Currently, the UMC receives > 250 000 reports annually.

Reference:
(http://www.who-umc.org).

Genomic biomarkers

US FDA releases list for predicting drug response

The US FDA has updated a table of genomic biomarkers with established roles in drug response. These genomic biomarkers can play an important role in identifying responders and nonresponders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. Currently, pharmacogenomic information is contained in about 10 per cent of labels for US FDA-approved drugs.

Reference:
(www.fda.gov).

Antiepileptics

Study suggests "small risks" of suicidal thoughts

UK. Any antiepileptic drug "may rarely be associated with a small increased risk of suicidal thoughts and behaviour" according to a recent Europe-wide review, published in the *Drug Safety Update* of UK's Medicines and Healthcare products Regulatory Agency (MHRA).

The review considered data from published literature, postmarketing surveillance, and a meta-analysis conducted by the US FDA, including placebo-controlled trials for 11 antiepileptic drugs among a total of 43 800 patients. An increased risk of suicidal thoughts and behaviour was found among those who received antiepileptic drugs (0.43 per cent of patients) versus those who received placebo (0.22 per cent). The increase was observed among all antiepileptic drugs studied and was evident as early as one week after starting treatment. On the basis of these findings, patients are advised to be alert to any mood changes, distressing thoughts or feelings about suicide or harming themselves during antiepileptic treatment. However, they

Ceftriaxone

Fatal reactions with calcium

Canada. The antibiotic ceftriaxone should not be mixed or co-administered with calcium-containing solutions. Health Canada issued the warning to hospitals after cases of fatal reactions in neonates and infants were reported. While in most cases there was simultaneous administration of the two drugs, the interaction has been reported where ceftriaxone and calcium-containing products were given at different times and using different infusion lines.
The Agency also advises that for patients aged less than 10 weeks, intravenous ceftriaxone and calcium-containing solutions should not be administered within five days of each other. In all other patients, intravenous ceftriaxone and calcium-containing solutions should not be administered within 48 hours of each other.

Reference:
Health Canada, 31 July 2008 (www.hc-sc.gc.ca).

Lenalidomide

Adverse events associated with lenalidomide use

thalidomide, which was launched in the UK in June 2008 for multiple myeloma. To date, there have been no reports involving *in utero* exposure to lenalidomide or thalidomide.

At the time of launch, lenalidomide was assumed to be a human teratogen due to its similarity to thalidomide, and both drugs are subject to risk-minimization measures including a Pregnancy Prevention Programme and dispensing restrictions. Recently, preliminary results from a study of embryofetal development in primates showed that the offspring of those receiving lenalidomide during pregnancy had developmental anomalies similar to those typically associated with thalidomide. Developmental anomalies were also seen among the offspring of control animals receiving thalidomide during pregnancy, but were not observed among the offspring of control animals that received no drugs. These early results "provide the strongest evidence to date that lenalidomide is teratogenic in primates," according to the MHRA.

Reference:
Reactions 1215:3, 16 August 2008 (www.adisonline.com).