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.

Quality Assurance and Safety: Medicines, EMP-HSS
World Health Organization,
1211 Geneva 27, Switzerland
E-mail address: pals@who.int

This Newsletter is also available on our Internet website:
http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring
Tel; +46-18-65.60.60
Fax: +46-18-65.60.80
E-mail: sten.olsson@who-umc.org
Internet: http://www.who-umc.org.

Contents

No 3, 2009

In addition to the usual sections (Regulatory Matters and Safety of Medicines) this issue includes the summary of recommendations from the sixth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) that was held earlier this year in Geneva.

The thirty-second Annual meeting of National Pharmacovigilance Centres will take place at Rabat, Morocco, 2-5 November 2009. Pre-meeting events will include a training workshop in the use of MedRA (Medical Dictionary for Regulatory Activities), a workshop on strategies for identifying and preventing medication errors, and a technical briefing on pharmacovigilance to all new members joining the WHO Programme for International Drug Monitoring. We hope to see many of you at this meeting.

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Regulatory Matters

Safety of Medicines

Feature

Botulinum toxins Type A and Type B

Warnings to be strengthened about distant spread of toxin effects

USA. The United States Food and Drug Administration (US FDA) has notified health-care professionals that after an ongoing safety review, the manufacturers of licensed botulinum toxin products (Botox, Botox Cosmetic, Myobloc) will be required by the Agency to strengthen warnings in the product labelling and add a boxed warning regarding the risk of adverse events when the effects of the toxin spread beyond the injection site. Botulinum toxin products have been approved for temporary improvement in the appearance of glabellar lines, treatment of strabismus, blepharospasm, cervical dystonia and primary axillary hyperhidrosis.

The US FDA will also require that manufacturers develop and implement a Risk Evaluation and Mitigation Strategy (REMS), including a communication plan to provide more information on the above mentioned risk, and to explain that botulinum toxin products cannot be interchanged. The REMS would also include a Medication Guide that explains the risks to patients, their families and caregivers.

In addition, the US FDA is requiring the manufacturers to submit safety data after multiple administrations of the product in a specified number of children and adults with spasticity to assess the signal of serious risk regarding the spread of toxin effects beyond the injection site.

In the Agency's review of postmarketing safety data,

- in the pediatric adverse event case reports, botulinum toxin products were mostly used to treat muscle spasticity in cerebral palsy, which has not been approved. The reported cases of spread of botulinum toxin effect beyond the site of injection were described as botulism or involved symptoms. Serious case reports described hospitalizations involving ventilatory support and reports of death;
- the majority of the adult case reports of distant spread of toxin effects occurred following use of botulinum toxin for the treatment of spasticity (an unapproved use) or cervical dystonia. Some cases resulted in hospitalization, including placement of a gastric tube or mechanical ventilation. Although there were several deaths in adults, it is not possible to attribute them to the botulinum toxin because the patients also suffered from complications due to their pre-existing conditions.

Reports in WHO Global ICSR database, Vigibase:
Botulinum toxin Type A
Number of reports: 752
Number of events:
Eyelid ptosis 203
Diplopia 60
Constipation 14
Dysphagia 249
Death 22
Botulism 32
Muscular weakness 185
Facial palsy 49
Speech disorder 48
Dyspnoea 133
Respiratory depression 4
Pneumonia aspiration 18

Botulinum toxin Type B
Number of reports: 79
Number of events:
Eyelid ptosis 8
Constipation 17
Dysphagia 43
Death 3
Botulism 1
Muscular weakness 6
Facial palsy 1
Speech disorder 4
Dyspnoea 10
Pneumonia aspiration 4

(See WHO Pharmaceuticals Newsletter No.2, 2009, No.1, 2009 and No. 2, 2008 for similar information issued in Australia, Canada and the USA, respectively).

Reference:
Follow-up to the early communication about an ongoing safety review, US FDA, 30 April 2009 (www.fda.gov).

Ceftriaxone

Updated recommendations concerning the interaction with calcium-containing products

USA. The US FDA has notified health-care professionals of an update to an earlier alert (September 2007) that addresses the interaction of ceftriaxone (broad-spectrum cephalosporin antibiotic marketed as Rocephin and generics) with calcium-containing products, based on previously reported fatal cases in neonates. The manufacturer of ceftriaxone conducted two *in*

vitro studies using neonatal and adult plasma to assess the potential for precipitation of ceftriaxone-calcium when ceftriaxone and calcium-containing products are mixed in vials and in infusion lines. Based on the results from these studies, the US FDA has recommended the following:

- Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates (28 days of age and under). Ceftriaxone should not be used in neonates (28 days of age and under) if they are receiving (or are expected to receive) calcium-containing intravenous products.
- In patients aged over 28 days, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.
- Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions via a Y-site in any age group.
- Ceftriaxone and calcium-containing products may be used concomitantly in patients aged over 28 days, using the precautionary steps above because the risk of precipitation is low in this population. The US FDA had previously recommended, but no longer recommends, that in all age groups, ceftriaxone and calcium-containing products should not be administered within 48 hours of one another.

(See WHO Pharmaceuticals Newsletter No. 4, 2007 for revisions to the prescribing information in the USA).

Reference:
Information for Healthcare Professionals, US FDA, 21 April 2009 (www.fda.gov).

Chromic Phosphate P32

Risk of acute lymphocytic leukaemia

Canada. Health-care professionals have been alerted about the risk of acute lymphocytic leukaemia associated with chromic phosphate P 32 (Phosphocol® P 32). This product is authorized for intracavitary instillation for the treatment of peritoneal or pleural effusions caused by metastatic disease.

According to Health Canada and the company, two children (9 and 14 years) with haemophilia developed acute lymphocytic leukaemia approximately 10 months after intra-articular injections of chromic phosphate P 32 (Phosphocol® P 32) (0.6 and 1.5 mCi total dose). The product is not indicated in the treatment of haemarthroses.

The Canadian Product Monograph will be updated to include the above warning as well as post-marketing reports of radiation injury (necrosis and fibrosis) to the small bowel, caecum and bladder following peritoneal administration of the product.

Reference:
Advisories, Warnings and Recalls, Health Canada, 30 March 2009 (www.hc-sc.gc.ca).

Cough and cold medicines

Advisory on use in children

Canada(1). Health Canada has advised the public that certain over-the-counter cough and cold medicines should not be used in children under 6 years of age, following a review of additional data. The Agency also says that cough and cold medicines marketed for use in children will require enhanced labelling and packaging and that it is working with manufacturers to revise the labelling of these products.

New Zealand(2). In December 2007, the Medicines Adverse Reactions Committee (MARC) reviewed the safety and efficacy of cough and cold medicines in children and recommended that these products should be contraindicated in children under two years of age, based on limited evidence for efficacy in this age group, an absence of evidence-based dosing, and evidence of significant toxicity in overdose. The product packaging will be amended to include the warning that these products must not be used in children under two years of age. The affected products are those containing bromhexine, brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, ipecacuanha, oxymetazoline, phenylephrine, pholcodine, promethazine, pseudoephedrine, triprolidine and xylometazoline. Medsafe and MARC are continuing to review the safety and efficacy of cough and cold medicines in children over two years of age.

(See WHO Pharmaceuticals Newsletters No.2, 2009 for advice on use of over-the-counter cough and cold medicines for children in Kenya and the UK).

References:
(1) Canadian Adverse Reaction Newsletter Volume 19, Issue 2, Health Canada, April 2009 (www.hc-sc.gc.ca).

(2) Prescriber Update Vol. 30, No.2, May 2009 (www.medsafe.govt.nz)

Dietary supplements

Warning about potential risks with Hydroxycut

USA. The US FDA has alerted the public and health-care professionals about dietary supplement products named Hydroxycut that are associated with serious liver injuries, and warned consumers not to take these products. They contain a variety of ingredients and have been marketed for weight-loss, as fat burners, as energy-enhancers, as low carbohydrate diet aids, and for water loss. The products have been recalled by the company.

The Agency has received 23 reports of serious health problems ranging from jaundice and elevated liver enzymes to liver damage requiring liver transplants.
One death due to liver failure has been reported. Other health problems reported include seizures, cardiovascular disorders, and rhabdomyolysis.

The US FDA continues to investigate the potential relationship between Hydroxycut dietary supplements and liver toxicity or other adverse events.

Reference:
Media release, US FDA, 1 May 2009 (www.fda.gov).

Erlotinib

New safety information on cases of gastrointestinal perforation, Stevens-Johnson syndrome and corneal perforation

Canada and USA. Health-care professionals have been notified of new safety information regarding the use of erlotinib (Tarceva). The product is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor. Erlotinib (Tarceva) monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

The information comes from routine pharmacovigilance activities involving clinical trials, spontaneous reports and literature. Cases of gastrointestinal perforation (including fatalities), cases of bullous, blistering and exfoliative skin conditions suggestive of Stevens-Johnson syndrome and Toxic epidermal necrolysis, which in some cases were fatal, and cases of corneal perforation or ulceration have been reported in patients treated with the product. Prescribers have been advised that treatment with erlotinib should be interrupted or discontinued in patients developing any of these adverse reactions.

The Canadian Product Monograph is being reviewed by Health Canada in conjunction with the manufacturer regarding the above mentioned safety concerns and will be updated accordingly. The US prescribing information has been changed to include the new information in the WARNINGS AND PRECAUTIONS sections.

References:
(1) Advisories, Warnings and Recalls, Health Canada, 11 May 2009 (www.hc-sc.gc.ca).
(2) Media release, US FDA, 8 May 2009 (www.fda.gov).

Etanercept

Risk of histoplasmosis and other invasive fungal infections

Canada. Health-care professionals have been alerted about the risk of invasive fungal infections in patients taking etanercept (Enbrel). The product is a soluble form of a fully human tumour necrosis factor (TNF) receptor protein authorized for the treatment of rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and plaque psoriasis. The Boxed Warning and Warnings and Precautions (Infections) sections of the Canadian Product Monograph have been revised to include information regarding the risk of invasive fungal infection, including histoplasmosis.

According to Health Canada and the company, there have been reports of serious pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis infections, sometimes with fatal outcomes, in patients taking tumour necrosis factor-α blockers (TNF blockers), including etanercept (Enbrel). For a patient taking a TNF blocker who presents with signs and symptoms of systemic illness, such as fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, health-care professionals have been advised to ascertain if the patient has lived or worked in or traveled to areas of endemic mycoses. If so, appropriate empiric antifungal treatment may be initiated while a diagnostic workup is being performed. The TNF blocker

should be stopped until the infection has been diagnosed and adequately treated.

Reports in WHO Global ICSR database, Vigibase: Etanercept
Fungal infectious disorders: 507
Most reported reactions:
Candidiasis 44
Oral candidiasis 52
Vulvovaginal candidiasis 35
Coccidioidomycosis 23
Fungal infection 202
Fungal skin infection 13
Onychomycosis 11
Vulvovaginal mycotic infection 32
Acute pulmonary histoplasmosis 12
Pneumocystis jiroveci pneumonia 11

(See WHO Pharmaceuticals Newsletter No.3, 2008 and No.6, 2004 for risk of infections in children in the USA and for reports of infections in Canada, respectively).

Reference:
Advisories, Warnings and Recalls, Health Canada, 23 April 2009 (www.hc-sc.gc.ca).

Hydroxyzine hydrochloride

Alert on skin necrosis and ulcer

Japan. The Ministry of Health, Labour and Welfare (MHLW), Japan has alerted health-care

of skin necrosis and ulcer at the injection site that required necrectomy or skin graft were identified.

Following an expert review, MHLW requested relevant companies to revise package inserts of hydroxyzine hydrochloride. The revision includes adding a description of injection site skin necrosis/ulcer in the "clinically significant adverse reactions" section, and in the "important precautions" section, the instruction to apply gentle pressure to the injection site and not knead strongly after intramuscular injection.

Reference:
Pharmaceuticals and Medical Devices Safety Information No.256, MHLW, March 2009 (www.pmda.go.jp/english/).

Salicylate containing oral gels

New advice on use in children

UK(1). The Medicines and Healthcare products Regulatory Agency (MHRA) has sent a letter to health-care professionals, stating that the Commission on Human Medicines (CHM) has recommended that topical oral pain relief products containing salicylate salts should be

syndrome and were more likely to reflect salicylate toxicity, but nevertheless, substantial systemic levels of salicylate were achievable after overuse of salicylate-containing dental gels. Up to April 2009, the Agency has received three suspected serious adverse drug reaction reports in association with the use of topical oral gels in children containing choline salicylate. In all cases, Reye's syndrome was suspected but in none of the cases was Reye's syndrome confirmed. The CHM concluded that these products should be contraindicated in children and young people under the age of 16 years in line with other oral salicylate-containing preparations, as a precautionary measure to remove the theoretical risk of Reye's syndrome if these products are overused.

Ireland(2). After the announcement of the restriction of use of salicylate-containing products for oral use in children in the UK, the Irish Medicines Board (IMB) has issued an Advisory, stating that following its own review, the Board has concluded that the risk-benefit for the use of salicylate-containing products in children is positive when used according to their approved conditions of use. The Board has advised parents and care-givers that oral gels containing choline salicylate should be applied