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ADVERSE REACTION NEWSLETTER 1999:4

NATIONAL DRUG MONITORING CENTRES -
DRUG SAFETY ISSUES

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NATIONALLY CIRCULATED INFORMATION

Canada

Canadian Adverse Drug Reaction Newsletter Vol 9, No 4,
October 1999

Serious haematologic reactions associated with ticlopidine

Ticlopidine hydrochloride is a thienopyridine derivative that inhibits platelet aggregation irreversibly by inhibiting adenosine-diphosphate-induced platelet-fibrinogen binding. It was first approved for sale in Canada in 1991 and is indicated for the "reduction of the risk of first or recurrent stroke for patients who have experienced at least one of the following events: complete thromboembolic stroke, minor stroke, reversible ischaemic neurological deficit, or transient ischaemic attack including transient monocular blindness." Other uses not listed in the product monograph are to reduce the risk of myocardial infarction in patients with unstable angina, to improve patency in vein bypass grafts used to treat peripheral vascular disease, to treat intermittent claudication and, in combination with ASA, to prevent thrombus formation after coronary artery stenting.

Ticlopidine has been associated with serious or fatal adverse drug reactions including thrombotic thrombocytopenic purpura (TTP), thrombocytopenia, bone marrow aplasia, anaemia, pancytopenia, agranulocytosis and neutropenia. Recent reports have drawn attention to the increased risk of TTP associated with the use of ticlopidine after coronary artery stenting. A recent retrospective study involving 43 322 patients who underwent stenting revealed 1 case of TTP per 4814 patients (0.02%).

Between July 1991 and June 1999 the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 464 reports of adverse reactions associated with the use of ticlopidine. Of these, 138 concerned adverse reactions of a haematologic nature (Table 1).

The CADRMP also looked at reports in which ticlopidine had been used in patients who had undergone coronary angioplasty alone or with stent insertion (Table 2). Thirteen of the 32 reports found were of platelet, bleeding or clotting disorders, and 4 were of granulocytopenia or agranulocytosis, for a total of 17 reports of serious or fatal haematologic reactions.

The number of serious and fatal adverse reactions evident from the CADRMP reports is consistent with what is known about the risks associated with ticlopidine. Haematologic monitoring of the leukocyte count along with a differential and a platelet count is recommended at baseline and every 2 weeks until the end of therapy. If therapy has been discontinued, an additional complete blood count with differential should be done 2 weeks after the discontinuation of therapy because of the long half-life of ticlopidine (terminal elimination half-life 4-5 days). However, haematologic reactions have been reported to occur within 1 week of beginning ticlopidine therapy and up to 19 days after the completion of therapy. Steinhubl and associates have questioned whether routine monitoring of blood counts is likely to "unmask TTP prior to clinical presentation." It is therefore recommended that patients be counselled about early warning signs of haematologic problems including signs of infection, bleeding or neurologic deficit.

Table 1: Haematologic adverse reactions associated with ticlopidine use reported to the CADRMP between July 1991 and June 1999

Adverse reaction	No. of reports* (and no. of deaths)
Granulocytopenia, leukopenia or agranulocytosis	72 (3)
Pancytopenia (or pancytopenic picture†)	15 (6)
Thrombotic thrombocytopenic purpura	7
Disseminated intravascular coagulation	1 (1)
Thrombocytopenic purpura	1
Thrombocytopenia	12 (2)
Thrombocytopenia with granulocytopenia	5
Thrombocytopenia with anaemia	3
Granulocytopenia with anaemia	5
Anaemia	6
Bleeding with or without anaemia	9 (3)‡
Lymphopenia	2
Total	138 (15)

*Each report is included in only one adverse reaction category.

†Thrombocytopenia, granulocytopenia/leukopenia and anaemia.

‡One death was unrelated to drug administration; another was associated with hepatorenal syndrome and hepatic necrosis.

Table 2: Summary of adverse reactions in patients receiving ticlopidine who had undergone either coronary angioplasty or coronary angioplasty with stent insertion.

Procedure; no. of reports

Adverse reaction	Angioplasty with stent insertion	Angioplasty	Total
Thrombotic thrombocytopenic purpura		2	3
Thrombocytopenia	1	7	8
Hemorrhage		2	2
Granulocytopenia	1	2	3
Agranulocytosis		1	1
Other*	6	9	15
Total	9	23	32

*Includes reports that do not contain haematologic reactions.

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Ropinirole (Requip™): sleep disorder

Sudden sleep attack associated with ropinirole use, a non-ergoline dopamine agonist indicated in the treatment of Parkinson's disease, was reported to the CADRMP.

Chile

Boletín Informativo sobre Medicamentos Vol 16, No 1, April 1999

Gastric haemorrhage associated with short-term treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in children

The prescription of NSAIDs for treatment of fever in children with acute respiratory tract infection is increasing in Chile in the last years. NSAIDs are used alone or in combination with antibiotics or nasal decongestants.

There are several reports of adverse reactions associated with NSAIDs, mainly mild cutaneous or digestive disorders. However, between May 1997 and March 1998, six children were admitted in the Pediatric Intensive Care Unit of "Clinica Davila" (a private hospital). The age of the children ranged between 3 and 9 years and the sex distribution was 1:1. At admission all had febrile respiratory tract infections of 3 or 4 days duration. Four children received oral ibuprofen 10 mg/kg three or four times daily (range 2-4 days). One patient was treated with naproxen 10 mg/kg twice daily for two days, and the other patient received aspirin in therapeutic dosage for two days. Three children had concurrent use of other drugs: 1 erythromycin, 1 clarithromycin and one received diclofenac one rectal dose.

All of the six children were admitted to the Emergency Department for gastric bleeding, four with tachycardia and pallor and three with severe abdominal pain. No one had hypotension. Their initial hematocrit ranged between 29 and 38%, and one child required blood transfusion.

Endoscopy showed erosive gastritis in all of the six patients without other lesions, except two children with oesofagitis also.

Denmark

Ugeskr Laeger 1999; 161:6650-2

Nitrofurantoin - hepatic injury

Forty-four cases of nitrofurantoin-associated hepatic injury were reported to the Danish Centre for Monitoring of Adverse Drug reactions from 1968 to 1998.

Forty-one were women with a median age of 69 years.

They had been treated with nitrofurantoin for a median of one year (two days - seven years), and all had biochemical and clinical signs of hepatitis. In five cases the injury had been provoked by a rechallenge.

Twenty-seven liver biopsies showed an equal amount of acute

and chronic histopathological changes. Cirrhosis was diagnosed in seven cases. Four died in liver failure; the others apparently recovered without long-term symptoms. In rare cases, nitrofurantoin can cause toxic hepatitis.

Finland

Tabu, Vol 7, No 4, 1999

Adverse reactions of serotonergic antimigraine drugs

The ADR Register of the National Agency for Medicines has until now received a total of 32 reports on suspected adverse reactions associated with selective 5HT₁ agonists. 29 of them have been reported in patients using sumatriptan (female 23, male 6; age 15-55 years) and 3 using zolmitriptan (female 2, male 1; age 16-49). In two cases the patient had taken another drug concomitantly (moclobemide, naproxen). The adverse reaction was considered as serious in ten cases associated with sumatriptan. The serious adverse reactions were mainly cardiac and circulatory symptoms.

The most common ADRs associated with the use of sumatriptan have been symptoms related to the nervous cardiac and circulatory system. There have been three reports of various ischaemic attacks, and two reports of both atrial fibrillation and shortness of breath. There is a great variety of neurological symptoms associated with the use of sumatriptan, many of them can be attributed to migraine.

Adverse effects associated with the use of zolmitriptan include dysaesthesia, conjunctivitis, joint pain, increase in weight, confusion, sleeplessness, nightmares, rise in liver enzymes and anaemia.

Adverse reactions of oral antidiabetics

Twenty-four cases of adverse drug reactions (ADR) involving glibenclamide have been reported to the ADR register of the National Agency for Medicines. In three of the cases, metformin was taken concomitantly.

Inappropriate antidiuretic hormone secretion, leukocytopenia and thrombocytopenia, cholestatic hepatitis and hypoglycemia have been reported in users of glipizide, a single case of each kind.

Seven cases of ADRs related to the new sulfonylurea compound, glimepiride, have been reported, including four cases of dermal reactions, two of hypoglycaemia, and one of gastric symptoms. One itching dermal reaction, which recurred when the patient was re-exposed to the drug, has been attributable to repaglinide, a drug that differs structurally from sulfonylureas, but has a similar mechanism of action.

The use of acarbose, an alpha-glucosidase agonist, is suspected

of causing hepatic damage and eczema (one case of each).

Thirty cases of ADRs associated with the use of metformin have been reported to the ADR register. The majority of these cases (17) concerned lactic acidosis in elderly patients (average age 73 years). In one case only were gastric symptoms (dyspepsia, stomach pain) typical of metformin, predominant. The other adverse reactions associated with the drug include diabetic coma (4 cases), thrombocytopenia (3 cases), pruritus (2 cases), bullous lesion (1 case), acidosis (1 case), and ketosis (1 case). In two cases, the thrombocytopenia and in one case of hepatic dysfunction, the patients were also using glibenclamide.

India

National Pharmacovigilance Centre Newsletter Vol 1, No 1, December 1999

Nimesulide and hepatic reactions

Nimesulide is a non-steroidal anti-inflammatory drug whose mechanism of action is characterized by selective inhibition of cyclooxygenase-2. Selective COX-2 inhibitors are believed to have decreased incidence of gastrointestinal side effects that are so commonly observed with non selective COX inhibitors. However, the number of adverse reports associated with nimesulide usage are on the rise of late. The potential for hepatic adverse events following exposure to nimesulide is an ongoing concern. Serious hepatic adverse events and fatalities have been reported. A report revealed that two hepatic failures proved to be fatal following nimesulide usage. In addition, nimesulide, when combined with amoxicillin and clavulanate, potentiates the hepatic dysfunction induced by any of these drugs. The drug is contraindicated in patients with hepatic failure and gastrointestinal bleeding.

Atypical antipsychotics - an Indian experience

Atypical antipsychotic drugs are gaining wide acceptance because of their favourable toxicity profile.

Since the time that intensive monitoring of ADR has been initiated at the National Pharmacovigilance Centre at the Department of Pharmacology of the All India Institute of Medical Science, the centre has periodically received reports of adverse drug reactions with atypical antipsychotics from the wards of the psychiatry department. Till date reports of 15 adverse drug reactions attributed to the usage of these drugs have been received. Agranulocytosis was observed with clozapine usage in 2 patients. The other side effects observed with clozapine were constipation in 1 patient, extrapyramidal

symptoms in 3 patients, and sialorrhea in 1 patient. Similarly involuntary movements of hands were observed in 1 patient and extrapyramidal symptoms were seen in 5 patients being treated with risperidone.

Report in WHO-file: Clozapine: Agranulocytosis 1344, extrapyramidal disorder 84. Risperidone: Agranulocytosis 7, extrapyramidal disorder 353

Malaysia

Berita Ubat-ubatan 15 (2), 1999

Propylthiouracil - Neutropenia

A 36 year old man with a history of hyperthyroidism was prescribed propylthiouracil after he developed neutropenia secondary to carbimazole treatment. Approximately three and a half months after therapy, the patient presented with symptoms of infection and was found to have repeatedly low white blood cell count.

Propylthiouracil was stopped and the patient subsequently recovered after receiving a course of therapy with a granulocyte stimulating factor.

Agranulocytosis is potentially the most serious adverse effect associated with the use of propylthiouracil and usually occurs within two months of therapy but rarely may occur after four months of therapy.

Warfarin - Topical salicylate interaction

A 71 year old man was admitted to hospital with a complaint of spontaneous bleeding gums and melanic stools. He had a history of a recent fall which resulted in pain over the right hip. The patient was on amlodipine, frusemide, trimetazidine for treatment of congestive cardiac failure and amiodarone and warfarin for atrial fibrillation. The patient admitted to self medicating himself with a topical salicylate liniment used as a massage for approximately a week prior to admission to ease the pain experienced over the hip.

There is potential interaction between warfarin and topical salicylates.

New Zealand

<http://www.medsafe.govt.nz/Profs/Safety/selegiline.htm>

Web site: November 1999

Selegiline in Parkinson's Disease

Selegiline delays the need for levodopa therapy, probably by a mild symptomatic benefit. There is no compelling evidence that selegiline is neuroprotective. The available evidence indicates that the delay of levodopa therapy does not postpone the onset of levodopa-related motor fluctuations and, therefore, the effect

may not confer a long-term benefit.

Selegiline may smooth motor fluctuations in more advanced Parkinson's disease.

The Parkinson's Disease Research Group (PDRG) data suggests, but does not prove, that selegiline may increase mortality in patients with dementia or falls.

Web site: 16 November 1999

Viramune (nevirapine)/ Methadone Interaction

Viramune, as well as other antiretroviral agents, is a known inducer of cytochrome P450 enzymes including CYP3A4 and CYP2B6. The potential therefore exists to reduce plasma levels of other drugs similarly metabolised, including methadone which is extensively metabolised by cytochrome CYP3A4 in human liver microsomes (Chem Res Toxicology 1996;9:365-73).

Based on the known metabolism of methadone, Viramune may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Clinical reports have been received that suggest patients who are taking methadone may experience narcotic withdrawal symptoms when they begin Viramune therapy. Therefore, the dose of methadone may need to be increased based on the emergence of withdrawal symptoms in some patients who begin Viramune therapy. Methadone-maintained patients beginning Viramune should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Web site: November 1999

Cisapride and Arrhythmias

Cisapride (Prepulsid) causes QT-prolongation which may worsen to life-threatening torsade de pointes. The WHO database holds 159 reports of these events. Many patients were taking interacting medicines, most commonly erythromycin, fluconazole, clarithromycin and amiodarone. Excessive dose and electrolyte disturbances also featured in the cases.

Cisapride should be avoided with substances which inhibit cytochrome P450 3A4, with other agents which prolong the QT-interval, in patients with predisposing factors for arrhythmia or pre-existing QT-prolongation and in patients with hepatic failure.

Web site: October 1999

Vigabatrin and Visual Field Defects

The antiepileptic medicine vigabatrin (Sabril) causes visual field constriction in around 30% of users. Most cases are asymptomatic because vigabatrin affects the peripheral fields but does not impair central visual acuity. The effects appear to

be irreversible, or incompletely reversible, in all cases after discontinuation of vigabatrin. Patients using vigabatrin who have a developmental age of > 10 years should have baseline threshold visual field testing and follow-up at 6-monthly intervals. Visual field testing is not usually possible before a developmental age of 12 years, but in some centres a method which has not been validated for defects caused by vigabatrin and which is based on visual evoked potentials is available for younger children. Patients should be instructed to report any new problems with vision such as blurring, double vision and signs of peripheral vision impairment.

Vigabatrin is indicated for epilepsy which is not adequately controlled by other agents. Use should occur only after a careful risk-benefit assessment, including a comparison of the risks and benefits of alternative agents. Each patient currently using vigabatrin should be reviewed to ascertain whether the risk-benefit assessment supports continued use of this medication.

The abstract of **Salmeterol and eformoterol** from New Zealand was incorrectly attributed to Ireland in the previous newsletter, which we apologise for.

Sweden

http://www.mpa.se/biverkningar/nn_bivindex.html

Web site: December 1999

Sudden onset of sleep with dopamine agonists

Sifrol, (pramipexole), and Requip, (ropinirole), are two dopamine agonists used in Parkinsons disease. During the summer of 1999, sudden onset of sleep was reported with pramipexole. The manufacturer, Boehringer Ingelheim, made a change of the labelling. Similar cases have now been reported with Requip. Internationally there are 17 reported cases of sudden onset of sleep with Requip. The patients fell asleep without any preceding warning signals. Seven of the cases occurred during driving.

At the time of approval of these drugs, fatigue and grogginess, were known adverse effects but not sudden onset of sleep. The recommendation is that all patients taking Requip or Sifrol should avoid activities that call for sharpened attention.

Information from the MPA, Vol 10, No 6, Nov. 1999

ACE-inhibitors and angiotensin II-antagonists may cause anaemia

The MPA has done a review of ACE-inhibitors and angiotensin II-antagonists causing anaemia. In Sweden there are 6 cases reported. The conclusion of the review is to recommend closer

monitoring of haemoglobin levels, especially in patients with renal impairment.

Information from the MPA, Vol 10, No7 November 1999

Hyaluronic acid - effects on joints

In Sweden, there are two products containing hyaluronic acid; Synvisc and Artzal. These two products differ in the mean molecule weight, concentration and number of recommended doses. Furthermore, there are some differences in the manufacturing process. In Sweden there are 103 reported cases of hyaluronic acid in association with arthritis, joint swelling, arthralgia and synovitis. The MPA has started to investigate effects on joints after treatment with hyaluronic acid. Focussing on whether the adverse effects may be due to problems with quality and/or handling of the product.

Vigimed discussion 1st December 1999

Drug interactions with Hypericum perforatum

Extracts of S:t John's Wort (*Hypericum perforatum*) are an ingredient of natural remedies sold freely in Sweden. These products are traditionally used in the treatment of slight mood lowering, minor nervous tension and temporary insomnia.

Since 1998 the MPA has received 7 reports on decreased warfarin effect in association with concomitant use of S:t John's Wort. More recently, knowledge has been gained through more reports, including company reports, published literature and information from other regulatory agencies, on decreased effect of a number of drugs. In summary, the reported cases of interactions with warfarin, cyclosporin, theophylline (decreased effects) and oral contraceptives (break-through bleedings) together with the pharmacokinetic data (decreased levels) with hydroxycortisol, dextromethorphan, amitriptyline, nortriptyline, phenprocoumon and digoxin provide strong signals that S:t John's Wort is an inducer of a broad range of drug metabolising enzymes. In addition, interactions between S:t John's Wort and antidepressants of suspected

pharmacodynamic origin, have been reported in the literature. The clinical symptoms of the patients suggest a serotonin syndrome. Measures taken: The MPA has contacted the companies and requested studies on extent and implications of the interaction problem. While waiting for the results from the requested studies (within about 6 months), the companies are requested to declare on the package that S:t John's Wort products should not be used concomitantly with any medicinal product. A press release was issued in Sweden on November 29, 1999.

United Kingdom

Vigimed document, October 27, 1999

Quixil human surgical sealant- neurotoxic reactions

Quixil, is a human plasma derived fibrin sealant kit product, licensed for facilitating haemostasis and reducing bleeding during liver surgery. It contains human clottable protein and thrombin and a number of excipients, including glycine, arginine and tranexamic acid. The product is authorised only in the UK, Israel, Brazil and Mexico.

Since this product was licensed in the UK in September 1999, there were two reports of fatal neurotoxic reactions associated with its unlicensed use in neurosurgical procedures.

An urgent message to inform relevant health professionals is as follows: "Quixil should not be used in surgical operations where contact with the CSF or dura mater would occur, such as neurosurgery and spinal surgery."

EMEA (European Medicines Evaluation Agency)

London, 19 July 1999

Public statement on pramipexol - sudden onset of sleep

The European Commission granted marketing authorisations for the European Union to Boehringer Ingelheim International GmbH on 14 October 1997 for Sifrol, to Dr. Karl Thomae GmbH on 27 October 1997 for Daquiran and to Pharmacia & Upjohn S.A. on 23 February 1998 for Mirapexin. Pramipexole containing medicinal products were first launched in the European Union in June 1998 and are currently marketed as Mirapexin in Greece, Italy, Spain and United Kingdom and as Sifrol in Denmark, Finland, Germany, the Netherlands and Sweden. Daquiran has not yet been launched in the European Union.

Pramipexole is one of the current available dopaminergic agonists authorised in the European Union for the treatment of signs and symptoms of advanced idiopathic Parkinson's disease in combination with levodopa. Pramipexole is available as 0.088mg, 0.18 mg, 0.7 mg and 1.1 mg tablets.

Sudden onset of sleep has been rarely reported and occur at any time during treatment and without awareness of warning signs. Patients being treated with pramipexole should be strongly advised not to drive or engage in other activities where impaired alertness could put themselves or others at risk of serious injury or death (e.g. operating machines).

London, 22 October 1999

Leflunomide - reports of pancytopenia and serious skin reactions

The European Commission granted marketing authorisations for the European Union to Hoechst Marion Roussel Deutschland GmbH on 2 September 1999 for the medicinal product Arava, which contains the active substance leflunomide. Arava is not yet marketed in the European Union.

Arava is indicated for the treatment of adult patients with active rheumatoid arthritis as a disease-modifying antirheumatic drug (DMARD). The European Medicines Evaluation Agency's (EMA) wishes to draw attention to the following:

1. Recent treatment with hepatotoxic or haematotoxic DMARDs may result in increased side-effects. Therefore, the balance of risks and benefits has to be carefully considered before treatment with leflunomide is initiated.
2. Since the active metabolite of leflunomide is slowly eliminated from the organism, serious undesirable effects might occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions) even if the treatment with leflunomide has been stopped. Therefore, when such toxicity occurs or when switching to another DMARD after treatment with leflunomide or in case of desired pregnancy, a washout procedure should be performed.
3. Considering that the risk associated with combination therapy, in particular in long-term treatment, is unknown and since such therapy can lead to additive or even synergistic toxicity, combination of leflunomide with another DMARD (e.g. methotrexate) is not advisable.
4. Patients who experience symptoms such as paleness, tiredness, increased proneness to infections, bruising, skin rash or mucous membrane lesions (esp. in the mouth) should contact their doctor immediately.
5. In case of a desired pregnancy, patients wishing to become pregnant or father children should inform their doctor beforehand.

Zimbabwe

Drug Information Bulletin Vol 3, No 3, Sept 1999

Aspirin and Reye's syndrome

Aspirin has been widely used to reduce inflammation, fever and mild to moderate pain for more than a century.

A rare, but potentially fatal adverse effect of aspirin called Reye's syndrome, that occurs exclusively in children, is less known.

Reye's syndrome is an acute illness, characterised by acute non-inflammatory encephalopathy and deterioration of liver function. The same symptoms may occur in some inborn metabolic disorders and Reye's syndrome can only be distinguished from these hereditary disorders by electron microscopic examination of liver biopsy tissue. Acute encephalopathy without reasonable explanation for cerebral abnormalities together with liver dysfunction manifested by elevated ammonia or liver-enzyme concentrations became the clinical definition of Reye's syndrome.

Depending on the severity of the symptoms the outcome of Reye's syndrome can range from complete recovery through mild to severe permanent neurological damage to death. Epidemiological studies showed that about 30% of children who presents with Reye's syndrome die or suffer from long-term neurological complications. Mortality is significantly increased in children of less than five years of age, by presence of diarrhoea during antecedent viral illness, by black race, by serum ammonia levels above 26 $\mu\text{mol/L}$ and serum glucose levels below 3.3 mmol/L .

The most widely available non-steroidal analgesic and anti-inflammatory agent in Zimbabwe is aspirin. It is available in pharmacies and food stores, supermarkets, etc. the other alternative minor analgesic-antipyretic agent, paracetamol products are restricted to sale within pharmacies.

There is no data available on incidence of Reye's syndrome in Zimbabwe. However, considering the strong evidence from international studies, Reye's syndrome undoubtedly occurs in children in Zimbabwe, even though it is not diagnosed as such or associated with aspirin use.

REGULATORY DECISIONS

Portugal

Clobenzorex and fenproporex suspension

The Portuguese Medicines Evaluation Committee has recommended to the Board of INFARMED the suspension of the marketing authorisations of all medicinal products containing the anti-obesity products clobenzorex (Dinintel) and fenproporex (Pesex-R, Drenur and Tegiseq), considering the unfavourable benefit-risk assessment referred in the final opinion of the CPMP dated from 31st August.

On the 8th September, the Board of INFARMED has decided to suspend the above mentioned marketing authorizations within 30 days.

Spain

New batches of Endobulin

From the 2nd November 1999, Baxter is allowed to resume release of new batches of endobulin (Immuno Globulin Intravenous; MAH; Baxter-Immuno) in Spain.

Batches that were on the Spanish market on 28th July 1999, when two cases of hepatitis-C 3a were detected, will remain on hold as a precautionary measure until the investigations are completed and the source has been identified.

The Spanish Medicines Agency (AGEMED) continues with an in-depth investigation of the potential sources of infection of the two patients (either the medicinal product or a nosocomial infection).

DRUG WITHDRAWALS

India

National Pharmacovigilance Centre Newsletter Vol 1, No 1, December 1999

Live oral, Tetravalent rotavirus vaccine - withdrawn

On October 18, 1999, the rotavirus vaccine was withdrawn from the Indian market. The vaccine was reported to cause acute small bowel obstruction. Rotavirus vaccine was approved for the prevention of gastroenteritis in infants. The vaccine, after reconstitution, contained four live viruses, a rhesus rotavirus (serotype3) and three rhesus human reassortant viruses (serotype 1, 2 and 4). The first dose was recommended at the age of 6 weeks. At the time of approval, adverse effects mentioned were fever, decreased appetite, and irritability and decreased activity.

The vaccine was approved in 1998.

United Kingdom

27 October 1999

Glaxo Wellcome voluntarily withdraws Raxar (grepafloxacin)

Glaxo Wellcome plc announces that it is voluntarily withdrawing its oral fluoroquinolone antibiotic, Raxar (grepafloxacin), with immediate effect, as a result of emerging safety concerns. In coming to this decision the company has recognised the need to strike a balance between the therapeutic benefits of the medicine, the potential risk of side effects, and the availability of alternative treatments.

Glaxo Wellcome has monitored the safety profile of

grepafloxacin since its launch 1997, and has observed a small number of severe cardiovascular events among patients.

Raxar is indicated for the treatment of a variety of infections including pneumonia, bronchitis, and some sexually transmitted infections. Glaxo Wellcome licensed Raxar from Otsuka in 1996, and currently markets the medicine in tablet form in over 30 countries, primarily in Europe, North America and Latin America. A co-marketing agreement exists between the two companies in Spain. The medicine is marketed as Raxar or Vaxar.

USA

October 14, 1999

Rotavirus Vaccine (RotaShield)- withdrawn

Wyeth Lederle, USA. The manufacturer of the RotaShield Rotavirus Vaccine (Live, Oral, Tetravalent), Wyeth-Lederle Vaccines, has sent a letter to healthcare providers announcing its decision to withdraw the vaccine.

On July 16, 1999, the company temporarily suspended further distribution and administration of RotaShield until more data on the potential association between vaccine administration and intussusception became available. That action was taken in consultation with the Food and Drug Administration (FDA) following a recommendation from the Centers for Disease Control and Prevention (CDC) to postpone administration because of reports to the Vaccine Adverse Events Reporting System (VAERS) of a possible association between the use of RotaShield and the development of intussusception.