EDITORIAL

In addition to the usual updates on recent drug safety and regulatory information for medicines, this issue of the newsletter features an article summarizing the decisions regarding the use of Selective Serotonin Reuptake Inhibitor (SSRI) -antidepressants in children. Most of these products appear to have a negative benefit-risk balance when used in treating major depressive disorder (MDD) in children.

HIV/AIDS was one of the key health issues that figured in the discussions of the recently concluded Fifty-seventh World Health Assembly (WHA) in Geneva. Through Resolution WHA57.14 on HIV/AIDS (http://www.who.int/gb), the WHA requested the Director-General to strengthen the WHO prequalification project managed by the World Health Organization (WHO) for pharmaceutical and diagnostic products to diagnose, treat and manage HIV/AIDS and urged Member States to make best use of WHO's list of prequalified antiretroviral drugs that meet international quality standards (see http://mednet3.who.int/prequal for key facts on the WHO prequalification project).

With the global focus on treating HIV, and consistent with WHO's 3 by 5 initiative to provide treatment to three million HIV patients by the year 2005, it is timely that a training course will be held in September 2004 in South Africa to encourage the integration of pharmacovigilance for antiretrovirals in some sub-Saharan African countries. Details of this course as well as the complete course material will be made available on the website of the Department of Essential Drugs and Medicines Policy (EDM) http://www.who.int/medicines at a later date, after the course.
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ARIPIPRAZOLE, CLOZAPINE, QUETIAPINE AND OTHER ATYPICAL ANTI-PSYCHOTICS

Label to indicate risk of hyperglycaemia and diabetes

USA. The United States Food and Drug Administration (US FDA) has requested that Bristol-Myers Squibb Company, the manufacturer of the atypical antipsychotic drug aripiprazole (Abilify) should update the prescribing information for the drug to reflect the risk of hyperglycaemia and diabetes in patients treated with this drug. More recently, Novartis, under advice from the US FDA has also made similar changes to the prescribing information for clozapine (Clozaril) antipsychotic tablets. The US FDA has recommended these revisions after reviewing data related to the use of atypical antipsychotics and hyperglycaemia with its related symptoms (e.g., polydipsia, polyuria, polyphagia and weakness). The FDA has concluded that all atypical antipsychotics should be updated to include information about the potential for these adverse events. Patients with risk factors for diabetes should undergo baseline screening before treatment with any atypical antipsychotic drug and routine monitoring should be undertaken throughout therapy to mitigate the risk of patients developing serious metabolic complications. In January 2004 AstraZeneca Pharmaceuticals LP, manufacturer of atypical antipsychotic agent quetiapine fumarate (Seroquel), had warned health professionals that patients should be monitored for glucose control before starting treatment with atypical antipsychotics. More recently, in April 2004, the company has issued an additional letter that besides pre-treatment monitoring, patients should also be monitored periodically for worsening of glucose control throughout treatment.

References:

MUROMONAB-CD3

Serious adverse reactions in paediatric patients

Canada. Janssen-Ortho Inc., under advice from Health Canada is warning health professionals that muromonab-CD3 (ORTHOCLONE OKT*3) is not approved for paediatric use (age up to 17 years) in Canada. Muromonab-CD3 is a murine monoclonal antibody indicated for the treatment of acute renal, cardiac, and hepatic allograft rejection refractory to conventional anti-rejection therapy or when conventional therapy is contraindicated in adult patients. Paediatric patients treated with this product may be at an increased risk of developing serious neurological complications, most notably cerebral oedema and herniation; nine cases of cerebral oedema have been reported worldwide since 1986, with six deaths due to cerebral herniation. Paediatric patients treated with muromonab-CD3 may also be at increased risk of lymphoproliferative and infectious complications compared to adults. A large proportion of children may not have been infected by pathogens such as herpes viruses prior to transplantation and are therefore more susceptible to developing primary infections from the grafted organ following immunosuppression with muromonab-CD3. Janssen-Ortho Inc. is currently working with Health Canada to update the Canadian Product Monograph to include the above information.

Reference:

NU BAO

Presence of animal derivatives and human tissue poses health risks

UK. The patient information leaflet for a traditional Chinese medicine named Nu Bao lists human placenta, deer antler (Corna cervi oantotrichum) and donkey skin (Colla cori astini) as the ingredients present in the capsules of the product. Although the information on the source of these ingredients is limited, the Medicines and Healthcare Products Regulatory Agency (MHRA) advises that all animal and human tissue derivatives carry a potential risk of infectious diseases due...
to the transmission of infective bacteria and viruses. The MHRA is therefore advising that consumers should not take this product. Current users should stop taking the product and should consult their doctor if they feel unwell. The MHRA has written to suppliers to cease marketing Nu Bao with immediate effect.

Reference:
Available from URL:
http://medicines.mhra.gov.uk

OTC DRUGS
New labelling rules to increase safety

USA. New US FDA labelling rules for over-the-counter (OTC) drugs will increase safety for patients with certain medical conditions. Warning and content labelling will be strengthened for oral OTC drugs that contain calcium, sodium, magnesium or potassium above specific levels, as they could be harmful to patients with special sensitivities. The FDA has also proposed an extension to the sodium-labelling rules to include OTC rectal drugs containing sodium phosphates, as there may be a risk of serious electrolyte imbalances in patients with certain underlying medical conditions. The new rules came into effect on 23 April 2004, with full compliance required by 25 September 2005.

Reference:
Available from URL:
http://www.fda.gov

SHITEK TONGKAT ALI PLUS 400MG
Presence of tadalafil

Malaysia. The Drug Control Authority of Malaysia has detected the presence of tadalafil in a traditional medicine sold under the name of Shitek Tongkat Ali Plus 400mg in Malaysia. The product had a fraudulent marketing authorization number printed on its package and was manufactured by a contract manufacturer, Shitek Micro Algae Sdn Bhd. Tadalafil is a prescription drug and could pose serious health hazards if used without medical supervision. The Malaysian Drug Authority has issued a press release to advise people against using the Shitek Tongkat Ali Plus 400mg capsules. The agency has also taken action against the contract manufacturer of the product and the Pharmacy Enforcement division has conducted a nationwide surveillance to seize all batches of the product from the market.

Reference:

TOLCAPONE
Marketing re-authorized, but more stringent monitoring recommended

Europe. The scientific committee of the European Medicines Evaluation Agency (EMEA) has appraised new data on the safety of tolcapone (Tasmar) and has concluded that the drug can be re-approved for marketing in Europe. Tolcapone is indicated in the treatment of Parkinson’s disease. The marketing authorization for tolcapone was suspended in Europe in November 1998 following concerns about hepatotoxicity and neuroleptic malignant syndrome associated with the use of this drug. However, based on its recent safety evaluation, the committee has stated that the drug may be reintroduced into the European market under stringent monitoring for liver function effects. The committee also recommends that the drug should be contraindicated in patients with certain medical histories, including liver disease and neuroleptic malignant syndrome.

Reference:

TRAZODONE
Interactions with CYP3A4 inhibitors/inducers

USA. FDA and Bristol Myers Squibb have notified healthcare professionals of revisions to the Clinical Pharmacology and Precautions sections of the labelling for trazodone (Desyrel) indicating the potential for interactions between trazodone and CYP3A4 inhibitors/inducers. Trazodone is indicated for the treatment of depression and appears to be metabolized by the CYP450 3A4 (CYP3A4) enzyme system (other metabolic pathways may also be involved). The metabolic clearance of trazodone could be impaired by CYP3A4 inhibitors ketoconazole, ritonavir, and indinavir, with a resultant increase in plasma trazodone level and a potential for adverse drug effects. On the other hand, CYP3A4 inducers such as
carbamazepine could enhance the metabolism of trazodone, thus reducing the plasma concentration of the drug, with a potential effect on therapeutic outcome. In one study, the short-term administration of ritonavir (200 mg twice daily, 4 doses) in 10 healthy subjects decreased the plasma clearance of a single dose of trazodone (50 mg) by 52%. Adverse effects including nausea, hypotension and syncope were observed when ritonavir and trazodone were co-administered. The co-administration of carbamazepine (400mg/day), with trazodone, 100-300 mg daily, reduced plasma concentrations of trazodone by 76% and 60% respectively. Careful monitoring of patients is thus necessary to see if there is a need for dose adjustment when trazodone is prescribed with any of the above drugs. The product label for trazodone has been appropriately revised to reflect the above information.

Reference:
Available from URL: http://www.fda.gov
CARVEDILOL
Reports of diarrhoea

New Zealand. The Centre for Adverse Reactions Monitoring (CARM) has received four reports of diarrhoea with carvedilol (Dilatrend), a non-cardioselective beta-blocker with alpha-blocking activity, indicated in the management of essential hypertension, angina pectoris, and as adjunctive therapy in chronic heart failure. Patients were receiving carvedilol in the dose range of 6.25 to 25mg daily. In three reports, severe diarrhoea developed within a week; and in the fourth case, the diarrhoea was moderate and began during the first month of carvedilol treatment. In all cases, symptoms improved on stopping the medicine. Diarrhoea is a recognised adverse effect of all beta-blockers. Prescribers may have to discontinue treatment with beta blockers and switch patients to alternative therapy if diarrhoea persists or gets severe. However, the drug needs to be withdrawn gradually, over two weeks, since abrupt withdrawal can precipitate rebound hypertension, angina or myocardial infarction, especially in individuals with ischaemic heart disease.

Reference:

CYCLO-OXYGENASE-2 INHIBITORS
Reports of visual disturbances

New Zealand. The Pharmacovigilance Centre in Dunedin, New Zealand has received nine reports of visual changes associated with the use of cyclo-oxygenase-2 (COX-2) inhibitors, celecoxib (six reports) and rofecoxib (three reports). The visual disturbances included blurred vision, abnormal vision, scintillating scotomata, visual field defect and temporary blindness. In all but one report, the duration to onset from first taking the COX-2 inhibitor was within four weeks. The eyesight changes were bilateral in eight of the cases. Blurred vision, cataract, conjunctivitis, eye pain and glaucoma are listed as adverse effects in the celecoxib (Celebrex) data sheet and blurred vision in the rofecoxib (Vioxx) datasheet. In all of the eight reports patients recovered quickly on withdrawal of the COX-2 inhibitor. The visual disturbances did not recur during periods of observation of up to seven months following withdrawal. Similar events have also been reported with non-specific anti-inflammatory agents. There is evidence that the cyclo-oxygenase enzymes COX-1 and COX-2 are involved in the regulation of retinal blood flow. However, other mechanisms for the observed visual disturbances with COX-inhibitors remain to be explored. If eyesight changes occur, the anti-inflammatory medicine should be immediately withdrawn and the patient assessed for improvement of visual symptoms. Future exposure to anti-inflammatory agents should be avoided in patients with a severe eye disturbance following first exposure.

Reference:

FURANO-COUMARINS
Presence in a herbal preparation

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) is alerting herbal interest groups to a report of a severe adverse skin reaction after a patient was prescribed an unlicensed herbal preparation containing a mixture of herbal ingredients for the treatment of eczema. The herbal preparation was prepared by the patient as a decoction in boiling water, cooled and then applied to the skin. This resulted in severe inflammation and blistering. The herbal mixture consisted of Cnidium monnieri fruit, Angelica sinensis root, Atractylodes lancea rhizome, Coix lacryma-jobi seed, Smilax glutabra root, Sophora flavescens root, Kochia scoparia fruit, and Pseudolaricis kaempferi bark. It is not possible to determine the herbal ingredient(s) responsible for the skin reaction because of the complexity of the herbal mixture. However, since the adverse reaction was similar to skin reactions with Psoralea fruit, the most likely causative ingredient is thought to be the Cnidium monnieri fruit. Cnidium monnieri fruit is reported to contain furanocoumarin derivatives, two of which, xanthotoxin and bergapten, were identified in the herbal mixture. However, it is possible that other ingredients may also have contributed to the adverse reaction. The MHRA advises caution while using any of these herbal ingredients, especially Cnidium monnieri, on the skin. The MHRA is in
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development of more information on the extent of actual usage, nature of usage etc. before deciding on further advice and action, if any.

Reference:

LEFLUNOMIDE

Awareness and monitoring can reduce the impact of adverse effects

New Zealand. According to a recent Prescriber Update article available from Medsafe, New Zealand, serious multi-system adverse effects are possible with leflunomide, an effective disease modifying agent for rheumatoid arthritis. The adverse reactions associated with the use of this drug involve haematological, hepatic, immune, dermatological and respiratory systems. International reports include liver failure (15 cases, nine with fatal outcome), neutropenia, thrombocytopenia, thrombocytosis, severe pancytopenia, Stevens-Johnson syndrome, bullous eruptions and skin necrosis, interstitial pneumonitis and pulmonary infiltration and infections due to immune response impairments including sepsis. Post-marketing experience with leflunomide estimates the frequency of severe hepatic, dermatological, respiratory, haematological and infection reactions as being very rare (less than 1 in 10,000) and for blood dyscrasias as being rare (between 1 in 1000 and 1 in 10,000). According to the article, the long half-life of leflunomide may delay resolution of some of the reactions but regular monitoring and patient education of early warning signs (e.g. easy bruising, tiredness, pallor, skin lesions, shortness of breath etc.) can reduce morbidity. To minimize the risk of serious blood and liver adverse reactions, all patients taking leflunomide should have their haematological and liver function monitored. Per-treatment baseline values should be established for these functions first before starting therapy, every month after initiating therapy for the first six months and, every six to eight weeks thereafter. Ongoing monthly monitoring is recommended if methotrexate is used concurrently.

Reference:

OXANDROLONE

Warning for interaction with warfarin

USA. Savient Pharmaceuticals Inc., in consultation with US FDA has issued a letter to health professionals regarding the potential for interaction when oxandrolone, an anabolic androgenic steroid and warfarin, an anticoagulant, are prescribed together. Oxandrolone is used as adjunctive therapy to promote weight gain in patients following extensive surgery, chronic infections, etc. According to a recent clinical study, concurrent dosing of oxandrolone and warfarin might prolong the half-life of warfarin with a resultant increase in the International Normalized Ratio (INR) or Prothrombin Time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain a desirable INR level and diminish the risk of potentially serious bleeding. Patients should be carefully monitored for INR or PT values and for signs and symptoms of occult bleeding.

Reference:

SHUBAO SLIMMING CAPSULES

Presence of fenfluramine and nitrosofenfluramine

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) is alerting herbal interest groups and consumers about the presence of fenfluramine and nitrosofenfluramine in an unlicensed traditional Chinese medicine preparation, Shubao Slimming Capsules, supplied illegally as a slimming agent in the UK. Fenfluramine is an appetite suppressant and was banned globally in 1997 due to concerns about the drug’s effect on the heart while nitrosofenfluramine is known to be toxic to the liver. Globally the illegal adulteration of slimming products with nitrosofenfluramine and fenfluramine has been associated with a large number of reports of liver toxicity. There was one report of liver failure in a patient receiving Shubao Slimming Capsules in the UK; the patient required a liver transplant. The MHRA has directed that the supply and sale of Shubao capsules

Reference:
should be stopped immediately and has requested cooperation from the herbal sector in minimizing the risks to consumers posed by the illegal inclusion of fenfluramine and nitrofenfluramine in these capsules.

**Reference:**

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### STATINS

**Important to measure creatine kinase levels**

**New Zealand.** A Prescriber Update article from Medsafe, New Zealand, while referring to the risk of myopathy and rhabdomyolysis associated with the use of statins, reminds prescribers to measure creatine kinase (CK) levels in patients presenting with muscle pain or weakness. Muscle pain or weakness accompanied by a CK level more than 10 times the upper limit of normal would suggest clinical myopathy. Rhabdomyolysis, a severe form of myopathy with muscle breakdown leading to myoglobinuria, may result in renal failure and death. Monitoring helps improve outcome. CK measurements must be performed when symptoms occur. Patients with additional risk factors (diabetes, older age, hypothyroidism, liver or renal disease) may be more at risk of rhabdomyolysis and should be observed closely for signs and symptoms of myopathy. Statin treatment should be discontinued immediately if an elevated CK level is found (CK>10 x upper limit of normal) or where myopathy is suspected or diagnosed. CK levels should be monitored weekly and specialist advice sought if there is a moderate increase in CK levels (3-10 x upper limit of normal). Health professionals are also reminded that other concomitant medicines may increase risk of myopathy, particularly if they can cause myopathy on their own (e.g. fibrates). Such a potentiation of risk could also occur when the concomitant drugs are potent inhibitors of the CYP 3A4 enzyme system (e.g. erythromycin, itraconazole, amiodarone, verapamil) because several statins such as simvastatin and atorvastatin are CYP 3A4 substrates. To minimize the risk of interaction, lower starting doses of simvastatin and atorvastatin should be used in patients already being treated with fibrates, cyclosporine, amiodarone, verapamil and other potent CYP 3A4 inhibitors; if a patient is already on statins, the dose of statins should be reduced before starting concomitant therapy with other interacting drugs.

**Reference:**

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### TEGASEROD

**Warning about diarrhoea and ischaemic colitis**

**USA, Canada.** Novartis Pharmaceuticals has issued a letter to health professionals regarding serious consequences of diarrhoea with new information about rare reports of ischaemic colitis with tegaserod, a drug indicated in the symptomatic treatment of irritable bowel syndrome with constipation (IBS-C) in female patients. According to Novartis

- serious consequences of diarrhoea, including hypovolemia, hypotension, and syncope have been reported in clinical studies and during marketed use of tegaserod (Zelnorm);
- rare cases of ischaemic colitis and other forms of intestinal ischaemia have been reported in patients receiving tegaserod during marketed use of the drug;
- tegaserod should be discontinued immediately in patients who develop hypotension or syncope, and in patients who develop symptoms of ischaemic colitis such as rectal bleeding, bloody diarrhoea or new or worsening abdominal pain;
- patients should be advised to stop taking tegaserod in case of above symptoms and should seek medical advice if they experience new or worsening abdominal pain, with or without rectal bleeding and/or blood in the stool.

**Reference:**

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### THIOMERSAL IN VACCINES

**Recent evidence supports safety**

**Europe.** The EMEA has issued a public statement that recent evidence supports safety of thiomersal-containing vaccines for human use. Thiomersal is an...
antimicrobial organic mercury compound used either in the early stages of manufacturing, or as a preservative in some vaccines. The antimicrobial action of thiomersal relates to ethylmercury, which is released after breakdown of thiomersal into ethylmercury and thiosalicylate. Previously, the Committee for Proprietary Medicinal Products (CPMP), while stating that thiomersal vaccines posed no health risk, had advised the general use of vaccines without thiomersal and other mercury containing preservatives as a global measure for reducing environmental exposure to mercury. In March 2004, the CPMP reviewed the latest evidence relating to the safety of thiomersal-containing vaccines including several well-designed epidemiological studies. Based on this review, the CPMP has concluded that

- there is no association between vaccination with thiomersal-containing vaccines and specific neurodevelopmental disorders;
- the immunisation with vaccines containing thiomersal continues to offer outstanding benefits to the general population, including infants;
- the presence of thiomersal and other preservatives should be stated on the label of the vaccine and a warning regarding the risk of sensitization in relation to thiomersal and other preservatives should be included in the Summary of Product Characteristics and package leaflets of such preparations;
- in line with the global goal of reducing exposure to mercury, the development of vaccines without thiomersal or with the lowest possible levels of thiomersal and other mercury containing preservatives should continue to be promoted.

Reference:

ZAFIRLUKAST
Reports of serious hepatic events

Canada. AstraZeneca Canada Inc., in consultation with Health Canada is warning health professionals about post-marketing reports of serious hepatic effects associated with the use of zafirlukast (Accolate). From 1997 to 31 December 2003 one case of hepatitis, four cases of hepatobiliary disorders or possible hepatitis, one case of hydrocholecystitis and four cases of elevated liver enzymes have been reported in Canadian patients receiving zafirlukast (Accolate). Worldwide a total of 46 reports of hepatitis, 14 reports of liver failure, and 59 reports of other significant liver dysfunction have been noted; a fatal outcome was seen in seven cases. The exposure to zafirlukast is estimated to be more than 1.9 million patient years worldwide. Health professionals are being informed that elevations in serum transaminases could represent early evidence of hepatotoxicity. Immediate termination of zafirlukast treatment is advised following the appearance of signs and symptoms of hepatotoxicity (malaise, lack of energy, loss of appetite, pain on right side of stomach just below ribs, dark urine and discoloured

and/or pale stools) or development of abnormal transaminase and/or bilirubin levels. Serum testing should be done at baseline and periodically during zafirlukast treatment. Physicians should be aware of, and educate patients on the symptoms of liver injury. Zafirlukast is not recommended for patients with hepatic impairment including hepatic cirrhosis.

Reference:
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs):

Use in children with Major Depressive Disorder

Depressive disorder is the fourth most important cause of disability worldwide. Though less recognized and lesser studied, the disorder affects a sizeable percentage of children and adolescent population. For example, the lifetime prevalence of major depressive disorder in adolescents has been estimated to range from 15-20 percent.

Complexities of diagnosis coupled with the ethics of conducting clinical trial research in children have limited our understanding of childhood depression and the development of antidepressant drugs for specific use in this sub-population of depressives. However, it is known that physicians, for want of treatment alternatives in children, often resort to off-label prescribing of many antidepressants that are licensed only for adult-use.

Of all the available antidepressants the SSRIs or Selective Serotonin Reuptake Inhibitors have received much recognition as being a safer and more acceptable treatment of depression in adults. However, the safety of prescribing SSRIs to children and adolescents, particularly in the absence of adequate safety and efficacy studies with SSRIs in this population, has been the subject of increasing concern in the community and the medical profession. Several recent recommendations have been issued by the government and industry cautioning against the use of SSRIs in children below 18 years of age following reports of increased suicidal ideations in children being treated with some of these drugs. Below is a summary of recent opinions and directives on the use of SSRIs:

Several adverse drug reactions advisory committees worldwide (Australia, Ireland, Netherlands, UK, USA) have acknowledged the international concern about a possibility of increased suicidal ideation and self-harm behaviour in children and adolescents treated with SSRIs for major depressive disorder (MDD). The US FDA and the UK Committee on Safety of Medicines have both independently evaluated clinical data from trials in MDD in children and adolescents for the SSRIs and a related drug venlafaxine. It may be noted that none of these drugs is approved for the treatment of MDD in children although off-label use of these drugs for this purpose is known.

In December 2003 the UK CSM stated that:
1. The risks of treating depressive illness in children under 18 years of age with certain SSRIs outweigh the benefits of treatment.
2. Based on available data, the SSRIs paroxetine, sertraline, citalopram, escitalopram and the related drug venlafaxine are now contraindicated in paediatric MDD in the under 18s.
3. There are no data on the safety and efficacy of fluvoxamine in paediatric MDD, and therefore this product should not be used in this age group.
4. Fluoxetine has been demonstrated to have positive benefit-risk balance in the treatment of MDD in children under 18. However, fluoxetine does not have a marketing authorization for MDD in this age group; any decision to prescribe fluoxetine for paediatric MDD in a patient under 18 should be made with specialist advice.
5. Young people with depressive illness currently taking any SSRI other than fluoxetine should not stop taking their medicine but should consult their doctor for advice on treatment.

In view of the UK position on the use of SSRIs in children, the Irish Medicines Board (IMB) has reminded health professionals and the public that SSRIs have never been licensed for the treatment of MDD in children under the age of 18 in Ireland. The IMB will continue to monitor the quality, safety and efficacy of SSRIs and initiate any further regulatory action, as appropriate.

Health Canada has advised that patients under 18 years of age, who are currently being treated with an SSRI or an SNRI (Serotonin Noradrenaline Reuptake Inhibitors) should consult their physician to determine if the benefits of these drugs still outweigh their risks in light of recent safety concerns. Health Canada also notes that none of the drugs bupropion, citalopram, fluvoxamine, mirtazapine, paroxetine, sertraline and venlafaxine are
approved for use in patients under 18 years of age in Canada. The prescribing of these drugs in this population is therefore a physician's responsibility.

The Australian Adverse Drug Reactions Advisory Committee (ADRAC)\(^7\) reminds that none of the SSRIs are approved for the treatment of MDD in children or in adolescents in Australia. The ADRAC considers that the current data are not conclusive regarding the efficacy and safety of SSRIs in MDD in children and adolescents and therefore recommends that any SSRI use in children should be undertaken only within the context of comprehensive management of the patient according to clinical practice guidelines for depression in young people, with careful monitoring for the emergence of suicidal ideation and behaviour. The choice of the SSRI for children with MDD should be made only after taking into account recent evaluation of clinical trial data and the Product Information. ADRAC draws attention to the fact that the current Australian product information for paroxetine and venlafaxine recommends against their use in children and adolescents.

The US FDA's assessment\(^7\) of the SSRIs is in broad agreement with the UK CSM conclusions. In March 2004 the US FDA issued a Public Health Advisory about a possible increased risk of suicidality with these medications. The FDA warns that only fluoxetine is approved for the treatment of paediatric major depressive disorder. The FDA has directed manufacturers of antidepressant drugs fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, bupropion, venlafaxine, nefazodone and mirtazapine to include the following in their product labelling:

1. Health-care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose is either increased or decreased.
2. Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania and mania have been reported in adult and paediatric patients being treated with anti-depressants for MDD as well as for other indications. There is concern that patients who experience one or more of these symptoms may be at increased risk for worsening depressions or suicidality and therapy may need to be discontinued when symptoms are severe, abrupt in onset or are not part of the patients presenting symptoms.
3. Patients, their families and caregivers should be instructed to recognize and report the emergence of the above symptoms as well as symptoms of agitation and irritability.
4. If a decision is made to discontinue treatment, the medication should be tapered and not withdrawn abruptly.

The Medicines Adverse Reactions Committee (MARC) in New Zealand has reviewed the efficacy and safety of SSRIs when used to treat MDD in children under 18 years of age and considers the data to be inconclusive\(^8\). In New Zealand none of the SSRIs have been approved for use in treating MDD in children or adolescents. The MARC is awaiting further data on the use of these drugs in children. In the meantime, health professionals are advised that pharmacological treatment is only the second-line therapy in the treatment of MDD in children; children and adolescents who are responding well to SSRI therapy should complete the usual course of treatment and if response is inadequate, specialist advice should be sought.

The Medicines Evaluation Board (MEB) in the Netherlands has called for caution in the use of SSRIs in children with depressive disorders\(^9\). It has drawn attention to the existing statement in the Product Information on SSRIs in the Netherlands: that the safety and efficacy of short-term use of these drugs have not yet been investigated adequately in children with depressive disorders. No product is currently indicated for the treatment of depression in children and adolescents in the Netherlands.

The current scenario with the SSRIs emphasizes, yet again, how important it is to continuously evaluate the benefit-risk profile of all medicines.

References:


