Welcome to a new venture for the Adverse Drug Reactions Section of the N.D.A.B.!

This newsletter is the first of what is intended to be an occasional publication to communicate issues of interest and concern to physicians and pharmacists. We would welcome all constructive comments and indeed, suggestions relating to issues which could be covered in future newsletters.

Correspondence should be marked for the attention of Dr M Teeling/Ms N Arthur, ADR Section.

Co-Amoxiclav (Augmentin)

A small number of reports of hepatobiliary reactions have been notified to the Board since 1994. Reports have also been notified internationally in the Medical Literature. The product authorisation documents currently include the following information:

"Hepatitis and cholestatic jaundice have been reported rarely. These events have been noted with other penicillins and cephalosporins. The hepatic events associated with Augmentin may be severe, and occur predominantly in adult or elderly patients. Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. In most cases, resolution has occurred with time. A moderate rise in AST and/or ALT has been noted in patients treated with ampicillin class antibiotics, but the significance of these findings is unknown.

You are reminded to report any suspected reactions to the National Drugs Advisory Board.

Cisapride (Prepulsid)

We have recently received new safety information concerning the prescribing of cisapride (prepslild).

This concerns concomitant administration of cisapride microbial agents. The data suggest that the resulting interaction leads to markedly increased concentrations of cisapride resulting in Q-T prolongation which predisposes to serious ventricular arrhythmias.

You are reminded of the following:-

Concomitant administration of Cisapride with oral or parenteral (but not topical) forms of fluconazole, erythromycin, clarithromycin, ketoconazole, itraconazole and miconazole is contraindicated as they interact to markedly increase Cisapride concentration.

In order to assist in the monitoring of interactions please report any suspected cases to the National Drugs Advisory Board.

Co-trimoxazole

Trade Names: Bactrim, Septrin, Trimoxol, Cotrimel, Tricomed, Duobact, Rimazole.

Co-trimoxazole (a fixed 1:5 combination of trimethoprim and sulphamethoxazole) has been authorized in Ireland since the mid 70's. It has been
used in the treatment of respiratory tract infection, genito-urinary tract infection, pneumocystis carinii infection and a number of other conditions. Regular review at the time of five yearly renewal has taken account of changes in medical practice together with worldwide adverse reactions reports, with resultant appropriate modification and qualification of the indications, contraindications, precautions, warnings, and interactions of the product information, particularly with regard to use in elderly patients.

More recently the N.D.A.B. requested companies to submit for urgent review, an up to date evaluation of both the safety and efficacy of this compound with particular attention to any synergistic or additive effect of the combination over trimethoprim alone and other comparative anti-microbials. The following recommendations have emerged from that review:

1. For simple urinary tract infections, trimethoprim or another single antimicrobial agent is the preferred treatment. Trimethoprim is also as efficacious as co-trimoxazole for the prophylaxis of recurrent urinary tract infections.

2. In respiratory tract infections, the evidence for equal efficacy of trimethoprim and co-trimoxazole is less strong and use of a single agent of a different class should be considered. Co-trimoxazole may be used as second line therapy in chronic obstructive airways disease or other respiratory tract infections, including acute otitis media, where sensitivity has been demonstrated or is highly probable.

3. Co-trimoxazole use has been established in the management of pneumocystis carinii pneumonia.

4. Co-trimoxazole may be useful in the management of other serious conditions such as nocardiasis, toxoplasmosis and brucellosis.

The adverse event profile has been well documented and when used as recommended, does not appear to have changed materially since first authorised. Minor adverse effects, mainly gastro-intestinal, are somewhat more frequent and severe than with trimethoprim, but overall have a similar frequency to that of other oral anti-microbials in general.

The most frequently reported worldwide adverse events are skin and upper gastro-intestinal tract reactions, including glossitis. A majority of these are benign and rapidly reversible after discontinuation of treatment. More severe and even fatal reactions have occurred at low incidences with both co-trimoxazole and trimethoprim. These serious reactions are mainly blood dyscasias, mucocutaneous syndromes (e.g. Stevens Johnson syndrome, Lyells syndrome) and hepatic reactions. There appears to be a relationship between occurrence of all such adverse events and the duration of treatment.

The elderly are more likely to suffer from severe adverse reactions. Therefore the drug should be used only where specifically indicated and for as short a time as possible and only with particular caution in elderly patients.

Revision of the relevant data sheets is in progress.

In order to facilitate on-going surveillance of the safety profile of co-trimoxazole, suspected adverse reactions should be reported in the usual way to the Board.

"Third Generation" Oral Contraceptives

As you are aware there has been considerable discussion about the safety of the so called third generation oral contraceptives. When these agents were introduced, they were suggested to be safer than the second generation agents because of lesser androgenic effects. The NDAB has always required that identical precautions apply to both second and third generation agents and these are well described in the prescribing information. The UK's Committee on Safety of Medicines wrote to doctors on 18th October advising restrictions in the use of thromboembolism. The results of three separate but as yet unpublished epidemiological studies suggested an approximate doubling of this risk. One additional study (excluding women with risk factors) did not identify a different incidence of cardiovascular death among users of levonorgestrel, desogestrel or gestodene. To date, there is no information on norgestimate-containing agents. It cannot be excluded that unknown biases contributed to the differences in the studies. There is also a suggestion, (based on very small numbers), that the risk of acute myocardial infarction is less with the third generation agents.

At a specially convened meeting of the European Committee for Proprietary Medicinal Products (CPMP) on 26th and 27th October, these findings and their implications were considered and it was decided that no regulatory action need be taken at this time.

As a result the National Drugs Advisory Board has adopted the following position:

1. You are reminded that there are well defined risks attached to the use of all oral contraceptives steroids and patients receiving them should be kept under regular
surveillance. The results of the present studies are not such as to require that any of these products should be withdrawn at this time.

2. Patients should not abruptly discontinue their medication, but should continue until the end of their current treatment cycle and then discuss their circumstances with you.

3. Patients who are prescribed third generation agents should be informed of the results of these studies prior to starting or renewing therapy. It should be stated that there is an apparent twofold increased risk of venous thromboembolism with use of these products compared to levonorgestrel containing products. The increased risk is small and in absolute terms amounts to approximately 2 extra cases per 10,000 women years. The risk of venous thromboembolic events with all combined oral contraceptives is still substantially less than the risk of such events in pregnancy.

4. Treated patients judged to be at particular risk for venous thromboembolic events should be reviewed in the light of this information. Known risk factors include obesity, varicose veins and a positive family history. Use of oral contraceptives continues to be contraindicated in patients with a history of, or existent venous thromboembolic disorders.

5. The National Drugs Advisory Board will continue to keep the matter under review and will advise you if any data become available which has a material impact on these recommendation.

The currently authorised third generation products are: Desogestrel-containing: Mercilon, Marviol Gestodene-containing: Femodene, Minulet, Triodene, Tri-Minulet

Safety of Carbaryl Containing Products in the Treatment of Lice

The Board has received copies of a press release by the UK’s Medicines Authorities describing a risk of cancer associated with the use of carbaryl which is used as a shampoo or lotion for the treatment of lice.

The Board will review the data in detail but in the meantime would like to clarify the risk to people who have used or are using such products. The cancers were produced by administering very large doses of carbaryl to animals for periods of up to two years. In context this would be equivalent to a child consuming a dozen or more bottles of carbaryl-containing lotion or shampoo per day for this period. It is not possible to receive doses of the required magnitude by using the shampoos and lotions in the recommended manner. The UK’s press release points out that the risk is a “theoretical one” and that there are no reports of tumours in association with carbaryl exposure in humans after 40 years of use.

Following completion of its review, the National Drugs Advisory Board will, if necessary, issue further recommendations at an appropriate time. As a general principle, all medicines should be used with care, only when they are required and in accordance with the recommended dosing instructions.