IRISH MEDICINES BOARD

DRUG SAFETY NEWSLETTER

6th Edition

Accolate (Zafirlukast)

Accolate, a leukotriene receptor antagonist, is a relatively new treatment available for the management of patients with severe asthma. It is currently available in Belgium, Finland, Portugal, Canada and the US, as well as Ireland.

Approximately nine months after its introduction to the US market, the company notified the Irish Medicines Board (IMB) that approximately 20 cases of suspected Churg-Strauss Syndrome (CSS) out of an estimated population of 550,000 treated patients had been reported there.

Churg-Strauss syndrome is a rare form of vasculitis characterised clinically by allergic rhinitis, sinusitis, asthma, pulmonary infiltrates, blood eosinophilia and eosinophilic tissue infiltration with granuloma formation. Both the arterial and venous circulation may be involved. [1]

The cases have, in general, arisen in patients with severe steroid dependent asthma and in several instances there is evidence that CSS has been present prior to exposure to Accolate. Several cases have emerged after the cessation or reduction of oral steroid treatment suggesting the possibility that these patients may have had occult CSS controlled by corticosteroids. However, tissue eosinophilia has occurred in patients not taking oral steroids, and a causative relationship with Accolate cannot be excluded. [2]

When treating patients, particularly those with severe asthma, attention should be paid to the possibility that they may have CSS. This becomes specially important if an apparent improvement in asthma control due to the introduction of Accolate seems to allow the reduction or cessation of previously required oral steroid treatment. In those patients receiving concomitant oral steroid and Accolate therapy, withdrawal or reduction of the oral steroid dose should only be undertaken with great caution. Following review of this issue with the company a "Dear Doctor" letter was circulated to practitioners and the prescribing information was revised to reflect the available data and restrict use of Accolate in severe asthmatics, especially those taking oral steroids to hospital specialists with facilities to monitor Accolate use in their patients.

Any suspected adverse reactions should be notified to the IMB.

References:

1) *British Medical Journal* 1997; **315:** 330
2) *JAMA* 1998: **79** : 455 - 458

Drug Safety - March 1998 - Issue No.7

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Carbaryl

In a previous edition of the Drug Safety Newsletter (Issue No.1 - December 1995) an article referred to tumour inducing effects of carbaryl which had been observed during animal studies.The doses necessary to induce these tumours, over 12mg/kg/day for a life time, exceed any likely exposure from the use of carbaryl containing lotions or shampoos for lice infestation. In context, this would be equivalent to a child consuming a dozen or more bottles of carbaryl - containing lotion or shampoo per day, for periods of up to two years.

It is not possible to receive doses of that magnitude by using the shampoos and lotions in the recommended manner therefore the risk of tumour induction in humans is considered extremely low. There have been no cases of tumours reported in association with carbaryl exposures in humans after 40 years of use.

Following assessment of the available data the IMB is currently revising the recommendations for use of carbaryl-containing products with the companies concerned. The revised changes are summarised as follows:

- Carbaryl-containing products should only be used for treatment of live lice infestation and not for prevention.

- Continued prolonged treatment with carbaryl containing products should be avoided. They should not be used more than once a week and for no longer than three consecutive weeks.

It is important to remember that over time lice may become resistant to the insecticides used in their treatment. It is therefore advisable that hospitals and Health Boards recommend rotation of the products used approximately every three years.

Carbaryl-containing products include Carlyderm, Derbac C, Suleo C, Clinimal, Clinicide

Anexate & Anectine

The IMB has received several anecdotal reports of inadvertent use of one or other of the above parenteral products because of confusion arising with their respective product names. The potential for hazard should one of these products be used in place of the other is clearly significant.

You are reminded to exercise care when verbally requesting or writing either product name. It may also be helpful to use the non-proprietary names in order to prevent further cases of confusion and thereby avoid potential disasters.
(Anectine - Suxamethonium, Anexate -Flumazenil)

Thiazide Diuretics

The steep dose response of many thiazide diuretics means that increasing the dose may not increase the efficacy but may have an impact on the incidence of adverse reactions. The IMB is currently reviewing the safety and efficacy of the doses of currently authorised diuretics in conjunction with the relevant companies and reducing the recommended dose when this is found to be appropriate.

This has resulted in withdrawal of certain diuretics from the Irish marketplace while in other cases the recommended dose have been reduced. All changes have been or will be incorporated in the prescribing information for each product concerned. Prescribers are advised to check the doses recommended in the data sheet/Summary of Product Characteristics (SPC).

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Meloxicam (Mobic)

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) indicated for short-term symptomatic treatment of acute exacerbations of osteoarthritis and in the long term symptomatic treatment of rheumatoid arthritis and the symptomatic treatment of ankylosing spondylitis.
Analysis of world-wide post-marketing surveillance data has shown that in common with other NSAIDs, serious and sometimes fatal gastrointestinal adverse reactions, including gastrointestinal haemorrhage, peptic ulcer and perforation, have occurred in association with meloxicam treatment. In some cases these reactions have occurred in patients known to be at risk of serious gastrointestinal reaction (e.g. past history of gastrointestinal disorders).

Meloxicam was authorised for use in Ireland in 1996 and since then the IMB has received 13 suspected adverse reaction reports associated with its use. Of these, eight involved gastrointestinal disorders namely anorexia, dyspepsia, nausea, diarrhoea, haematemesis, perforated gastric ulcer and melaena. One of these cases resulted in a fatal outcome.

Following review of the data a "Dear Doctor" letter was circulated by the company and the product information has been revised, advising prescribers to monitor patients for any gastrointestinal disorders and to inform them about the risk of peptic ulceration, perforation and haemorrhage associated with meloxicam treatment.

You are reminded that in order to reduce the risk of serious gastrointestinal disorders, meloxicam should not be co-prescribed with other NSAIDs. Any suspected adverse reactions should be notified to the IMB.

Phentermine (Ionamin)

Since 1995 anorectic agents have been under review at European level. This review included the following medicinal products, amfepramone (Apisate and Tenuate), dexfenfluramine (Adifax), fenfluramine (Ponderax) and phentermine (Duromine & Ionamin). Amfepramone - containing medicinal products (Apisate and Tenuate) and one phentermine-containing medicinal product (Duromine) were voluntarily withdrawn from the Irish marketplace by the companies in 1995 and 1996.

In September 1997 dexfenfluramine (Adifax) and fenfluramine (Ponderax) were voluntarily withdrawn from all worldwide markets by the company, because of an association with the occurrence of valvular heart disease. [1]

Ionamin is now the only anorectic agent available for use in Ireland and prescribers are reminded of the following restrictions to its use.

Therapeutic Indications

Adjunctive therapy to diet, in patients with obesity and a body mass index (BMI) of 30 kg/m2 or higher who have not responded to an appropriate weight-reducing regimen alone.

Posology and Method of Administration

It is recommended that treatment should be monitored under the care of physicians experienced in the treament of obesity.

Duration of Treatment

The duration of treatment is 4-6 weeks and should not exceed three months.

Contraindications

- Pulmonary artery hypertension
- Severe arterial hypertension
- Current or past medical history of cardiovascular disease or cerebrovascular disease
- Current of past medical history of psychiatric disorders including anorexia nervosa and depression
- Propensity towards drug abuse, known alcoholism
- Children below 12 years.

Special Precautions for Use

Cases of severe, often fatal, pulmonary artery hypertension, have been reported in patients who have received anorectics of the type in this product. An epidemiological study has shown that anorectic intake is a risk factor involved in the development of pulmonary artery hypertension and that the use of anorectics is strongly associated with an increased risk for this adverse drug reaction. [2, 3, 4]

Undesirable Effects

Cases of pulmonary artery hypertension have been reported in patients treated with this agent. [2, 3, 4]

References:
1) *Drug Safety Newsletter - Issue No.6, October 1997*
2) *New England Journal of Medicine* 1996; **335: 337: 9:** 609-616
3) *New England Journal of Medicine* 1997; **337: 9:** 602-606
4) *New England Journal of Medicine* 1997; **337: 9:** 581-588

Adverse Reaction Reporting

In Ireland, approximately 30% of adverse drug reaction (ADR) reports are notified by general practitioners annually, with approximately 15% of reports notified from all hospital sources (Doctors, Pharmacists and Nurses). Studies have shown that ADRs which necessitate hospital admission are estimated at 3 - 8% of all such admissions and this figure increases to 10% in patients over 65 years of age. (1, 2) Furthermore, 10 - 20% of patients are expected to develop ADRs during their hospital stay. [3, 4] Given these figures the number of reports currently received from hospital sources indicates significant underreporting which IMB is anxious to redress.

The burdensome nature of form filling for busy healthcare professionals is appreciated, however, the collection of adverse reaction reports is necessary in order to ensure the continued surveillance of the safety and quality of all licensed medical products. Furthermore, although an individual practitioner's experiences may be limited to one or two cases however, when collated with additional reports from other sources such reports are vital in the assessment and evaluation of possible hazards.
In order to increase the reporting rate from hospitals the IMB is keen to help set up and establish good drug monitoring and ADR reporting practices. Any hospitals who wish to develop their reporting systems should contact the Pharmacovigilance Unit of the IMB.

References:
1) *Annals of Pharmacotherapy* 1993; **27:** 832-840
2) *British Journal of Clinical Pharmacology* 1992: **33 :** 61-68
3) *JAMA* 1991; **266:** 2847 - 2851
4) *Journal of Acquired Immune Deficiency Syndrome* 1993; **6 :** 919-926

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