IRISH MEDICINES BOARD

DRUG SAFETY NEWSLETTER

8th Edition

Terfenadine
(Triludan, Terfenor, Terfenadine)

Terfenadine is a non-sedating antihistamine which has been authorised in Ireland for over seventeen years. It was available as an "over the counter" medicine from 1987 - 1997. In 1997, its status was changed to a prescription-only medicine following evaluation of its potential to induce cardiac arrhythmias, particularly when used in combination with other medicinal products (including ketoconazole, itraconazole and related imidazole anti-fungal agents, erythromycin, clarithromycin and related macrolide antibiotics).

This was the subject of a formal referral, on safety grounds to the EU Committee for Proprietary Medicinal Products (CPMP). The IMB in association with the CPMP undertook an extensive review of the safety of terfenadine and other non-sedating antihistamines. The review, which was completed towards the end of 1998, concluded that the risk/benefit profile of the 120mg product was unfavourable and as a result, this product was withdrawn from all EU markets.

A positive CPMP Opinion was issued in respect of the 60mg product which remains available on the Irish market as a prescription-only medicine for the symptomatic relief of allergic rhinitis and conjunctivitis and of allergic skin disorders.

You are reminded that patients should be advised:-

- not to take terfenadine with any other medicine (including other antihistamines or OTC preparations), without first checking with their physician or pharmacist, because of the risk of cardiac arrhythmias.
- not to exceed the maximum dose, even in case of insufficient relief.

Selective Serotonin Re-Uptake Inhibitors (SSRIs) and Related Antidepressants

(Fluoxetine - Prozac, Paroxetine - Seroxat, Citalopram - Cipramil, Fluvoxamine - Faverin, Nefazodone - Dutonin, Venlafaxine - Efexor)

The issue of withdrawal reactions associated with use of selective serotonin re-uptake inhibitors (SSRIs) and related antidepressants (as named above), has been considered by the IMB in conjunction with the Pharmacovigilance Working Party of the European Committee on Proprietary Medicinal Products (CPMP).

This review concluded that withdrawal reactions may occur following discontinuation of treatment with these medicinal products.

The majority of withdrawal reactions are mild and self-limiting, although reports of more severe reactions have been identified. When such reactions occur they can be reversed by re-starting the drug, followed by a more gradual tapering of dosage.

At present, there is no strong evidence which allows definitive statements about the frequency of withdrawal reactions occurring with these antidepressants.

As a result of this review, the IMB is currently working with companies to amend the prescribing information for these products.

Please report any suspected adverse reactions to the IMB, who will keep this issue under review.

Drug Safety - July 1999 - Issue No.8
Correspondence/Comments should be marked for the attention of:
The Pharmacovigilance Unit, Irish Medicines Board,
Earlsfort Centre, Earlsfort Terrace, Dublin 2. Tel: 676 4971-7 Fax: 676 7836

Nimesulide (Aulin)

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) authorised in Ireland since 1995.

The potential for hepatic adverse events following exposure to nimesulide has been an ongoing concern to the Irish Medicines Board. In the light of recent reports of serious hepatic adverse events including rare cases of fatalities in patients treated worldwide with nimesulide, the IMB has amended the prescribing information as follows:

Contraindications

Use in **patients with hepatic impairment.**

Please note that the use of nimesulide is contraindicated in children and there are no paediatric formulations available on the Irish market. Isolated fatalities in children following treatment with nimesulide have been reported in Portugal and the paediatric formulation has been withdrawn from that market.

Precautions and Warnings.

Hepato-biliary disorders: changes in the hepatic parameters (transaminases), mostly transitory and reversible. Isolated cases of acute hepatitis, fulminant hepatic failure (some fatalities reported).

Patients who experience symptoms compatible with hepatic injury during treatment with nimesulide (e.g. anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine, or jaundice) should be carefully monitored.

Patients who develop abnormal liver function tests should have treatment discontinued. These patients should not be re-challenged with nimesulide. Hepatic adverse drug reactions have been reported following periods of treatment of less than one month.

In addition, the IMB has recently reviewed the data relating to the claimed COX-2 selective inhibitory activity of nimesulide. As a result of this review, it was considered that there is no unequivicol evidence to suggest that claims for favourable gastrointestinal tolerability can be made. Consequently, the IMB has amended the prescribing information as follows:

Precautions and Warnings

Gastrointestinal disorders: most commonly reported: nausea, gastric pain, abdominal pain, diarrhoea, constipation. Rarely: peptic ulcers, perforation or gastrointestinal bleeding, which may be severe may occur.

In the rare instances where gastrointestinal bleeding or ulcerations occurs in patients receiving nimesulide, the drug should be withdrawn. As with other NSAIDs, gastrointestinal bleeding or ulceration /perforation can occur at any time during treatment without warning symptoms or a previous history of gastrointestinal events.

You are reminded that nimesulide is contraindicated in patients with active peptic ulcer, a history of recurrent ulceration, or with gastrointestinal bleeding and should be used with caution in patients with a history of peptic ulceration or inflammatory bowel disease. These patients should be monitored for gastrointestinal symptoms, especially bleeding.

Any suspected adverse reactions should be reported to the IMB who will continue to monitor the safety profile of this product.

Astemizole (Hismanal)

The IMB has recently been informed by the Marketing Authorisation Holder (Janssen-Cilag) of their intention to discontinue supply of astemizole (Hismanal), in Ireland. It is however, the company's intention to maintain a sufficient supply of the product for the duration of this year's hay-fever season.

Astemizole is a non-sedating anti-histamine, used for the treatment of hay fever and other allergic conditions and was authorised for use in Ireland in 1984. Like terfenadine, astemizole has been associated with prolongation of the QTc interval and thus has the potential to induce cardiac arrhythmias, particularly if used at high doses or in conjunction with potentially interacting medicines (such as anti-arrhythmics, neuroleptics, tricyclic anti-depressants, thiazide diuretics, ketoconazole, erythromycin, clarithromycin and related macrolide antibiotics and selective serotonin reuptake inhibitors (SSRI's).

Infanrix (DTPa)

Following review of the most recently available pharmacovigilance information on this vaccine, the prescribing information for Infanrix has been updated to include the following statement in the Undesirable Effects section:

"Extremely severe cases of collapse or shock-like state (hypotonic - hyporesponsiveness episode) and convulsions within 2-3 days of vaccination have been reported. All the subjects recovered totally and spontaneously without sequelae"

Inhaled Corticosteroids

Following review of international data on inhaled corticosteroids and leukotriene antagonists, variations have been initiated to amend the prescribing information to warn about the potential unmasking of systemic eosinophilic conditions such as Churg-Strauss syndrome.

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

The potential unmasking of conditions such as Churg-Strauss syndrome may arise in connection with reduction or withdrawal of systemic corticosteroid therapy. To date, no direct causal relationship has been established. However, the prescribing information for the relevant products is currently being amended to include the appropriate warning statements.

Reference: British Medical Journal 1997; **315 : 330.**

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic, anti-pyretic, anti-inflammatory and platelet-inhibitory effects.

This class of drugs is responsible for a significant number of adverse drug reaction reports to regulatory authorities throughout the world. [1] In light of this, the Irish Medicines Board has recently reviewed the adverse event profile and has introduced standard warnings applicable to all NSAIDs. The IMB is particularly concerned about the long-term use of NSAIDs in conditions such as chronic osteoarthritis, which in many cases is not associated with active inflammation.

Please note the following recommendations for using NSAIDs:

- In general, NSAIDs should only be used when an anti-inflammatory effect is required
- NSAIDs should be used with particular caution in the elderly who are more prone to adverse events
- The lowest dose compatible with adequate safe clinical control should always be used. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

In addition, you are reminded of the following:

Contraindications

Patients with active peptic ulceration.

Patients with a history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to aspirin or non-steroidal anti-inflammatory drugs.

Special Warnings & Special Precautions for Use

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.
In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

NSAIDs should be used with caution in patients with a history of peptic ulceration or inflammatory bowel disease.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

All suspected adverse reactions associated with NSAIDs should be submitted to the IMB who will continue to monitor the safety of these medicinal products.

Reference:

Anti-inflammatory and antipyretic analgesics and drugs used in gout.

In: *Side Effects of Drugs Annual 20* 1997:**86-102**
Elsevier Science Publishers B.V

UPDATE ON ADVERSE DRUG REACTION (ADR) REPORTING

During 1998, the IMB received a total of 1,086 nationally occurring ADR reports. All cases were reviewed and evaluated prior to inclusion on the IMB's ADR database. Almost 50% of the reports received were classified as serious within the accepted definition of this term. The following table shows the breakdown of reports by source:-

GP's	49.9%
Pharmaceutical Companies	25.3%
Hospital Doctors	13.6%
Pharmacists	10.1%
Nurses	0.9%
Dentists	0.2%

All case reports were reviewed, evaluated and followed up with feedback information provided to reporters, as appropriate.

The IMB's ADR database includes information on an anonymised case reports which is regularly reviewed to identify and evaluate adverse drug effects and when considered appropriate to revise prescribing information accordingly.

ADR report forms are available from the IMB or may be accessed from the IMB's website at:

http://www.imb.ie

This website includes an index of topics covered in the IMB's Drug Safety Newsletters, together with a down loadable version of each issue. In addition, a copy of the IMB's ADR report form is included for the convenience of reporters. Completed forms should be posted in an envelope marked:

"Freepost,"
Pharmacovigilance Unit,
Irish Medicines Board,
Earlsfort Terrace,
Dublin 2.

Spontaneous reporting of suspected adverse reaction is a cheap and effective method for lifetime surveillance of medicines following their introduction to the market-place.

No surveillance for the ongoing safety and quality of medicines can be continued unless adverse reactions are reported. While an individual's experience may be limited to one or two cases, when collated with additional reports from other sources may contribute significantly to the assessment of a possible safety hazard.

You are particularly reminded to report:

- All suspected adverse reactions to new medicinal products (i.e. those on the market for less than two years).
- Serious suspected reactions to established medicines.
- Any suspected increase in the frequency of minor reactions.
- Any suspected teratogenic effects.
- Any suspected reactions associated with the use of vaccines.

The IMB is always keen to help encourage and establish ADR monitoring and reporting practices. Any centres wishing to develop their reporting systems should contact the Pharmacovigilance Unit of the IMB.