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AUST R and AUST L numbers – why are they important?

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Recent media articles have highlighted the importance of identifying the AUST L number on the label of complementary medicines suspected of causing adverse reactions.

The Therapeutic Goods Administration (TGA) can use the AUST L number to determine the exact identity of the complementary medicine suspected of causing the adverse reaction.

All medicines entered onto the Australian Register of Therapeutic Goods (ARTG) include a unique AUST L or AUST R number on the label. This labelling is required for the lawful supply of a therapeutic good in Australia.[1]

The L refers to listed medicines (primarily complementary medicines) and the R to registered medicines (primarily prescription and over-the-counter medicines) and should be readily identifiable on the label (Fig. 1).

If a health practitioner suspects that a medicine is responsible for an adverse event, requesting further information from the patient, including where it was purchased, is important in assisting to correctly identify the product. Where a serious adverse event is thought to have occurred, reporting the event to the TGA is strongly encouraged. Including the AUST L or AUST R number (or the absence of an Australian Register number) of the suspected medicine in the report will allow the TGA to ensure appropriate investigation and subsequent action.

Where the medicine label does not include an AUST L or AUST R number the TGA has not evaluated the quality, safety or efficacy of the product and therefore the safety of the product is unknown. Products without an Australian Register number may have been supplied illegally if bought in Australia, purchased over the internet by the consumer or have been imported from overseas for personal use.

The increasing use of the internet by Australian consumers to access medicines has resulted in the increased use of medicinal products that have not been evaluated by the TGA. As a result the importance of identifying an AUST L or AUST R number on the product label has increased. The identification of the AUST L or AUST R number and its concomitant entry on the ARTG can reassure consumers and practitioners of the product's safety.

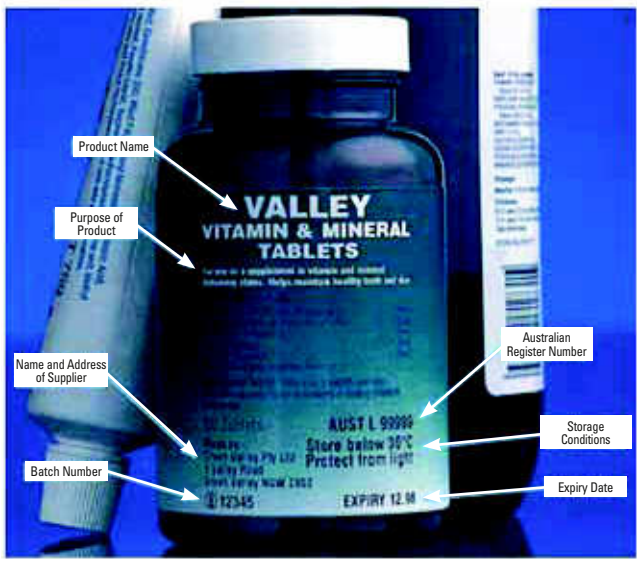
The TGA encourages all healthcare practitioners and consumers to report adverse events related to any medicine or medical device via the electronic reporting system available through the TGA website (www.tga.gov.au) or via the blue card system. Further information about medicine labels can be obtained on the TGA website.[2]

References

1. McEwen J. What does TGA approval of medicines mean? Aust Prescr 2004;27:156-8.
2. Buying medicines – What's on the label for me? www.tga.gov.au/docs/html/buymed.htm#mean [cited 2010 May 10]

Fig. 1

Label of complementary medicine



Sibutramine

Summary

Interim results of the SCOUT trial of sibutramine have revealed higher rates of heart attack and stroke in subjects who were overweight or obese and at high baseline risk of a cardiovascular event. The TGA is reviewing the safety of the product and while that review is ongoing has reinforced existing advice to healthcare professionals to carefully review the sibutramine Product Information (PI), before prescribing the product.

Introduction

Sibutramine is an orally administered serotonin (5-hydroxytryptamine, 5HT) and noradrenaline reuptake inhibitor, indicated for weight loss, and maintenance of weight loss, as part of a weight management program in obese adults. It should only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone. Sibutramine is not recommended for use in patients with a history of cardiovascular disease including inadequately controlled hypertension.

The SCOUT trial

Late last year the interim results of a clinical trial known as the Sibutramine Cardiovascular OUTcomes (SCOUT) trial, conducted by Abbott Laboratories, became available.[1] This study was a double-blind, randomized, placebo-controlled, parallel-group study into the effects of sibutramine (10 mg once-daily) on mortality in overweight and obese subjects at high risk of a cardiovascular event. All subjects were older than 55 years and had a history of manifest cardiovascular disease, or type 2 diabetes mellitus.

The study showed higher rates of cardiovascular events such as heart attack and stroke in patients using sibutramine, than in those receiving a placebo. While the rates were statistically significant in overweight and obese patients at high risk of a cardiovascular event, the difference was not statistically significant in overweight and obese patients with type 2 diabetes mellitus.

TGA monitoring

A review of the TGA's adverse drug reactions database (as at end March 2010) shows that 61 reports of suspected adverse reactions have been received by the TGA. The majority of these have occurred in women (47) who are also the predominant users of sibutramine. The most commonly reported adverse events were dizziness, palpitations, tachycardia and hypertension (which are listed in the PI); in addition chest pain and dyspnoea were also reported. There have been four reports each of angina, ventricular fibrillation and cardiac arrest in association with the use of sibutramine. Of concern is the number of reports where sibutramine has been used 'off label', i.e. prescribed for example to patients with a BMI less than that specified in approved indications for use (BMI greater or equal to 30 kg/m^2 in obese patients, and greater or equal to 27 kg/m^2 where diabetes mellitus type 2 or dyslipidaemia are present).

TGA action

In light of the interim results of the SCOUT study, the TGA has reinforced existing advice in the sibutramine PI regarding its use in patients with cardiovascular risk factors (current or past history of myocardial infarction or angina etc). It has also added a description of the SCOUT study and a precaution that the use of sibutramine should be ceased if it has not been effective in achieving weight loss within the expected timeframe (3 months for non-diabetics and 6 months for diabetics).

A statement regarding the use of sibutramine was published on the TGA's website safety alerts page in January 2010.[2]

Recommendations

Healthcare practitioners are advised to review any information regarding sibutramine, including 'Dear healthcare professional' letters sent by Abbott Australasia, the Australian sponsor of sibutramine, advising doctors of the changes to the PI and to ensure they consult the most current PI when prescribing. A copy of the current PI may be obtained from the TGA eBS Product and Consumer Medicine Information site.[3] In addition prescribers should note the use of sibutramine should be limited to one year in any patient and should not be recommenced if the patient had failed to lose weight with prior use of the drug.

The TGA's review of the safety of the product remains ongoing, and health practitioners are encouraged to report any adverse events occurring in association with the use of sibutramine to the TGA.

References

1. James WP. The SCOUT study: risk-benefit profile of sibutramine in overweight high-risk cardiovascular patients. Eur Heart J Suppl 2005;7(Suppl L):L44-8.
2. Reductil (sibutramine) product information. www.tga.gov.au/alerts/medicines/reductil.htm [cited 2010 May 11]
3. TGA eBusiness Services. www.ebs.tga.gov.au (go to TGA information) [cited 2010 May 11]

Drug-induced pancreatitis and exenatide (Byetta)

Dr Margaret Ward, Office of Medicines Safety Monitoring

Introduction

Drug-induced pancreatitis is estimated to account for between two and five percent of acute presentations of the condition. Medicines cause pancreatitis either by inducing a hypersensitivity reaction or by the generation of a toxic metabolite.[1] A 2005 review of drug-induced pancreatitis in the *Journal of Clinical Gastroenterology* lists many different medicines that may be implicated and suggests that drug-induced pancreatitis should always be considered when other aetiologies have been excluded.[2]

The review identified certain 'at risk' groups, including those who were:

- the elderly
- on multiple medications
- HIV positive
- diagnosed with cancer; or
- receiving immunomodulatory agents.

Adverse drug reaction reports of drug-induced pancreatitis

The TGA's adverse drug reactions database included 581 reports of pancreatitis as of February 2009. Eighteen of these reports documented a fatal outcome. Many different medicines have been implicated, but the most frequent reports include azathioprine (41 reports), valproate (35 reports) and simvastatin (26 reports).[3] Commonly implicated medicine classes include antiviral agents, hypolipidaemic agents and atypical antipsychotic medications.

Exenatide (Byetta)

While many different medicines have been associated with pancreatitis, prescribers should be aware that international postmarketing reports of adverse events associated with exenatide (Byetta) have included cases of pancreatitis.

Exenatide is a peptide amide with several antihyperglycaemic actions of glucagon-like peptide (GLP-1) and is registered for use as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, or a combination of these drugs, but are not achieving adequate glycaemic control.

To October 2007 the US Food and Drug Administration (FDA) had received 30 spontaneous adverse drug reaction reports of acute pancreatitis associated with the use of exenatide. A further six cases of haemorrhagic or necrotising pancreatitis, two of which were fatal, were reported by the FDA in August 2008.[4]

Reviews of the original case series of 30 patients (median age 60 years) showed the median time to onset of symptoms after initiation of therapy was 34 days. Abdominal pain was a presenting feature in 75% of cases.[5-7] At presentation amylase and lipase levels were usually substantially elevated, with amylase levels ranging from 40 to 1845 U/L (median 384 U/L; normal range 30–170 U/L) and lipase levels from 62 to 16970 U/L (median 545 U/L; normal range 7–60 U/L). There was at least one confounding factor (e.g. obesity, hypertriglyceridaemia or alcohol consumption) in 27 (90%) of the patients. In 22 cases the pancreatitis resolved on withdrawal of the drug and in three cases the pancreatitis recurred on resumption of the medicine. Hospitalisation was required in 21 cases and serious complications included acute renal failure and paralytic ileus.

Despite these spontaneous adverse drug reaction data, an analysis of data from a claims-based active drug surveillance system in the USA found no evidence of an increased risk of acute pancreatitis among patients treated with exenatide (around 28 000 patients) compared with those treated with metformin or a sulfonylurea.[8]

Australian adverse reaction reports

To date the TGA has received a total of 22 reports of suspected adverse drug reactions for exenatide. Eight (36%) of these reports relate to pancreatitis and/or elevation of pancreatic enzymes. In 4 of 5 cases reported as pancreatitis, exenatide was the sole suspected medicine. An additional four reports describe episodes of upper abdominal pain and/or ileus, raising the possibility of underlying pancreatitis, so that as many as 12 of the 22 reports may relate to an episode of pancreatitis.

While acute pancreatitis is listed as a rare adverse drug reaction in the Australian PI for exenatide, the TGA recommends that patients are informed of the characteristic symptoms of acute pancreatitis, and if this diagnosis is suspected exenatide and other potentially suspect medicines should be discontinued.

References

1. Greenberger NJ, Toskes PP. Acute and chronic pancreatitis. In: Fauci AS, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al, editors. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008.
2. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol 2005;39:709-16.
3. ADRAC. Drug induced pancreatitis. Aust Adv Drug React Bull 2006;25:22.

4. US Food and Drug Administration. Information for healthcare professionals: Exenatide (marketed as Byetta) - 8/2008 update. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm [cited 2010 May 10]
5. Gallwitz B. Benefit-risk assessment of exenatide in the therapy of type 2 diabetes mellitus. Drug Saf 2010;33:87-100.
6. Cure P, Pileggi A, Alejandro R. Exenatide and rare adverse events. N Engl J Med 2008;358:1969-70.
7. Ahmad SR, Swann J. Exenatide and rare adverse events. N Engl J Med 2008;358:1970-1.
8. Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Curr Med Res Opin 2009;25:1019-27.

WHAT TO REPORT? (You do not need to be certain, just suspicious!)

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. The TGA particularly requests reports of:

- ALL suspected reactions to **new medicines**
- ALL suspected medicines interactions
- Suspected reactions causing
  - death
  - admission to hospital or prolongation of hospitalisation
  - increased investigations or treatment
  - birth defects

For blue cards

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ('blue card') which is available from the website: www.tga.gov.au/adr/bluecard.pdf or from the Office of Medicines Safety Monitoring, phone 1800 044 114.

Reports can also be submitted:

online on the TGA website www.tga.gov.au click on 'Report a problem' on the left
by fax 02 6232 8392
by email ADR.Reports@tga.gov.au

For further information from the Office of Medicines Safety Monitoring:
Phone 1800 044 114 Fax 02 6232 8392 Email ADR.Reports@tga.gov.au