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Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it and sign up for free Medicines Safety Update email alerts on the TGA website at www.tga.gov.au/hp/msu.htm

In this issue:

Oral contraceptives containing drospirenone (Yaz and Yasmin) and venous thromboembolism

Summary

Recently published evidence suggests that drospirenone-containing oral contraceptives may be associated with an increased risk of venous thromboembolism compared with levonorgestrel-containing oral contraceptives. Health professionals should weigh the clinical needs of patients against the possible risk, and educate patients to recognise the signs and symptoms of venous thromboembolism.

New information about the risk of venous thromboembolism (VTE) is being included in the Product Information documents for drospirenone-containing combined oral contraceptives (Yaz, Yasmin) as a result of a recent safety review by the TGA.

Evidence of risk with drospirenone

Two recently published articles suggest a two- to three-fold increase in the risk of VTE (deep vein thrombosis and/or pulmonary embolism) in women taking drospirenone-containing contraceptives compared with those taking contraceptives containing the progestogen levonorgestrel.[1,2]

Previous studies comparing VTE risk in women using drospirenone- or levonorgestrel-containing contraceptives had conflicting results.[3-6]

Advice for health professionals

Health professionals are reminded that oral contraceptives are contraindicated in women with severe or multiple risk factor(s) for venous or arterial thrombosis. Risk factors include, for example, age >35 years, smoking and prolonged immobilisation.

The clinical needs of patients should be weighed against the possible slight increase in the risk of VTE, and patients should be educated to recognise the signs and symptoms of VTE. Health professionals are encouraged to report all adverse events associated with all oral contraceptives to the TGA.

References

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3. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009;339:b2890.
4. Van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921.
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6. Dinger JC, Heinemann LA, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception 2007;75:344-54.

Pioglitazone and risk of bladder cancer

Summary

Use of pioglitazone for more than a year may be associated with an increased risk of bladder cancer. Consider the risk of bladder cancer when prescribing pioglitazone. Avoid pioglitazone in patients with bladder cancer or a history of bladder cancer. Ask patients taking pioglitazone to report blood in the urine, urinary urgency, pain on urination, and back or abdominal pain.

Pioglitazone is used to treat type 2 diabetes mellitus inadequately controlled by diet and exercise. Recent studies have suggested a link between pioglitazone and bladder cancer. At the time of writing, Product Information documents for pioglitazone-containing medicines were being updated to reflect this new evidence.

Clinical evidence for bladder cancer risk with pioglitazone

In a cardiovascular outcomes study of patients with type 2 diabetes an increased incidence of bladder cancer was observed in subjects receiving pioglitazone (14 cases or 0.5%) compared with subjects in the placebo arm (5 cases or 0.2%).[1] After excluding patients in whom exposure to the study drug was <1 year at time of diagnosis of bladder cancer, there were six (0.2%) cases in the pioglitazone arm and two (0.1%) cases in the placebo arm.

Two recent observational cohort studies of diabetic patients ≥40 years of age have found an association between pioglitazone and bladder cancer (see table). In an interim analysis of a study conducted in the United States, the adjusted hazard ratio for bladder cancer in patients exposed to pioglitazone compared with other patients was 1.2 (95% confidence interval [CI] 0.9–1.5).[2] An unpublished French study (conducted by the government agency Agence Francaise de Securite Sanitaire des Produits de Sante) has confirmed these results.[3] In both studies, the effect was more pronounced in men than women.

Advice for health professionals

Until there is a better understanding of the link between bladder cancer and pioglitazone, it is prudent to avoid pioglitazone in patients with bladder cancer or a history of bladder cancer. This advice is based on the assumption that pioglitazone or a metabolite may affect bladder cancer initiation, promotion or progression, rather than on clinical evidence of deterioration in patients with bladder cancer or recurrence in patients with a history of bladder cancer.

Consider the risk of bladder cancer in the care of all patients treated with pioglitazone. Advise patients of a small absolute increased risk of bladder cancer with use of pioglitazone, and ask them to report any possible signs or symptoms of bladder cancer such as blood in the urine, urinary urgency, pain on urination, or back or abdominal pain.

Patients or healthcare professionals are encouraged to report cases of bladder cancer in patients who have taken pioglitazone – see 'What to report' on page 151.

References

1. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-89.
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3. Sponsor communication to the TGA, July 2011.

Table

Results of recent cohort studies investigating the potential association of pioglitazone with bladder cancer

	US study[2] (n=193 099)	French study[3] (n=1 491 060)
Percent ever exposed to pioglitazone	15.6%	10.4%
Adjusted hazard ratio* (95% CI†)	1.2 (0.9–1.5)	1.2 (1.05–1.4)
Hazard ratio (95% CI†); 12–23 months of use (vs never exposed)	1.4 (0.9–2.1)	1.3 (1.02–1.8)
Hazard ratio (95% CI†); ≥24 months of use (vs never exposed)	1.4 (1.03–2.0)	1.4 (1.04–1.8)

* chance of bladder cancer in patients on pioglitazone relative to chance in diabetic patients never on pioglitazone, adjusted for multiple risk factors

† CI = confidence interval

Modafinil (Modavigil) – safety update

Summary

Several safety-related changes and recommendations have been included in the recently updated Product Information for modafinil (Modavigil) as a result of a recent benefit–risk review by the TGA.

Modafinil is a wakefulness-promoting agent that has been available in Australia since July 2002. The precise mechanism of action is unclear.

The TGA has reviewed the available clinical trial data, national and international postmarketing spontaneous adverse event data and published literature relating to modafinil adverse drug reactions to 1 October 2010. This review was initiated because of postmarket reports of serious skin, psychiatric, nervous system and cardiovascular adverse events.

The TGA concluded that:

- some additional safety information should be included in the Product Information (see box)
- the benefits of modafinil continued to outweigh the risks for the indications to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy and in patients with obstructive sleep apnoea/hypopnoea syndrome as an adjunct to continuous positive airway pressure (CPAP)
- the indication to treat excessive sleepiness associated with moderate-to-severe chronic shift work sleep disorder should be revised to include only patients where non-pharmacological interventions (e.g. planned napping) are unsuccessful or inappropriate.

Important information when prescribing modafinil

Modafinil can improve the symptom of excessive sleepiness but does not treat the underlying cause. Therefore, when used to improve wakefulness in patients with obstructive sleep apnoea/hypopnoea syndrome, modafinil should only be used as an adjunct to CPAP.

Box

Key safety related updates to the modafinil Product Information[1]

Precautions	Safety details
Multi-organ hypersensitivity reactions	Have occurred soon after starting modafinil Very rare but potentially life-threatening Diverse presentation – typically fever, rash and other organ system involvement (e.g. hepatitis) If suspected, cease modafinil and do not restart
Psychiatric disorders	Includes exacerbation of pre-existing psychiatric disorders and psychiatric symptoms occurring *de novo* Modafinil has been associated with aggressive and hostile behaviour, suicidal ideation and suicide-related behaviour, psychotic symptoms, mania, depression and anxiety
Cardiovascular disease	Ischaemic heart disease has been reported in patients with and without a history of cardiovascular disease Atrial fibrillation and premature ventricular contractions have been reported Patients with coronary artery disease, a recent history of myocardial infarction or unstable angina should receive specialist evaluation before modafinil is considered Blood pressure should be adequately controlled in hypertensive patients before initiating treatment with modafinil A baseline ECG is recommended in all patients prior to starting modafinil
Dependence potential	Exercise caution when prescribing modafinil for patients with a history of substance abuse as it may cause psychoactive and euphoric effects
Use in children and adolescents	Modafinil is not approved for use in paediatric patients for any indication Neuropsychiatric and serious skin reactions have been reported in paediatric patients
Dose-related adverse reactions	The development of skin and hypersensitivity reactions and central nervous system, psychiatric and cardiovascular system adverse reactions appears to be related to higher doses of modafinil

Treatment with modafinil should be initiated and supervised by physicians with appropriate experience in the treatment of sleep disorders who have access to sleep laboratory diagnostic facilities. Modafinil is contraindicated in pregnancy.

The effectiveness of oral contraceptives may be impaired due to the induction of the metabolising enzyme cytochrome P450 3A4. Evaluate cardiovascular, psychiatric and substance abuse status before starting modafinil and monitor patients regularly for skin reactions, cardiovascular disease, psychiatric illness and signs of modafinil abuse. Start with the lowest recommended dose and monitor the patient at every dose adjustment. The updated Product Information for modafinil can be accessed from the TGA website (www.tga.gov.au).

Reference

1. Modavigil Product Information. CSL Limited. 2011 May.

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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. We particularly request 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, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the April, August and December issues of *Australian Prescriber*
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