



Medicines Safety Update

Volume 6, Number 3, June 2015

In this issue

- Methotrexate and hepatitis B reactivation
- Ivabradine and cardiovascular events in patients with angina
- Ethinylestradiol/etonogestrel vaginal ring and thromboembolic risk

Methotrexate and hepatitis B reactivation

Health professionals are advised that the Product Information for methotrexate has been updated to include a precaution regarding reactivation of hepatitis B virus.

Methotrexate is an immunosuppressive agent. Its principal mechanism of action is the competitive inhibition of the enzyme folic acid reductase.

It is indicated for the treatment of rheumatoid arthritis, severe psoriasis and certain types of cancers, including breast cancer, gestational choriocarcinoma and lymphosarcoma.

A report published in the *Journal of Gastroenterology and Hepatology* in October 2013 detailed a case of fatal acute liver failure due to hepatitis B reactivation in a patient being treated with methotrexate, despite prior serological evidence of hepatitis B immunity.¹

Hepatitis B reactivation is characterised by high levels of hepatic enzymes and fluctuations in viral DNA levels in a patient who is hepatitis B surface antigen positive.²

Hepatitis B reactivation had not previously been mentioned in the Product Information (PI) for methotrexate. However, the PI did carry warnings relating to potential hepatotoxicity and the need to test for hepatitis B prior to commencing treatment with the drug.

The updated precaution in the PI states that some cases of hepatitis B reactivation have occurred after discontinuation of methotrexate.

Adverse events

To 21 February 2015, the TGA has received two

reports of possible hepatitis B reactivation associated with methotrexate treatment, which includes the case that was featured in the *Journal of Gastroenterology and Hepatology*.

Analysis of these two cases found that they were confounded by other drug therapy. However, a causal role for methotrexate could not be excluded.

Considering the seriousness of complications associated with hepatitis B reactivation and the fact that methotrexate is now the most commonly used first-line drug therapy for rheumatoid arthritis in Australia, the TGA determined that health professionals should be provided further information about this potential adverse event.

Information for health professionals

The updated PI advises health professionals to perform clinical and laboratory evaluation of pre-existing liver disease in patients with prior hepatitis B or hepatitis C infections before commencing treatment with methotrexate.

The TGA also recommends that health professionals closely monitor such patients who are already taking methotrexate. Based on these evaluations, treatment or continuation of treatment with methotrexate may not be appropriate for some patients.

REFERENCES

1. Phillips T, Venugopol K, Kontorinis N. A case of fatal acute liver failure due to Hepatitis B reactivation in a patient on Methotrexate, despite prior serological evidence of hepatitis immunity. *Journal of Gastroenterology and Hepatology*, 2013 Oct 28: 170-170.
2. Villalba S, Miguel M, Sala R. How does one manage patients with RA and positive serology to HBV, HCV and HIV. *Reumatologia Clinica*, 2011(3):203-207.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

Ivabradine and cardiovascular events in patients with angina

The Product Information for ivabradine has been updated in an effort to reduce the risk of cardiovascular events in patients who take the medicine for angina.

Ivabradine is marketed in Australia as Coralan and has 5 mg and 7.5 mg dosage forms. It is a heart rate lowering agent, which acts by selective inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate.

The changes to ivabradine's Product Information (PI) include changes to its approved indications. The updated indications are:

- Symptomatic treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm and heart rate at or above 70 beats per minute (bpm), who are unable to tolerate or have a contraindication to the use of beta-blockers, OR in combination with atenolol 50 mg once daily when angina is inadequately controlled.
- Treatment of symptomatic chronic heart failure of New York Heart Association Classes II or III and with documented left ventricular ejection fraction $\leq 35\%$ in adult patients in sinus rhythm and with heart rate at or above 77 bpm, in combination with optimal standard chronic heart failure treatment.

The contraindications have been amended to change resting heart rate prior to treatment from '60 bpm' to '70 bpm', as well as to add examples of potent cytochrome P450 3A4 (CYP3A4) inhibitors and a new contraindication for 'combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties'.

The Precautions, Interactions with Other Medicines, Adverse Events and Dosage and Administration sections of the PI have also been updated to include new information to help reduce the risk of cardiovascular events for patients with angina.

Background

In May 2014, the sponsor, Servier Laboratories, notified the TGA about an emergent safety issue following the preliminary results of a pre-specified subgroup of patients with symptomatic angina

in the SIGNIFY phase III study ('Study assessing the morbidity-mortality benefits of the I_f inhibitor ivabradine in patients with coronary artery disease'). The randomised placebo-controlled study was performed in 19,102 coronary artery disease patients without clinical heart failure.¹

The TGA published an Early Warning System monitoring communication regarding ivabradine on 23 June 2014.

Since then, the TGA has completed an analysis of the findings of the SIGNIFY study.

SIGNIFY study findings

The findings indicated that a subgroup of patients with symptomatic angina had a small, statistically significant increase in the combined risk of cardiovascular death and non-fatal heart attack with ivabradine compared to placebo, corresponding with an odds ratio of 1.18, 95% confidence interval (CI) 1.03-1.35, $p=0.018$ (3.4% vs 2.9% yearly incidence rates). The data also indicated a higher risk of bradycardia with ivabradine compared with placebo (17.9% vs 2.1%).

In the SIGNIFY study, atrial fibrillation was observed in 5.3% of patients taking ivabradine compared to 3.8% in the placebo group.

In a pooled analysis including more than 40,000 patients from all the Phase II/III double blind controlled clinical trials (whatever the indication) with a duration of at least three months, the incidence of atrial fibrillation was 4.9% in ivabradine treated patients compared to 4.1% in controls, corresponding to an odds ratio of 1.26, 95% CI 1.15-1.39.

Analysis of the data indicates that cardiovascular adverse events may be associated with the patient's heart rate being less than 60 bpm.

Among the patients taking ivabradine who experienced bradycardia, more than 30% had a resting heart rate below 50 bpm on at least one occasion.

In the SIGNIFY study, ivabradine treatment did not demonstrate a beneficial effect on the primary composite endpoint of cardiovascular death or non-fatal myocardial infarction compared to placebo, corresponding to an odds ratio of 1.08, 95% CI 0.96-1.20, $p=0.197$ (3.0% vs 2.8% yearly incidence rates).

Information for health professionals

Health professionals are encouraged to review the updated PI for ivabradine. Please note that ivabradine is indicated only for symptomatic treatment of chronic stable angina. The drug has no benefit on cardiovascular outcomes, such as myocardial infarction or cardiovascular death, in patients with symptomatic chronic stable angina pectoris.

Ivabradine must not be initiated in patients who have a pre-treatment resting heart rate below 70 bpm and must not be used concomitantly with heart rate reducing calcium channel blockers, verapamil and diltiazem.

Serial heart rate measurements, electrocardiogram or ambulatory 24-hour monitoring should be considered when determining resting heart rate before commencing ivabradine treatment and in patients taking ivabradine when titration is considered.

If, during treatment, resting heart rate decreases persistently below 50 bpm or the patient experiences

symptoms related to bradycardia, such as dizziness, fatigue or hypotension, the dose must be titrated downward. If heart rate remains below 50 bpm or symptoms of bradycardia persist, treatment with ivabradine should be discontinued.

Concomitant use with QT-prolonging medicines should be avoided, as QT-prolongation can be exacerbated by heart rate reduction. If such treatment is necessary, close cardiac monitoring is required.

Exercise caution if using concomitantly with potassium-depleting diuretics, as hypokalemia can increase the risks of arrhythmia.

You are advised to discuss with patients the signs and symptoms of the cardiovascular events identified in the ivabradine PI and instruct them to contact a health professional if any are suspected.

REFERENCE

1. Fox K, Ford I, Steg PG, Tardif JC, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014; 371: 1091-9.

Ethinylestradiol/etonogestrel vaginal ring and thromboembolic risk

Health professionals are advised that the Product Information for ethinylestradiol/etonogestrel vaginal ring, marketed as NuvaRing, has been updated to provide further information about thromboembolic risks.

NuvaRing is a contraceptive ring for vaginal use, which releases ethinylestradiol and etonogestrel over a period of three weeks.

While NuvaRing is delivered vaginally, the active ingredients are the same as combined hormonal oral contraceptives, and the risks of arterial and venous thromboembolism (ATE and VTE) are similar for all of these products.

Health professionals are reminded that the risk of VTE increases with:

- increasing age
- a family history of VTE or ATE, or a hereditary predisposition
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma
- obesity.

It is possible that the risk of VTE may also increase with the presence of superficial thrombophlebitis and varicose veins.

Meanwhile, the risk of ATE complications increases with:

- increasing age
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- dyslipoproteinaemia
- obesity
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation
- a family history, including any occurrence of ATE in a sibling or parent at a relatively early age.

As with other hormonal contraception use, an increase in frequency or severity of migraine (which may be prodromal of a cerebrovascular event) may be a reason to consider immediate discontinuation of NuvaRing use.

Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE or VTE include Factor V Leiden mutation, activated protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency,

protein S deficiency and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease and sickle cell disease.

Considering the above risk factors, the Precautions section of **Product Information (PI)** has been updated with further information about thromboembolic events.

Information for health professionals

Health professionals are encouraged to review the updated PI for NuvaRing.

You should advise patients to contact them in the event of aggravation, exacerbation or first appearance of the above risk factors.

NuvaRing should not be used in the presence of any of the following conditions:

- Presence or history of ATE or VTE, such as deep venous thrombosis, pulmonary embolism or myocardial infarction, or of a cerebrovascular accident.

- Known predisposition for ATE or VTE.
- Presence or history of prodromi of a thrombosis, for example transient ischaemic attack or angina pectoris.
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.

Presence of a severe or multiple risk factor(s) for ATE or VTE may also constitute a contraindication.

Should any of the above conditions appear for the first time during the use of NuvaRing, it should be removed immediately.

Before prescribing, you are encouraged to discuss with patients the thromboembolic risks associated with NuvaRing.

The benefits and risks of using this product should be considered in each patient's individual circumstances.

Please report any suspected adverse events involving NuvaRing to the TGA.

This will contribute to the ongoing collection of information that enables the TGA to monitor the safety of these products in Australia.



What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and 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
- **online** at www.tga.gov.au
- **by fax** to 02 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Post-market Surveillance Branch on 1800 044 114.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

For correspondence or further information about Medicines Safety Update, contact the Post-market Surveillance Branch at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Post-market Surveillance Branch

Editor:
Dr Katherine Gray

Deputy Editor:
Mr Michael Pittman

Acting TGA Principal Medical Adviser:
Dr Tony Gill

Contributors include:
Dr Claire Behm
Dr Richard Hill
Dr Iga Policinska
Dr Pam Whalan

DISCLAIMER

Medicines Safety Update is aimed at health professionals. It is intended to provide practical information to health professionals on medicine safety, including emerging safety issues. The information in Medicines Safety Update is necessarily general and is not intended to be a substitute for a health professional's judgment in each case, taking into account the individual circumstances of their patients. Reasonable care has been taken to ensure that the information is accurate and complete at the time of publication. The Australian Government gives no warranty that the information in this document is accurate or complete, and shall not be liable for any loss whatsoever due to negligence or otherwise arising from the use of or reliance on this document.

© Commonwealth of Australia 2015.

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the Copyright Act 1968 or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to tga.copyright@tga.gov.au.