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Department of Health
Therapeutic Goods Administration

Medicines Safety Update

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Viekira PAK and Viekira PAK-RBV – interaction with ethinyloestradiol

Health professionals are advised that, while the Product Information documents for Viekira PAK and Viekira PAK-RBV carry a precaution for a potential interaction with ethinyloestradiol-containing medicines and use of these medicines is listed as a contraindiction, not all ethinyloestradiol-containing medicines currently provide similar information regarding Viekira PAK and Viekira PAK-RBV.

Viekira PAK is a composite pack containing paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets, and dasabuvir 250 mg tablets, while Viekira PAK-RBV contains paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets, dasabuvir 250 mg tablets and 200 mg, 400 mg or 600 mg ribavirin tablets. Viekira PAK and Viekira PAK-RBV are indicated for the treatment of genotype 1 chronic hepatitis C infection, including patients with compensated cirrhosis. Duration of therapy and addition of ribavirin are dependent on patient population.

Ethinylestradiol is a synthetic, steroidal estrogen and a derivative of estradiol, and is used in almost all formulations of combined birth control pills, as well as in contraceptive patches and contraceptive vaginal rings.

The Product Information (PI) documents for Viekira PAK and Viekira PAK-RBV state that during clinical trials transient, asymptomatic elevations of alanine transaminase (ALT) to greater than five times the upper limit of normal occurred in approximately 1% of all subjects. These ALT elevations were significantly more frequent in female subjects who were using ethinylestradiol-containing medicines. ALT elevations typically occurred during the first four weeks of treatment and declined within approximately two weeks of onset with continued dosing of Viekira PAK or Viekira PAK-RBV.

The PIs instruct that ethinylestradiol-containing medicines must be discontinued prior to starting therapy with Viekira PAK or Viekira PAK-RBV and alternative contraceptive agents used. Ethinylestradiol-containing medicines can be restarted approximately two weeks following completion of treatment with Viekira PAK or Viekira PAK-RBV.

While some sponsors of ethinylestradiol-containing medicines have added information about this interaction to their PIs, the PIs for all such medicines have not yet been updated.

Health professionals are encouraged to report any adverse events relating to this issue, or any other suspected serious or unexpected adverse effect, to the TGA or the relevant sponsors.

Additional product - Technivie

Please note that Technivie , a recently registered medicine for treatment of adult patients (in combination with ribavirin) with genotype 4 chronic HCV, is also affected by this issue. The PI for Technivie also carries a precaution for a potential interaction with ethinyloestradiol-containing medicines and use of these medicines is listed as a contraindication. Technivie is not yet marketed in Australia.

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

TGA Health Safety Regulation

Ingenol mebutate – hypersensitivity reactions, herpes zoster and eye injury

Health professionals are advised that information regarding the risk of hypersensitivity reactions, herpes zoster and ophthalmic injury has been added to the Product Information for ingenol mebutate.

Ingenol mebutate, marketed in Australia as Picato gel, is indicated in actinic keratosis. Its mechanism of action is to induce local lesion cell death and to promote an inflammatory response by production of proinflammatory cytokines and chemokines to infiltrate the immunocompetent cells. This mechanism in itself causes application site pain, pruritus, irritation, infection and oedema.

The TGA investigated safety concerns relating to ingenol mebutate following reports of severe allergic reactions, herpes zoster, ophthalmic injury and local skin reactions in the United States. Some of the cases were associated with the medicine not being used in accordance with its directions for use.

The TGA investigation found that the risk of local skin reactions was well-communicated in the Product Information (PI). However, the PI did not address the potential adverse events of hypersensitivity/anaphylaxis, herpes zoster reactivation or ophthalmic injury.

Based on this, the TGA worked with the sponsor to update the Precautions and Adverse Effects sections of the PI for ingenol mebutate with appropriate information.

The Consumer Medicine Information (CMI) for ingenol mebutate instructs patients to 'follow carefully all directions given to you by your doctor or pharmacist'. With this in mind, provide your patients clear instructions regarding application of this medicine and consider providing them a copy of the CMI.

Testosterone and arterial thromboembolism/venous thromboembolism

Health professionals are reminded that testosterone replacement therapy should only be prescribed in line with the registered indications and Pharmaceutical Benefits Scheme restrictions. This advice follows a TGA review of testosterone in relation to the risk of arterial thromboembolism/venous thromboembolism.

Testosterone products registered in Australia have one or more of the following indications:

- androgen replacement therapy for confirmed testosterone deficiency in males
- testosterone replacement therapy for confirmed testosterone deficiency in males
- testosterone replacement in primary and secondary male hypogonadism
- testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

Testosterone is an Authority Required Pharmaceutical Benefits Scheme (PBS) listing (see 'PBS restriction' section below for further details).

Background

The TGA has been monitoring testosterone in relation to the risk of arterial thromboembolism (ATE)/venous thromboembolism (VTE) since publication of US Food and Drug Administration (FDA) safety communications on 31 January 2014 and 19 June 2014 respectively.[1,2]

The European Medicines Agency (EMA) published a review of testosterone and increased cardiovascular risk on 21 November 2014, in which it concluded that there was no consistent evidence of an increased risk of ATE/VTE.[3,4,5]

On 3 March 2015, the FDA stated that, based on the available evidence from published studies and expert input, it had concluded that there was a

possible increased cardiovascular risk associated with testosterone use. These studies included aging men treated with testosterone. The FDA requested that manufacturers update their product labels to reflect the possibility of cardiovascular risk.[6]

As part of its review, the TGA sought advice from the Advisory Committee on the Safety of Medicines (ACSOM). At its 2 September 2016 meeting, ACSOM found that there was evidence of a weak signal of increased cardiovascular risks with use of testosterone medications in general (but not for specific events).[7]

The TGA noted this advice, but given there is only a weak signal, has determined that it is not necessary to update the Product Information documents for testosterone medicines at this time.

Information for health professionals

This safety concern relates to the potential for increased risk of ATE and serious VTE events with the use of medicines containing testosterone in all patients, but of particular concern are two specific patient populations:

- ageing men who are not hypogonadal, who use testosterone off-label to treat a normal age-related decline in testosterone levels ('age-related hypogonadism') and may be at higher risk of cardiovascular adverse events due to advancing age and comorbidities
- younger men who use testosterone off-label to achieve higher than normal testosterone levels for the purpose of building muscle mass.

There have been post-marketing reports of VTE, including deep vein thrombosis and pulmonary embolism , and ATE, including myocardial infarction and stroke, in patients using testosterone products. However, it should be noted that it is often difficult to determine causality for post-marketing reports.

The TGA has also received adverse event reports associated with off-label use. Off-label prescribing of testosterone to patients who do not meet the clinical and treatment criteria for testosterone deficiency may place them at increased risk of serious adverse events, including ATE and VTE.

Testosterone levels decline naturally with age and most men do not require testosterone replacement therapy.

Long-term randomised controlled trials specifically designed and adequately powered to assess the cardiovascular outcomes of testosterone replacement therapy in men have not been published. To date, the epidemiologic studies and randomised controlled trials that have been published are inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with use of testosterone replacement therapy in men.

Testosterone replacement therapy should only be prescribed to males who meet the clinical criteria for confirmed testosterone deficiency, and are under the care of a specialist medical practitioner; in line with the registered indications and PBS restrictions.

The TGA advises that health professionals consider the potential risk of VTE and ATE before prescribing testosterone to patients. Patients should be informed of this possible risk when deciding whether to use or continue to use testosterone.

PBS restrictions

The PBS restrictions for testosterone products are as follows:

Androgen deficiency

Clinical criteria:

- Patient must have an established pituitary or testicular disorder.

Treatment criteria:

- Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.

The name of the specialist must be included in the authority application.

Androgen deficiency

Clinical criteria:

- Patient must not have an established pituitary or testicular disorder,

AND

- The condition must not be due to age, obesity, cardiovascular diseases, infertility or drugs.

Population criteria:

- Patient must be aged 40 years or older.

Treatment criteria:

- Must be treated by a specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.

Androgen deficiency is defined as:

(i) testosterone level of less than 6 nmol per litre; OR

(ii) testosterone level between 6 and 15 nmol per litre with high luteinising hormone (LH) (greater than 1.5 times the upper limit of the eugonodal reference range for young men, or greater than 14 IU per litre, whichever is higher).

Androgen deficiency must be confirmed by at least two morning blood samples taken on different mornings.

The dates and levels of the qualifying testosterone and LH measurements must be, or must have been provided in the authority application when treatment with this drug is or was initiated.

The name of the specialist must be included in the authority application.

Micropenis

Population criteria:

- Patient must be under 18 years of age.

Treatment criteria:

- Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.

The name of the specialist must be included in the authority application.

Pubertal induction

Population criteria:

- Patient must be under 18 years of age.

Treatment criteria:

- Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.

The name of the specialist must be included in the authority application.

Constitutional delay of growth or puberty

Population criteria:

- Patient must be under 18 years of age.

Treatment criteria:

- Must be treated by a specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist or a Fellow of the Australasian Chapter of Sexual Health Medicine; or in consultation with one of these specialists; or have an appointment to be assessed by one of these specialists.

The name of the specialist must be included in the authority application.

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Medicine shortages information

The Medicine Shortages Information Initiative provides information about a temporary or permanent disruption to the supply of a prescription medicine. Health professionals and consumers are invited to subscribe to the Medicine Shortages email list to receive an alert when there is new or updated medicine shortage information reported to the TGA.

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 Pharmacovigilance and Special Access Branch on 1800 044 114.

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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 TGA's Pharmacovigilance and Special Access Branch at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Pharmacovigilance and Special Access Branch

Editor:
Dr Jane Cook

Deputy Editor:
Mr Michael Pittman

TGA Principal Medical Adviser:
Adj Prof Tim Greenaway

Contributors include:
Dr Claire Behm
Dr Iga Policinska