Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Ustekinumab and serious skin conditions

Health professionals are advised that the Product Information for ustekinumab has been updated with a precaution regarding serious skin conditions.

Ustekinumab, marketed in Australia under the trade name Stelara, is a human monoclonal antibody that is indicated for the treatment of:

- moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy
- signs and symptoms of active psoriatic arthritis (used alone or in combination with methotrexate) in adult patients where response to previous non-biological disease-modifying antirheumatic drug therapy has been inadequate.

The Product Information (PI) update followed a TGA investigation relating to serious skin conditions, namely exfoliative dermatitis (also known as erythroderma) and erythrodermic psoriasis, associated with ustekinumab treatment. Before the update, the ustekinumab PI did not mention exfoliative dermatitis or erythrodermic psoriasis.

This safety concern was also identified and investigated by other regulators, including the European Medicines Agency and Health Canada.

Exfoliative dermatitis most commonly causes widespread scaly, erythematous dermatitis on the skin. This scaling can have severe metabolic effects, including loss of heat, water, protein and electrolytes, and susceptibility to infection. The mortality rate of exfoliative dermatitis is about 30%. However, drug-induced exfoliative dermatitis has a good prognosis once the inciting medicine is withdrawn and appropriate treatment is provided.

Erythrodermic psoriasis is a severe variant of psoriasis, which if left untreated can lead to serious morbidity and even death. Clinically, it is characterised by diffuse red-violet erythema and fine scaling over all or most of the body surface area.

Adverse events

To 20 May 2015, the TGA received one report of erythrodermic psoriasis associated with ustekinumab treatment, and no reports that specified exfoliative dermatitis as an adverse event.

Information for health professionals

The TGA's investigation of this safety concern found that there was insufficient information at this point in time to establish a definite causal relationship between exfoliative dermatitis or erythrodermic psoriasis and treatment with ustekinumab.

However, given the seriousness of these adverse events and their potential reversibility after cessation of the inciting medicine, the TGA considered that health professionals should be made aware of this possible association.

The updated ustekinumab PI states that patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease.

As part of the monitoring of the patient's psoriasis, you should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur and a drug reaction is suspected, ustekinumab should be discontinued and treatment provided.

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

TGA Health Safety Regulation

Sodium glucose co-transporter 2 inhibitors and diabetic ketoacidosis

Health professionals are advised that serious cases of diabetic ketoacidosis have been reported in patients being treated with inhibitors of sodium glucose co-transporter 2. In some of these cases, the presentation of diabetic ketoacidosis was atypical.

Sodium glucose co-transporter 2 (SGLT2) inhibitors, such as canagliflozin, dapagliflozin and empagliflozin, belong to a class of medicine that improves glycemic control in patients with type 2 diabetes mellitus.

The SGLT2 protein is selectively expressed in the kidney, and is the predominant transporter responsible for the reabsorption of glucose from the glomerular filtrate back into the circulation.

Inhibition of this protein reduces renal glucose reabsorption, leading to urinary glucose excretion.

These medicines have the following indications:

- as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is contraindicated, or not tolerated
- as combination therapy in patients with type 2 diabetes with other anti-hyperglycaemic agents including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Diabetic ketoacidosis

Early signs and symptoms of diabetic ketoacidosis (DKA), typically developed over 24 hours, include abdominal pain, nausea, vomiting, anorexia, excessive thirst, difficult breathing, unusual fatigue and sleepiness.

If DKA is not diagnosed early and treatment initiated, more serious signs and symptoms including dehydration, deep gasping breathing, confusion and coma can potentially develop.

DKA occurs most commonly in patients with type 1 diabetes, although it can occur in type 2 diabetes.

It is usually accompanied by glucose levels greater than 14 mmol/L (250 mg/dL).

However, in some of the reported cases of DKA associated with SGLT2 inhibitors, patients demonstrated glucose levels of less than 11 mmol/L (200 mg/dL).

Information for health professionals

This article follows up a statement published on the TGA website on 13 August 2015, with additional information for health professionals.

The number of reports of DKA associated with SGLT2 inhibitors is low. However, DKA is a serious, potentially life-threatening complication and there is a risk of delay in diagnosis and treatment as a result of its presentation being atypical in some cases.

If you are treating patients who are taking SGLT2 inhibitors, you are advised to educate them regarding the signs and symptoms of metabolic acidosis.

Instruct them to immediately seek medical advice if any such signs or symptoms are experienced.

Patients being treated with these medicines should be assessed for DKA when they present with signs or symptoms of metabolic acidosis in order to prevent delayed diagnosis and patient management.

If DKA is suspected, treatment with SGLT2 inhibitors should be discontinued. Meanwhile, if DKA is confirmed, appropriate measures should be taken to correct the DKA and to monitor glucose levels.

In some of the reported cases, just before or at the same time as the DKA occurred, patients experienced acute illness (such as, urinary tract infection, urosepsis, gastroenteritis, influenza, trauma or surgery), reduced caloric or fluid intake, and/or reduced insulin dose.

The underlying mechanism for SGLT2 inhibitor-associated DKA has not been established.

Some of the reported cases involved off-label use in patients with type 1 diabetes.

Prescribers are reminded that SGLT2 inhibitors should be used according to their respective Product Information. Type 1 diabetes is not an approved indication for these medicines.

If you have any further questions about this issue, contact the relevant sponsor using the below details:

- canagliflozin: Janssen-Cilag – phone 1800 226 334 or email medinfo@janau.jnj.com.
- dapagliflozin: AstraZeneca – phone 1800 805 342 or email medinfo.australia@astrazeneca.com
- empagliflozin: Boehringer Ingelheim – phone 1800 226 315 or email medinfo.au@boehringer-ingelheim.com.

Registering to report adverse events online

Health professionals who report medicine and vaccine adverse events online (or who would like to start providing reports in this way) are encouraged to consider becoming a registered Adverse Drug Reaction System user.

The TGA relies on adverse event reports submitted by health professionals to help it effectively monitor the safety of therapeutic goods in Australia.

There are many benefits in registering as an Adverse Drug Reaction System (ADRS) user, especially if you are a frequent reporter.

Being a registered ADRS user enables you to:

- access a pre-populated reporting page
- view previous reports submitted under that log in
- return to existing reports to attach supporting documentation.

If you do not report on a regular basis, but you wish to report online, you can still report as a non-registered user. Reporting as a non-registered user means that you do not need to maintain login and password details.

To register or make an online report as a non-registered user, visit the TGA eBusiness Services ADRS webpage.

In addition to the online reporting facility, there are a number of other avenues available for reporting adverse events to the TGA. You can:

- submit a report directly from MIMS Online
- complete a 'Blue card' and submit it to the TGA via email, fax or mail
- send an email to ADR.reports@tga.gov.au
- call the TGA on 1800 044 114
- report adverse events directly to the sponsor of the medicine or vaccine.

Thank you to all health professionals who have provided medicine and vaccine adverse event reports. Your efforts are greatly appreciated.

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.

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

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