



# Medicines Safety Update

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## Infliximab safety information

Health professionals are advised that the Product Information for infliximab is being updated with new information relating to mycosis fungoides. Additionally, you are reminded that treatment with infliximab can result in lupus-like syndrome in some patients.

Infliximab is a chimeric human-murine monoclonal antibody that binds to human tumour necrosis factor alpha (TNF $\alpha$ ) and inhibits its activity. TNF $\alpha$  is a pro-inflammatory and immunoregulatory cytokine that, when overexpressed, mediates chronic inflammation.

It is indicated for the treatment of:

- rheumatoid arthritis (in combination with methotrexate)
- ankylosing spondylitis
- psoriatic arthritis
- psoriasis
- Crohn's disease
- ulcerative colitis.

Infliximab is marketed in Australia as Remicade, as well as biosimilar brands, Inflectra and Renflexis.

### Mycosis fungoides

The TGA identified a safety signal based on three local adverse event reports, which gave an elevated proportional reporting ratio for mycosis fungoides (a type of cutaneous T-cell lymphoma) and the use of infliximab. Based on these reports and further analysis of the signal, the TGA is working with the sponsor of Remicade to add information about this condition to the Adverse Effects section of the [Product Information](#) (PI). Once Remicade, as the innovator brand, makes changes, sponsors of biosimilar

products are required to update their PI documents to reflect the new information.

Mycosis fungoides is a rare disease but is the most common type of cutaneous T cell lymphoma.<sup>1</sup>

Patients commonly present with localised or widespread skin patches, plaques, skin tumours and/or generalised erythroderma. Non-sun-exposed skin is commonly affected. Especially in the early stages, the skin lesions can resemble common skin disorders such as eczema and psoriasis, making diagnosis difficult.<sup>1,2</sup>

The course of mycosis fungoides is variable. Some patients have disease that remains limited to the skin whereas others develop extra cutaneous disease affecting the lymph nodes, blood or visceral organs.<sup>1</sup>

Early stage disease confined to the skin (patch or plaque disease) can be treated with skin-directed therapies (such as radiotherapy, ultraviolet light therapy, topical chemotherapy and topical immunomodulatory therapy) and has a much better prognosis than later stage disease, which is largely incurable.<sup>3</sup>

The cause of mycosis fungoides remains unclear but is thought to involve genetic and epigenetic abnormalities.<sup>4</sup> Possible links with TNF $\alpha$  therapy<sup>2,5</sup> and psoriasis itself<sup>2</sup> have been described. The three reports of mycosis fungoides associated with infliximab received by the TGA occurred in the setting of the treatment for indications other than psoriasis.

Health professionals are reminded to closely monitor the skin of patients treated with infliximab and consider the diagnosis of mycosis fungoides in patients who present with lesions, such as erythematous patches or plaques.

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

## Lupus-like syndrome

The relative deficiency of TNF $\alpha$  caused by treatment with infliximab is well documented and can result in the initiation of an autoimmune process in a subgroup of susceptible patients.

The PI for infliximab includes information about lupus-like syndrome in the Special Warnings and Precautions for Use, and Adverse Effects sections. The reaction is listed as uncommon.

Routine TGA monitoring has identified an increase in the number of adverse event reports involving infliximab and systemic lupus erythematosus or lupus-like syndrome during 2017 and 2018. In 2017, the TGA received 21 reports (20 listing infliximab as sole-suspected) and in 2018 up to 11 September 2018 the TGA has received 15 reports (13 listing infliximab as sole suspected). In comparison, 6 reports were received in 2015 and 9 reports were received in 2016.

As at 11 September 2018, there is a total of 114 reports of lupus-like syndrome or systemic lupus erythematosus associated with infliximab in the TGA Database of Adverse Event Notifications (DAEN), with 103 of these reports listing infliximab as the sole-suspected medicine.

Patients with drug-induced lupus-like syndrome can develop a variety of systemic manifestations. The most common include:<sup>6</sup>

- fever
- myalgias
- arthralgias
- arthritis
- serositis
- rash

Patients usually present with some combination of arthralgia, myalgia, malaise, fever, rash, and/or serositis, but patients with drug-induced lupus-like syndrome often do not exhibit a sufficient number of manifestations to satisfy criteria for idiopathic systemic lupus erythematosus. Drug-induced subacute cutaneous lupus erythematosus typically presents as an annular or psoriasiform, photo-distributed cutaneous eruption.<sup>6</sup>

Hematologic abnormalities and more severe manifestations, such as kidney disease and central nervous system involvement, are uncommon, although they may occur with lupus-like syndrome.<sup>6</sup>

If a patient develops symptoms suggestive of lupus-like syndrome after treatment with infliximab and is positive for antibodies against double-stranded DNA, treatment should be discontinued.

## REFERENCES

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## Medicine shortages – easing the impact on prescribers and patients

Health professionals are advised that reforms to the way medicine shortages (including those arising from discontinuations or recall actions) are managed and communicated will directly benefit you and your patients.

From 1 January 2019, a new mandatory reporting system will require medicine sponsors to report all shortages within legislated timeframes (ranging from two to ten working days).

Replacing the previous voluntary reporting system, these changes will ensure that you can be informed about all critical shortages of prescription medicines and a small number of essential over-the-counter medicines as soon as possible and can take action to minimise their effects on your patients, such as implementing alternative treatments or medications.

The TGA will publish information about all current and anticipated shortages of critical patient impact at [www.tga.gov.au/medicine-shortages-information-initiative](http://www.tga.gov.au/medicine-shortages-information-initiative). We will also strongly encourage sponsors

to publish information about low or medium impact shortages on our website. We can also publish this information in the interests of public health.

This means you are now better able to advise and assist patients affected by medicine shortages. You may be able to recommend alternative treatments or arrange supply of an alternative product (for example, through the Special Access Scheme – [www.tga.gov.au/form/special-access-scheme](http://www.tga.gov.au/form/special-access-scheme)).

The reforms establish a Medicines Watch List, which identifies medicines that have been pre-assessed as being critical. Shortages of medicines that are not on the Medicines Watch List can still be assessed as critical and therefore be subject to more stringent reporting timeframes and mandatory publication.

We also encourage you to subscribe to the email alert service by visiting [www.tga.gov.au/medicine-shortages-alert-service](http://www.tga.gov.au/medicine-shortages-alert-service). This will ensure you are notified of medicine shortages in a timely manner.

For further information about medicine shortages in Australia, visit [www.tga.gov.au/medicine-shortages-information-initiative](http://www.tga.gov.au/medicine-shortages-information-initiative).



### 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 (see [Black Triangle Scheme](#))
- 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:

- **online** at [www.tga.gov.au](http://www.tga.gov.au)
- **by email** to [ADR.Reports@tga.gov.au](mailto:ADR.Reports@tga.gov.au)
- **by fax** to 02 6232 8392
- **using the 'blue card'** available from the TGA website

For more information about reporting, visit [www.tga.gov.au](http://www.tga.gov.au) or contact the TGA's Pharmacovigilance and Special Access Branch at [ADR.Reports@tga.gov.au](mailto:ADR.Reports@tga.gov.au)

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](mailto:ADR.Reports@tga.gov.au)

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

Acting Editor:  
Dr Grant Pegg

Deputy Editor:  
Mr Michael Pittman

Contributors include:  
Dr Angela Gowland  
Dr Clare King  
Dr Jessica Tidemann

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