

INFLIXIMAB

1 March 2008

NOTE:

Any queries concerning the arrangements to prescribe infliximab may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Written applications for authority to prescribe infliximab should be forwarded to:

Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

Further prescribing information is on the Medicare Australia website at <http://www.medicare.gov.au/provider/pbs/drugs/index.shtml>

TREATMENT OF ADULT PATIENTS WITH SEVERE ACTIVE RHEUMATOID ARTHRITIS

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological disease modifying anti-rheumatic drugs (bDMARDs) for adults with severe active rheumatoid arthritis. Where the term bDMARD appears in the following notes and restrictions it refers to the tumour necrosis factor (TNF) alfa antagonists (adalimumab, etanercept, infliximab), the chimeric anti-CD20 monoclonal antibody (rituximab) and the interleukin-1 inhibitor (anakinra) and the T-cell co-stimulation modulator (abatacept).

Patients are eligible for PBS-subsidised treatment with only 1 of the above biological disease modifying anti-rheumatic drugs at any 1 time.

PBS-subsidised infliximab, anakinra and rituximab must be used in combination with methotrexate at a dose of at least 7.5 mg weekly. Where a patient cannot tolerate 7.5 mg of methotrexate weekly, they are only eligible to receive PBS-subsidised etanercept and adalimumab.

In order to be eligible to receive PBS-subsidised treatment with rituximab, a patient must have already failed to demonstrate a response to at least 1 course of treatment with a PBS-subsidised TNF-alfa antagonist.

From 1 March 2008, under the PBS, all patients will be able to commence a Treatment Cycle where they may trial PBS-subsidised bDMARD agents without having to experience a disease flare when swapping to an alternate agent. Under these interchangeability arrangements, within a single Treatment Cycle, a patient may continue to receive long-term treatment with a bDMARD while they continue to show a response to therapy.

A patient who received PBS-subsidised bDMARD treatment prior to 1 March 2008 is considered to be in their first Cycle as of 1 March 2008.

Within the same Treatment Cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised bDMARD more than once.

Once a patient has either failed or ceased to respond to treatment 3 times, they are deemed to have completed a Treatment Cycle and they must have, at a minimum, a 5-year break in PBS-subsidised bDMARD therapy before they are eligible to commence the next Cycle.

For patients who have failed PBS-subsidised treatment with 3 bDMARDs prior to 1 March 2008 please contact Medicare Australia on 1800 700 270.

The 5-year break is measured from the date of the last approval for PBS-subsidised bDMARD treatment in the most recent Cycle to the date of the first application for initial treatment with a bDMARD under the new Treatment Cycle.

A patient who has failed fewer than 3 bDMARDs in a Treatment Cycle and who has a break in therapy of less than 5 years, may commence a further course of treatment within the same Treatment Cycle.

A patient who has failed fewer than 3 bDMARDs in a Treatment Cycle and who has a break in therapy of more than 5 years, may commence a new Treatment Cycle.

There is no limit to the number of Treatment Cycles a patient may undertake in their lifetime.

If patients fail to respond to a particular bDMARD within a single Treatment Cycle, they are not eligible to receive further PBS-subsidised treatment with that drug until they commence the next Cycle.

(1) How to prescribe PBS-subsidised bDMARD therapy after 1 March 2008.

(a) Initial treatment.

Applications for initial treatment should be made where:

- (i) a patient has received no prior PBS-subsidised bDMARD treatment in this Treatment Cycle and wishes to commence such therapy, excluding rituximab (Initial 1); or
- (ii) a patient has received prior PBS-subsidised (initial or continuing) bDMARD therapy and wishes to trial an alternate agent (Initial 2) [further details are under 'Swapping therapy' below]; or
- (iii) a patient wishes to re-commence treatment with a specific bDMARD following a break in PBS-subsidised therapy with that agent (Initial 2).

Initial treatment authorisations will be limited to provide a maximum of 16 weeks of therapy for etanercept, adalimumab and anakinra, 22 weeks of therapy for infliximab and 2 infusions of rituximab.

From 1 March 2008, a patient must be assessed for response to any course of initial PBS-subsidised treatment (excluding rituximab) following a minimum of 12 weeks of therapy and this assessment must be submitted to Medicare Australia no later than 4 weeks from the date that course was ceased.

Rituximab patients must be assessed following a minimum of 12 weeks after the first infusion, and this assessment must be submitted to Medicare Australia within 4 weeks.

Where a response assessment is not submitted to Medicare Australia within these timeframes, the patient will be deemed to have failed to respond to treatment with that bDMARD.

For second and subsequent courses of PBS-subsidised bDMARD (excluding rituximab) treatment it is recommended that a patient is reviewed in the month prior to completing their current course of treatment and that an application is submitted to Medicare Australia no later than 2 weeks prior to the patient completing their current treatment course.

Rituximab patients:

A further application may be submitted to Medicare Australia 24 weeks after the first infusion. New baselines may be submitted with this application if appropriate.

(b) Continuing treatment.

Following the completion of an initial treatment course with a specific bDMARD (excluding rituximab), a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing bDMARD treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response.

It is recommended that a patient be reviewed in the month prior to completing their current course of treatment to ensure uninterrupted bDMARD supply.

Assessments of response to a course of PBS-subsidised therapy must be submitted to Medicare Australia no later than 4 weeks from the date that course was ceased.

Rituximab patients:

A patient may qualify to receive a further course of treatment (every 24 weeks) with this agent providing they have demonstrated an adequate response to treatment following a minimum of 12 weeks after the first infusion of their most recent treatment with rituximab. The patient remains eligible to receive a course of rituximab every 24 weeks providing they continue to demonstrate a response as specified in the restriction.

Where a response assessment is not submitted to Medicare Australia within these time frames, the patient will be deemed to have failed to respond to treatment with that bDMARD.

(2) Swapping therapy.

Once initial treatment with the first PBS-subsidised bDMARD is approved, a patient may swap to an alternate bDMARD within the same Treatment Cycle without having to requalify with respect to the indices of disease severity (i.e. the erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP) levels and the joint count) or the prior non-bDMARD therapy requirements. However the requirement for concomitant treatment with methotrexate, where it applies, must be met for each bDMARD trialled.

Patients who are not able to complete a minimum of 12 weeks of an initial treatment course will be deemed to have failed treatment with that agent.

A patient may trial an alternate bDMARD at any time, regardless of whether they are receiving therapy (initial or continuing) with a bDMARD at the time of the application. However, they cannot swap to a particular bDMARD if they have failed to respond to prior treatment with that drug within the same Treatment Cycle.

In order to trial rituximab, a patient must have trialled and failed to demonstrate a response to at least 1 PBS-subsidised TNF-alfa antagonist treatment.

To ensure a patient receives the maximum treatment opportunities allowed under the interchangeability arrangements, it is important that they are assessed for response to every course of treatment approved, within the timeframes specified in the relevant restriction.

PBS subsidy does not allow for patients to receive treatment with another PBS-subsidised biological agent during the required treatment-free period applying to patients who have demonstrated a response to their most recent course of rituximab. This means that patients who have demonstrated a response to a course of rituximab must have a PBS-subsidised biological therapy treatment-free period of at least 22 weeks, immediately following the second infusion, before swapping to an alternate bDMARD. Patients who fail to respond to rituximab and who qualify and wish to trial a course of an alternate bDMARD may do so without having to have any treatment-free period.

To avoid confusion, an application for a patient who wishes to swap to an alternate bDMARD should be accompanied by the approved authority prescription or remaining repeats for the bDMARD the patient is ceasing.

NOTE:

(3) Baseline measurements to determine response.

Medicare Australia will determine whether a response to treatment has been demonstrated based on the baseline measurements of the joint count, ESR and/or CRP submitted with the first authority application for a bDMARD. However, prescribers may provide new baseline measurements any time that an initial treatment authority application is submitted within a Treatment Cycle and Medicare Australia will assess response according to these revised baseline measurements.

To ensure consistency in determining response, the same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be provided for all subsequent continuing treatment applications. Therefore, where only an ESR or CRP level is provided at baseline, an ESR or CRP level respectively must be provided to determine response. Similarly, where the baseline active joint count is based on total active joints (ie more than 20 active joints), response will be determined according to a reduction in the total number of active joints. Where the baseline is determined on total number of major joints, the response must be demonstrated on the total number of major joints.

The baseline joint and blood counts should be performed whilst the patient is still on treatment or within one month of ceasing prior treatment.

(4) Patients 'grandfathered' onto PBS-subsidised treatment with rituximab or abatacept
From 1 March 2008, a patient who commenced treatment with rituximab for severe rheumatoid arthritis prior to 7 March 2007 and who was 'grandfathered' on to PBS-subsidised therapy, and who continues to receive treatment in the same Treatment Cycle, will have further applications for treatment with rituximab or abatacept assessed under the continuing treatment restriction.

A patient may only qualify for PBS subsidised treatment under this criterion once. A maximum of 24 weeks of treatment with abatacept will be authorised under this criterion.

'Grandfather' arrangements will only apply for the first Treatment Cycle. For the second and subsequent Cycles, a 'grandfather' patient must requalify for initial treatment under the criteria that applies to a new patient. See 'Re-commencement of treatment after a 5-year break in PBS-subsidised therapy' above for further details.

Public hospital authority required

Initial 1 (new patients)

Application for initial PBS-subsidised treatment with infliximab, in combination with methotrexate at a dose of at least 7.5 mg weekly, by a rheumatologist or clinical immunologist with expertise in the management of rheumatoid arthritis, of adults who:

- (a) have severe active rheumatoid arthritis; and
- (b) have received no prior PBS-subsidised treatment with a bDMARD for this condition in this treatment cycle; and
- (c) have failed to achieve an adequate response to the following treatments:
 - (i) methotrexate at a dose of at least 20 mg weekly; and
 - (ii) methotrexate (at a minimum dose of 7.5 mg weekly), in combination with 2 other non-biological disease modifying anti-rheumatic drugs (DMARDs), for a minimum of 3

months; and

(iii) a minimum of 3 months' treatment with:

- leflunomide alone; or
- leflunomide in combination with methotrexate; or
- cyclosporin..

If treatment with any of the above-mentioned drugs is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application.

If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, please provide details of the degree of this toxicity at the time of application. Details of the accepted toxicities, including severity, can be found on the Medicare Australia website [<http://www.medicare.gov.au/provider/pbs/drugs/index.shtml>].

The following initiation criteria indicate failure to achieve an adequate response and must be demonstrated in all patients at the time of the initial application:

an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 15 mg per L;

AND either

- (i) a total active joint count of at least 20 active (swollen and tender) joints; or
- (ii) at least 4 active joints from the following list of major joints:
 - elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or
 - shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).

All tests and assessments should be performed preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment.

If the above requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reasons why this criterion cannot be satisfied.

The authority application must be made in writing and must include:

- (1) a completed authority prescription form; and
- (2) a completed Rheumatoid Arthritis PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (<http://www.medicare.gov.au/provider/pbs/drugs/index.shtml>)] which includes details of the patient's ESR and CRP measurements and the patient's active joint count which must have been assessed no earlier than 1 month prior to the date of application; and
- (3) a signed patient acknowledgement..

A maximum of 22 weeks of treatment will be authorised under this restriction..

At the time of the authority application, medical practitioners should request the appropriate quantity of vials, based on the weight of the patient, to provide sufficient for a single infusion at a dose of 3 mg per kg. Up to a maximum of 3 repeats may be authorised..

Where fewer than 3 repeats are requested at the time of the initial application, authority approvals for sufficient repeats to complete a maximum of 22 weeks of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)..

Assessment of a patient's response to an initial course of treatment must be made after at least 12 weeks of treatment so that there is adequate time for a response to be demonstrated. This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to Medicare Australia no later than 1 month from the date

of completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to Medicare Australia within these timeframes, the patient will be deemed to have failed to respond to treatment with infliximab..

Patients who fail to demonstrate a response to treatment with infliximab under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug, in this treatment cycle. Patients may re-trial infliximab after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised bDMARD was approved in this cycle and the date of the first application under the new cycle.

Public hospital authority required

Initial 2 (change or re-commencement)

Application for an initial course of PBS-subsidised treatment with infliximab, in combination with methotrexate at a dose of at least 7.5 mg weekly, by a rheumatologist or clinical immunologist with expertise in the management of rheumatoid arthritis, of adults who:

- (a) have a documented history of severe active rheumatoid arthritis; and
- (b) have received prior PBS-subsidised bDMARD treatment for this condition in this treatment cycle and are eligible to receive further bDMARD therapy..

The authority application must be made in writing and must include:

- (1) a completed authority prescription form; and
- (2) a completed Rheumatoid Arthritis PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (<http://www.medicare.gov.au/provider/pbs/drugs/index.shtml>)]

Applications for patients who have received PBS-subsidised treatment with infliximab within this treatment cycle and who wish to re-commence therapy with this drug within this same cycle, must be accompanied by evidence of a response to the patient's most recent course of PBS-subsidised infliximab treatment, within the timeframes specified below.

A maximum of 22 weeks of treatment will be authorised under this restriction..

At the time of the authority application, medical practitioners should request the appropriate quantity of vials, based on the weight of the patient, to provide sufficient for a single infusion at a dose of 3 mg per kg. Up to a maximum of 3 repeats may be authorised..

Where fewer than 3 repeats are requested at the time of the initial application, authority approvals for sufficient repeats to complete a maximum of 22 weeks of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)..

Where the most recent course of PBS-subsidised infliximab treatment was approved under either of the initial treatment restrictions (i.e. for patients with no prior PBS-subsidised bDMARD therapy or, under this restriction, for patients who have received previous PBS-subsidised bDMARD therapy), patients must have been assessed for response following a minimum of 12 weeks of therapy. This assessment must be provided to Medicare Australia no later than 4 weeks from the date that course was ceased..

Where the most recent course of PBS-subsidised infliximab treatment was approved under the continuing treatment criteria, patients must have been assessed for response, and the assessment must be submitted to Medicare Australia no later than 4 weeks from the date that course was ceased..

Patients who fail to demonstrate a response to treatment with infliximab under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug,

in this treatment cycle. Patients may re-trial infliximab after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised bDMARD was approved in this cycle and the date of the first application under the new cycle.

Public hospital authority required

Continuing treatment

Continuing PBS-subsidised treatment with infliximab, in combination with methotrexate at a dose of at least 7.5 mg weekly, by a rheumatologist or clinical immunologist with expertise in the management of rheumatoid arthritis, of adults:

- (a) who have a documented history of severe active rheumatoid arthritis; and
- (b) who have demonstrated an adequate response to treatment with infliximab; and
- (c) whose most recent course of PBS-subsidised bDMARD treatment in this treatment cycle was with infliximab..

An adequate response to treatment is defined as:

an ESR no greater than 25 mm per hour or a CRP level no greater than 15 mg per L or either marker reduced by at least 20% from baseline;

AND either of the following:

- (i) a reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or
- (ii) a reduction in the number of the following major active joints, from at least 4, by at least 50%:
 - elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or
 - shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth)..

The authority application must be made in writing and must include:

- (1) a completed authority prescription form; and
- (2) a completed Rheumatoid Arthritis PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (<http://www.medicare.gov.au/provider/pbs/drugs/index.shtml>)].

A maximum of 24 weeks of treatment will be approved under this restriction.

At the time of the authority application, medical practitioners should request the appropriate quantity of vials, based on the weight of the patient, to provide sufficient for a single infusion at a dose of 3 mg per kg. Up to a maximum of 2 repeats may be authorised.

Where fewer than 2 repeats are requested at the time of the application, authority approvals for sufficient repeats to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

All applications for continuing treatment with infliximab must include a measurement of response to the prior course of therapy. This assessment must be provided to Medicare Australia no later than 4 weeks from the cessation of that treatment course. If the application is the first application for continuing treatment with infliximab, it must be accompanied by an assessment of response to a minimum of 12 weeks of treatment with an initial treatment course.

Patients who fail to demonstrate a response to treatment with infliximab under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug, in this treatment cycle. Patients may re-trial infliximab after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised bDMARD was approved in this cycle and the date of the first application under the new cycle.