



New Zealand Society of Gastroenterology statement on the use of biological therapy in inflammatory bowel disease

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1. Introduction

The introduction of biological drugs in the mid-1990s revolutionised treatment of inflammatory bowel disease (IBD). For the first time, targeted drug treatment was available for patients who had struggled on conventional therapy. However, these new medications are not only expensive but early reports highlighted that with increased efficacy came severe and, in selected cases, fatal side effects. Growing experience with these drugs has shown the importance of a clear indication, early recognition of potential risks (e.g. exacerbation of tuberculosis (TB) and other opportunistic infections) and demonstrated ways to avoid some unwanted side-effects (e.g. antibody formation).

Currently two biologic agents, both anti-tumour necrosis factor- α (anti-TNF α) reagents, are available in New Zealand (infliximab—Remicade® by Merck; adalimumab—Humira® by Abbott) for the treatment of IBD. While both drugs work by blocking the activity of free and bound TNF α , there are important differences in the route of administration, structure and pharmacokinetics of the drugs. Furthermore, while both drugs have shown efficacy for the induction and maintenance of remission of Crohn's Disease (CD), infliximab is also indicated for the induction and maintenance of remission of ulcerative colitis (UC), and is indicated for fistulising disease and the treatment of perianal CD. Regarding the use of biologicals in IBD, research has shown these drugs to be most effective when used early in the disease process in younger patients with signs of aggressive disease (age <40, early need for corticosteroid treatment and steroid refractory disease, perianal and complicated disease).

Since 1 August 2009 the subcutaneous formulation adalimumab has been fully funded in NZ under strict guidelines for a subgroup of Crohn's Disease (CD) patients with severe active disease or extensive small bowel disease, who have been unsuccessfully trialled on conventional therapy including corticosteroids (CS) and immunomodulators and where surgery is not considered an option (www.pharmac.govt.nz). To access this drug, a gastroenterologist must apply for Special Authority.

Although only a small proportion of patients with IBD in NZ will benefit from the fully funded medication, we will undoubtedly see an increase in the overall use of the currently available biologicals. Given the nature of these medications the New Zealand Society of Gastroenterology (NZSG) has commissioned these local guidelines to support gastroenterologists in their decision making process by reviewing recently published consensus guidelines from other societies (Table 1) and

adapting these to the special funding situation and availability issues in NZ. These guidelines do not replace individual risk-benefit decisions for each patient and while gastroenterologists should prescribe these agents, the decision to introduce biological therapy should ideally arise from a multidisciplinary consensus including gastroenterological, surgical and pharmacy colleagues.

Table 1. Published guidelines on the use of biological therapies in IBD

Society	Guideline	Year
European Crohn's & Colitis Organisation (ECCO)	The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Foundation	2010 (in press)
World Gastroenterology Organisation (WGO)	World Gastroenterology Organisation Practice Guidelines for the diagnosis and Management of IBD in 2010 ¹	2009
European Crohn's & Colitis Organisation (ECCO)	European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in Inflammatory Bowel Disease ²	2009
Asian Pacific Association of Gastroenterology	Management consensus of Inflammatory Bowel Disease for the Asia-Pacific region ³	2006
IBDnet.ch (Switzerland)	TNF- α blockers in Inflammatory Bowel Disease: Practical consensus and a user's guide ⁴	2009
The Cochrane Collaboration	Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's Disease (Review) ⁵	2009
The Cochrane Collaboration	Tumor necrosis factor-alpha antibody for induction of remission in Crohn's Disease (Review) ⁶	2004
European Crohn's & Colitis Organisation (ECCO)	European evidence based consensus on the diagnosis and management of Crohn's Disease: current management ⁷	2006
European Crohn's & Colitis Organisation (ECCO)	European evidence-based consensus on the management of ulcerative colitis: current management ⁸	2008
American Gastroenterology Association (AGA)	American Gastroenterological Association Institute Medical Position Statement on Corticosteroids, Immunomodulators, and Infliximab in Inflammatory Bowel Disease ⁹	2006
Deutsche Gesellschaft für Verdauungs- und Stoffwechselerkrankungen (DGVS, Germany)	Clinical Practice Guideline on Diagnosis and Treatment of Crohn's Disease: Results of a German Evidence-based Consensus Conference ¹⁰	2008
American College of Gastroenterology (ACG)	Management of Crohn's Disease in Adults ¹¹	2009

2. Crohn's Disease

2.1 Induction of remission

2.1.1. Luminal Crohn's disease—In mild, predominantly small bowel disease, high-dose 5-aminosalicylates (5-ASA) can be trialled but oral or intravenous corticosteroids (CS) are currently regarded as the first line treatment for induction of remission in luminal CD in adults. CS should only be used in short courses due to side effects of long term use, steroid resistance, dependence and loss of efficacy.

Escalation of therapy should be considered if a patient is not steroid-free within 12-24 weeks of initiation of treatment, when multiple courses of CS are required, or where there are poor prognostic factors (Table 2). In these instances, immunomodulators (e.g. azathioprine, 6-mercaptopurine, methotrexate) should then be considered early in

the disease course, introduced overlapping with CS treatment. In addition, the detrimental effect of smoking on the course of CD, especially in the acute situation should be emphasised to all patients with CD.

Table 2. Prognostic Factors of Early Relapse in Crohn's Disease

Indications for early consideration of immunomodulators/biologicals
Onset in younger patients (age < 40)
Aggressive disease
Extensive small bowel involvement
Extraintestinal involvement
Peri-anal disease
Deep ulcerations on colonoscopy

Biological drugs (infliximab and adalimumab) are superior to placebo in inducing remission in patients with moderate-to-severe CD, reflected by a Crohn's Disease Activity Index (CDAI) of 220–450. The efficacy of infliximab is augmented by co-prescription of immunomodulators but this has not been tested for adalimumab. However, current Pharmac criteria state that adalimumab should be used as a 3rd line medication in patients who have failed CS and immunomodulators (thiopurines ≥ 6 months at ≥ 2.5 mg/kg or within the therapeutic range for thiopurine metabolites/methotrexate 25mg/weekly parenterally or highest tolerable dose ≥ 4 months), and in whom surgery is clinically inappropriate. However, a commitment to maintenance treatment needs to be agreed upon with the initiation of biological therapy as intermittent application of infliximab is less efficacious and will significantly increase the risk of antibody formation. There are no data concerning episodic use of adalimumab. Prior to the initiation of biologicals, a colonoscopy or other imaging is advised as, for instance, fibrostenotic disease has a poor response to treatment and surgery needs to be considered.

2.1.2. Fistulising (Perianal) Crohn's disease—Fistulising and perianal disease pose a significant burden on the affected patient, have a high morbidity and result in multiple surgical interventions in many patients. Principles of treatment include draining sepsis, placement of Seton sutures for ongoing drainage, treatment with appropriate antibiotics, and optimisation of standard immunomodulator treatment, especially with thiopurines. An initial perineal MRI or Endo-Anal Ultrasound (EUA) is recommended to define the extent of disease and exclude drainable collections.

Where patients have failed standard treatment (antibiotics and/or immunomodulators) then a TNF α inhibitor should be used in conjunction with perianal surgery to eliminate sepsis. Currently, infliximab is the only TNF inhibitor indicated for induction of remission of perianal CD, with efficacy demonstrated from early clinical trials. Although there are some promising data for adalimumab and other biologicals (subgroup analysis of clinical trials), these have not yet been shown to be efficacious in double-blind randomised controlled trials where fistula healing has been a primary or secondary endpoint. Maintenance of healing can be achieved with either agent.

2.1.3. Paediatric Crohn's disease—The standard therapeutic approach to induce remission in children with CD includes exclusive enteral nutrition (EEN) or

corticosteroids (especially in moderate-severe disease). EEN has numerous significant advantages, including superior mucosal healing and nutritional benefits. Early use of immunomodulator therapy is clearly demonstrated to enhance disease control and growth, especially in those with moderate-to-severe disease.

TNF α inhibitors are indicated in moderate-to-severe paediatric CD to induce remission. A recent multicenter North American study (the REACH trial) demonstrated high response rates to induction therapy with infliximab in children with luminal or perianal disease, along with improvements in bone turnover and growth patterns¹². Case series and retrospective studies also demonstrate that adalimumab is a safe and effective drug for moderate-severe CD in children. The funding guidelines for adalimumab in NZ apply to paediatric as well as adult populations.

2.1.4. Summary of Induction Regimens for Crohn's Disease—The standard induction regimen for infliximab involves three infusions of 5 mg/kg given intravenously over 6 weeks (weeks 0, 2 and 6) whether for luminal or fistulising disease. The standard and currently funded regimen for adalimumab involves 160mg at week 0, 80mg at week 2 and then fortnightly doses of 40mg by subcutaneous injection. Paediatric dose regimens for adalimumab can be based on an adjustment for body surface area.

2.2 Maintenance of Remission of Crohn's Disease

2.2.1. Luminal Crohn's disease—Cessation of smoking is important in the management of maintenance of remission in CD. Corticosteroids are not appropriate as maintenance therapy in adults or children. The medication of choice to maintain remission is either azathioprine or high dose parenteral methotrexate.

Maintenance treatment with biologicals is recommended for all patients who have had a useful initial clinical response to an induction course with biologicals. Induction of remission alone, not followed by maintenance treatment, will disadvantage the patient as any future treatment with TNF α inhibitors will be less effective due to antibody formation. This has been shown for infliximab but there are no data concerning episodic use of adalimumab. According to the recently published SONIC trial, maintenance of remission is superior if infliximab is combined with azathioprine if patients are considered to require a second line therapy¹³. The findings of the recent COMMIT trial, published as abstract only suggest that at least for patients requiring prednisone, there is not a clear need for combination therapy with methotrexate. Therefore, we suggest, the decision to continue immunosuppressive therapy once a patient is stabilized on maintenance anti-TNF treatment should be individualized as current data is still uncertain on this issue. This has not been tested for other biologicals but it can be assumed that similar effects can be observed.

Clinical response will usually be defined by a fall in CDAI of more than 100 points and clinical remission is defined as a CDAI <150 for clinical trials. However, useful clinical responses can be achieved with biological agents without fulfilling these strict criteria. This is reflected in the current Pharmac criteria i.e remission does not need to be achieved to justify maintenance treatment with adalimumab if overall the patient condition has been enhanced after 3 months of treatment. For patients with peri-anal disease, previous colectomy or multiple previous bowel resections, the clinical

response solely depends on clinical parameters as a CDAI cannot be reliably calculated. Treatment with infliximab should be continued at 5mg/kg every 8 weeks. Treatment with adalimumab should be continued at 40mg every 2 weeks.

The introduction of biologicals solely for maintenance purposes is not funded by Pharmac and in contrast to the Pharmac guidelines, biologicals for maintenance treatment may need to be introduced before immunomodulator treatment has been given a reasonable trial (3-4 months for azathioprine) if there are poor prognostic factors such as young age at disease onset, extensive disease (combined small bowel and colonic disease or fistulising disease), early need for corticosteroids and failure to respond or early relapse (see also 2.1.1).

The appropriate duration of treatment with infliximab or adalimumab is uncertain due to lack of long-term data. Clinical trial data suggests continuation of efficacy for 3 years although the dose may need to be increased in a proportion of patients. Planned discontinuation after a certain period in remission is a possible strategy but recommendations need to await more clinical data. Increasingly, the decision to stop treatment is becoming dependent on showing absence of inflammation endoscopically and by small bowel imaging.

2.2.2. Perianal Crohn's disease—In contrast to luminal disease where duration of maintenance treatment with a biological is ill defined, in peri-anal and fistulising disease MRI scanning or EUA (to document extent of healing) can be utilised as a guide to the length of biologic therapy. In this situation, complete healing of the fistula tract is the optimal endpoint. There is some evidence to support a strategy of continuing biologicals for 3-6 months after MRI evidence of healing of fistula. Both infliximab and adalimumab have been demonstrated to be effective at maintaining fistula closure but neither are funded in NZ for this indication.

2.2.3. Paediatric Crohn's disease—Along with monitoring of growth and development, the maintenance of remission is an important aspect of the management of paediatric CD. Immunomodulating drugs, especially when introduced early, have significant benefits. Biologicals are indicated for the maintenance of remission in children with moderate—severe Crohn's disease as in adult disease. The recent REACH study showed eight weekly maintenance therapy with infliximab to be superior to 12 weekly infusions in children¹². A recently published multicentre retrospective evaluation of adalimumab (RESEAT) in children demonstrated benefits in maintenance of remission to 12 months¹⁴.

2.2.4. Summary of maintenance regimens for Crohn's Disease—

Immunomodulators are the treatment of choice for maintenance of CD. However, with the introduction of biologicals to induce remission, a commitment for maintenance therapy with these agents should be made. Adalimumab is currently funded for maintenance at a dose rate of 40mg fortnightly. Evidence exists also for infliximab at 5mg/kg bodyweight eight weekly.

2.2.4.1—Post surgical maintenance—Treatment should be considered immediately after surgery and should not be delayed until clinical signs of recurrence are present. Evidence exists for the roles of antibiotics (3 months of metronidazole) and immunomodulators (azathioprine) in the maintenance of surgically-induced remission, with reduction in recurrence of disease. Biologicals may be considered if

immunomodulators fail or cannot be used due to intolerance or contraindications and prognostic factors predict early recurrence (in the first 6 months). Furthermore, biologicals should be considered if there is a high risk of severe disease recurrence (such as at second or greater resection). It is currently too early to recommend routine biologic use although one RCT shows that infliximab is more effective than placebo in the post-operative patient. Although there is little data on the role of infliximab in the peri-operative setting, there is a suggestion of increased rates of peri-operative sepsis. Neither biological is funded for this indication in NZ.

2.3. Stopping biological drugs

Response to biological drugs is often early and dramatic and is usually observed within 10-12 weeks. Patients who do not respond to one biological drug (primary non-responders), or have an adverse outcome, should have this medication ceased. Another biologic agent can then be considered, obviously along with other options such as surgery.

Some patients will have decreased effectiveness of biologic treatment over time. This is often observed with recurrent symptoms prior to the next drug administration.

There are currently three potential options for patients who lose response to biologic drugs (secondary non-responders): The frequency of administration can be increased (e.g. four weekly infliximab or weekly adalimumab) or the dose can be changed (infliximab can be increased to 10mg/kg bodyweight 8-weekly, no published data is available for an increased adalimumab dosage). If either of these options are undertaken, attempts should be made to revert to standard protocols once remission has been restored. If these options fail, as a third possibility, there is evidence supporting a change from infliximab to adalimumab. While the data are less strong supporting the reverse, infliximab after adalimumab can be tried.

If patients have a prolonged remission on a biologic drug then consideration can be given to stopping the drug. This decision needs to be made with a thorough knowledge of the activity and behaviour of the patient's disease activity (including colonoscopy and appropriate small bowel imaging). Alternative immunosuppression may be required as a maintenance agent in this setting if the biologic is ceased.

3. Ulcerative Colitis

Biologicals are not funded in NZ for the use in ulcerative colitis (UC) but may be used on a DHB by DHB basis depending on clinician and management decisions. However, infliximab has been shown to be efficacious in randomised placebo-controlled clinical trials. A similar trial has recently completed recruitment for adalimumab and should be reported in the next two years.

3.1. Induction of remission

3.1.1. Acute fulminant colitis—Close consultation with a colorectal surgeon is recommended for the successful treatment of these patients. Intravenous steroids are the treatment of choice but if these fail, i.v. ciclosporin or infliximab are superior to placebo. The choice of an agent may be guided by previous therapy (e.g. in previous immunomodulator naïve patients i.v. ciclosporin might be attempted). With the use of infliximab, a response within 10 days can be anticipated. Infliximab at 5mg/kg

bodyweight has been shown to reduce the colectomy rate by 50% within the current admission and this response is sustained for a two-year period.

There are currently no DBRCTs available to recommend the use of adalimumab in this setting.

3.1.2. Moderate-to-severe UC—In accordance to regimens used for the induction of remission of Crohn’s Disease, infliximab should be considered in patients who fail first line therapies. These include high dose oral \pm rectal 5-ASA, corticosteroids and immunomodulators. The use of maintenance corticosteroids or repeated corticosteroids should be avoided.

3.2 Maintenance of Remission—Infliximab is superior to placebo in patients who fail first line therapies (as above). In such patients, surgical options and the long term risk of colorectal dysplasia should also be discussed. Azathioprine treatment prior to acute presentation should be reviewed as this may not have been used for an adequate duration or at adequate dose to achieve maximal efficacy. Maintenance infliximab will be a strategy that is appropriate for a small proportion of patients who have achieved remission with acute treatment. If this approach is chosen then infliximab should be used in combination with immunomodulators to increase efficacy. This approach is unclear for other biologicals.

3.3. Paediatric ulcerative colitis

There are no DBRCTs of biological drugs in paediatric UC patients. However, a large prospective multicentre study in North America has recently demonstrated that infliximab is efficacious in children who have failed to respond to intravenous CS for moderate-to-severe colitis^{12, 14}.

3.4. Summary of treatment regimens for ulcerative colitis

In UC, surgery is available as a potentially curative treatment option. Therefore, high cost and high risk medications such as biologicals are less favourable in complex and difficult patients. Infliximab has a role in patients with a fulminant presentation despite immunomodulator therapy to bridge the patient for elective surgery. Dosing regimens are similar to CD.

4. Safety Considerations

4.1. Infusion reactions (infliximab)

These are uncommon and therefore routine pre-medication is not advised. However, in patients with a previous reaction, pre-medication with intravenous hydrocortisone, co-prescription of immunomodulators and scheduled maintenance rather than episodic use is recommended. Observations of vital signs should be taken every 30 minutes during the infusion and for 1 hour post infusion. For the first infusion, the infusion rate should be reduced according to the manufacturer’s specifications (<http://www.medsafe.govt.nz/profs/datasheet/r/Remicadeinj.htm>).

Patients should be monitored for infusion reactions like hypertension, headache, skin rashes, hives, flu-like symptoms and chills. The manufacturer’s infusion guide should be consulted with regards to the management of mild, moderate and severe reactions.

4.2. Injection site reactions (adalimumab)

The most common reactions are redness, rash, swelling, itching or bruising but these are mild and lead to local irritation only. Patients should be advised to place a cold, damp towel or ice pack on the affected injection site for 10-15 minutes every 1-2 hours. Patients should be well trained with injection technique and advised to rotate injection sites. Each new injection site should be given at least 3 cm from the previous site. For further information, the manufacturer's datasheet should be consulted (<http://www.medsafe.govt.nz/profs/datasheet/h/Humirainj.htm>).

4.3. Malignancies

Early reports indicated an increased risk of malignancies with the use of biologicals. These reports stem mainly from the rheumatological literature and it remains unclear if these results can be extrapolated to the use of biologicals in gastroenterological disorders. There may be an increased risk of developing non-Hodgkin lymphoma in the older population. A number of alarming reports have emerged regarding the risk of the development of hepatocellular T-cell lymphoma in young males usually when co-prescribed with immunomodulators. This led to the recommendation that the introduction of biologicals in this patient group needs to be cautiously evaluated.

4.4. Risk of Infection

All immunosuppressing medications increase the risk of opportunistic infections. Evidence, mainly from the rheumatological literature, indicates that the risk of such infections is related to the number of immunosuppressing agents a patient is taking and the patients' age. A thorough pre-treatment screening of the patient including immunisation status and risk factors can help to minimise the risk of opportunistic infections and complications.

4.4.1. Screening and Vaccination Summary

Table 3. Pre treatment for infectious diseases

	PreTreatment Screening	Considerations
TB	Preferential use of Interferon Gamma release assay (QuantiFeron Gold) but TB skin testing may also be used (≥ 5 mm threshold).	Low threshold to check CXR. Presence of findings consistent with old TB mandates treatment for latent TB.
Viral Hepatitis	Hep A & C antibodies Hep B surface antigen, anti-surface antibody, anti-core antibody. In highly suspicious cases, consider serum Hep B and/or C viral PCR.	Hep B titres should be checked in vaccinated individuals and booster vaccine offered if inadequate.
Varicella	Vaccinate unless: 1) Clear history of Chickenpox, 2) Herpes Zoster, 3) lab confirmed exposure or 4) adequate vaccination	
HIV	Check antibody in patients with any risk factor for sexually transmitted illnesses or other risky behaviour/exposures.	

Table 4: Vaccination Summary

Vaccine	Notes	Schedule
Ensure all childhood vaccination series are up to date.	Most adults will require 10 year maintenance Tetanus booster (in NZ this is aDT—Diphtheria & Tetanus)	
Pneumococcal vaccine	every 5 years	One dose
Influenza	Epidemic – yearly Pandemic – if available (give on or off therapy)	One dose
HPV	for females aged 9-26 years	Three doses 0,2, & 6 months
Travel/Exposure specific vaccinations as indicated	Yellow Fever (Live), Polio, Japanese Encephalitis, Typhoid, Rabies, etc.	
Varicella	Live Vaccine Finish vaccination at least three weeks before immune modulating therapy	2 doses 4 weeks apart
Hep A		2 doses 0 & 6 months
Hep B	boost if Hep B titre inadequate	3 doses 0,1, & 6 months

Vaccination with inactivated vaccines may be given with biologic therapy however, it must be noted that the efficacy of vaccination in this setting may be less effective.

Live Vaccines are contraindicated if the patient is on immune suppressive therapy (may be given if the patient is on prednisone < 20mg/day and has been off all other immune suppression for at least three months).

4.4.2. Specific Infections—The increased overall use and especially the combination of different agents affecting the immune system in the treatment of IBD has led to an increase in opportunistic infections. Albeit still the exception, many questions regarding prevention, diagnosis and treatment of the immunosuppressed patient remain unanswered.

4.4.2.1. Mycobacterium tuberculosis—Patients should have no evidence of active or latent TB at the time of treatment. All patients should undergo a detailed medical and travel history, a CXR and *in vitro* testing for Interferon Gamma release (QuantiFeron Gold, T-SPOT.TB). QuantiFeron Gold has the benefit of giving an indeterminate result rather than a false negative. In this instance, the test should be repeated before treatment with biological is initiated. A history of contact with patients with TB, travel to TB endemic areas and other risk behaviours should be sought and may be most important where other testing is indeterminate.

In patients with active tuberculosis, consultation with Respiratory Medicine and/or Infectious Diseases is strongly advised. Generally, active TB should be treated first and if clearly responding to treatment, biologic therapy may be instituted with close monitoring. Patients developing TB whilst on biological therapy will require individualised treatment in conjunction with Respiratory Medicine and/or Infectious Diseases. These patients have been successfully treated while continuing biologic

therapy but will require close monitoring and possibly directly observed therapy (DOT).

4.4.2.2. *Varicella Zoster Virus*—Attempt to vaccinate unless there is a clear history of Chicken pox, Herpes Zoster and/or lab confirmation of immunity. Active infection should resolve completely before therapy. Generally this is the case by crusting of skin lesions or resolution of relevant organ injury in multisystem disease.

4.4.2.3. *Hepatitis B*—Concurrent suppressive therapy (non-interferon) is required in those with Hep B surface Antigen positive status.

4.4.2.4. *Hepatitis C*—Generally no specific action needs to be taken.

4.4.2.5. *Influenza*—Yearly vaccination on or off therapy.

4.4.2.6. *Human Immunodeficiency Virus*—Co-management with HIV physician is required. The infection is not a barrier to treatment *per se*.

4.4.2.7. *Human Papilloma Virus*—Ensure females have regular yearly cervical smears that do not indicate premalignant lesions. 3-dose HPV vaccination is prudent in females aged 9-26 years.

4.4.2.8. *Diarrhoea*—*Clostridium difficile* enterocolitis should be excluded, especially in patients recently hospitalized or with recent or current antibiotic usage. In New Zealand it may be prudent to consider *Giardia*, *Cryptosporidium* and *Campylobacter* in certain patients with exposure to fresh water outdoors or in outbreak situations. Norovirus can cause episodic outbreaks in some communities and hospitals.

4.4.2.9. *Cytomegalovirus*—Simple antibody screening (IgG, IgM) is recommended.

4.4.2.10—*Non-endemic infections*—Consider travel history—especially to areas with endemic Fungi (Histoplasmosis—North & South America, Africa, Coccidiomycosis—Southwest US). Screening for tropical infectious diseases will be guided by country of origin.

5. Concluding Remarks

Biological agents used for appropriate indications in CD or UC can improve clinical outcomes significantly. Commencement of a biological agent in IBD should be preceded by clear discussion and identification of the potential risks and benefits for the individual patient. Dosing with biologicals should be undertaken using currently available evidence with appropriate monitoring and follow-up and should take the NZ context into account.

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