Inflammatory and autoimmune disorders such as Rheumatoid arthritis (RA), Ankylosing Spondylitis (AS), Juvenile idiopathic arthritis (JIA) and Crohn’s disease are chronic conditions that affect multiple organs and systems. They can lead to long-term sequelae and permanent disability if not treated appropriately on an early stage. The prevalence of these diseases is:

- RA: 0.3-1% globally
- AS: 0.18-0.25% globally
- JIA: 70.2/100,000
- Crohn’s disease: 0.3% in North America, Oceania and Europe. It is becoming more common in newly industrialized areas and in paediatric population.

Even when TNF-α inhibitors are not considered first-line therapy for these diseases they have proven to be effective and to have an important role in the management of patient who fail first line therapy or who continue to have frequent flare-ups. Their cost is an important limitation. Data on the current use of these medications shows that it is relatively high and it is expected to rise in the upcoming years as research expands.

(2) Have all-important studies/evidence of which you are aware been included in the application?

Yes ☐ No ☐

Please provide brief comments on any relevant studies that have not been included: 

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☐ No ☐

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:
The efficacy/effectiveness of TNF-α inhibitors has been shown by multiple systematic reviews in each of the previously mentioned diseases:

RA:
- One systematic review that evaluated patients with early RA showed that the combination of TNF-α inhibitors and methotrexate (MTX) resulted in higher chances of achieving favourable response and remission compared to MTX alone. This combination was also associated with less radiographic progression when compared with MTX or TNF-α inhibitors alone. There was not enough evidence to determine differences between individual TNF-α inhibitors. The strength of the evidence was low to moderate.
- One systematic review that evaluated patients with advanced RA showed that TNF-α inhibitors combined with MTX showed greater chances of achieving ACR 50 and remission compared to MTX alone and placebo. The combination was also associated with higher physical health-related quality of life score compared to MTX monotherapy. Of note, half of the included studies presented high risk of bias.

AS:
- One systematic review that included 21 randomized control trials (3308 participants) showed that TNF-α inhibitors where associated with increased risk of achieving ASAS 40 (after six months, strong evidence strength) and partial remission (moderate evidence strength) compared to placebo. Most of the included studies presented low or an unclear risk of bias.

JIA:
- One systematic review that included 8 randomized controlled trials comparing TNF-α inhibitors and MTX did not show statistically significant difference between the two treatment arms.

Crohn's Disease:
- One network meta-analysis (Singh 2015) showed similar effectiveness of TNF-α inhibitors against placebo in the induction of maintenance of remission inpatient processes.
- Another network meta-analysis showed benefit of Infliximab, Infliximab+Azathioprine and Adalimumab over placebo at inducing remission. Additionally these combinations were also superior to azathioprine/6-mercaptopurine. For the maintenance of remission, all TNF-α inhibitors and combinations proved to be superior to placebo with the exception of infliximab + methotrexate. Similar results were seen when compared to azathioprine/6-mercaptopurine.

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

The evidence presented comes from multiple systematic reviews developed in different countries (different ethnicities and incomes)

(4) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☐ No ☐
Please provide brief details:

The most common side effects reported in all TNF-α inhibitors were administration disorders associated, fatigue, malaise and pyrexia. A systematic review assessed the potential adverse effects of TNF-α inhibitors alone or in combination with other therapies. The median follow-up of the studies was six-months. The network meta-analysis compared with a placebo showed:

- Certolizumab was statistically associated with serious adverse events and serious infections
- Infliximab showed a statistically significant association with adverse events and withdrawal due to adverse events.

Standard meta-analysis compared with placebo did not show a statistically significant Association with tuberculosis reactivation coma lymphoma or congested heart failure (for the last two outcomes there was not enough information to obtain an estimate for all the drugs in the group)

The potential adverse effects of TNF-α inhibitors (in adult and paediatric population) include:

- Serious infections such as bacterial, mycobacterial, invasive fungal, viral and parasitic. It is unclear if the patients underlying disease and/or concomitant medications can also contributed to the risk of infection. In areas were there’s an elevated risk of tuberculosis patient should be monitored for reactivation, similar situation for area with specific parasitosis.
- Malignancies and/or hepatosplenic t-cell lymphoma. Very uncommon but it seem to be more prominent in paediatric patients. Causality is unclear
- Adalimumab has been associated with neurological effects such as numbness or tingling, altered vision, dizziness and weakness
- Certolizumab has been associated with worsening and new onset congested heart failure

Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

With appropriate screening prior to the initiation of the therapy as well as continues monitoring; TNF-α inhibitors can be safe and result in significant benefits.

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes [ ] No [ ]

Please provide brief details:
TNF-α inhibitors should be prescribed and monitored by providers with appropriate experience and training. Failure to first-line therapies should be confirmed, additionally after starting these medications monitoring of symptoms and progression of disease should continued.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes [ ] No [ ]

Please provide brief details:

According to the information provided all the TNF-α inhibitors proposed, are approved by the FDA, EMA, as well as, the Australian and Canadian agencies approve. This is not the case in Japan. Information about the developing world is not provided. Crohn’s disease is not listed as an indication for all of the TNF-α inhibitors.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes [ ] No [ ]

Please provide brief details:

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

All of these drugs are expensive; cost varies according to indications and doses.

RA:
- The cost of treating RA in the US with TNF-α inhibitors during a year varies between $14,385 and $19,283. The percentage of patients that were classified as effectively treated with this therapy was 19-32.3%.
- Systematic reviews have suggested that TNF-α inhibitors may be cost-effective in patients with inadequate response to DMARD. Benefit may be even more significant when they are started early in the course of the disease.

AS:
- A decision model to assess the cost effective dust of 5 TNF-α inhibitors (Infliximab, Adalimumab, Etanercept, Golimumab and Certolizumab) compared with NSAIDs showed that these are likely to be cost effective. Infliximab seemed to be the less favourable option.

JIA:
- The total drug cost for the treatment of JIA with TNF-α inhibitors in Canada is between $18,330 and $18,996 (based on 40 kg patient and a dose of 3 – 5 mg/kg)
A study determined the cost-effectiveness of TNF-α inhibitors in patients unresponsive to DMARDs in Canada. It showed that at one year, the mean incremental costs per additional ACR Pedi 30 were $26,061 (95% CI $17,070-$41,834), $46,711 (95% CI $30,042-$75,787), and $31,209 (95% CI $16,659-$66,220) for Etanercept, Adalimumab, and Infliximab, respectively.

Crohn’s disease:

- In the UK the mean cost per infusion of Infliximab (including administration) is £1,691, compared with £1430 for the cost of 8-weeks’ treatment with adalimumab and £43 for standard care.
- Canadian cost-utility analysis determined that the costs for Crohn’s Disease usual care, adalimumab, and infliximab strategies were $17,107, $45,480 and $54,084, respectively.
- Early initiation of Infliximab and Adalimumab had a 73.9 and 73.6% of being cost effective at a willingness-to-pay threshold of $50,000 per QALY, respectively.

Any additional comments?

Please frame the decisions and recommendations that the Expert Committee could make.

TNF-α inhibitors should be included as a family in the essential medication list for the treatment of RA, AS, Crohn’s disease, JIA due to its. It should be managed by trained personal with appropriate training for screening and monitoring in order to avoid preventable side effects and achieve the best possible outcomes.

References (if required)