(1) Does the application adequately address the issue of the public health need for the medicine?
   Yes  X  No

Please provide brief details:

The application adequately addresses the issues of public health needs for rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Chron’s disease. These are debilitating, chronic, progressive disorders that account for a significant decrement of the quality of life of sufferers, loss of productivity, and disability. Effective medicines for these disorders should be listed in the EML.

(2) Have all important studies/evidence of which you are aware been included in the application?
   Yes  X  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  X  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 quality of the evidence in support of the use of anti-TNF drugs in early rheumatoid arthritis is low to moderate and shows a potential benefit of adding a biologic to methotrexate. Yet, long-term follow ups of the disease history are not sufficient and it is therefore not known if this strategy, compared to sequential treatment, would favour patients.

The quality of the data and the effect size of using an anti-TNF drug in advanced rheumatoid arthritis, i.e. in patients that do not adequately respond to cDMARDs and corticosteroid appropriately, is solid.

Similarly, in ankylosing spondylitis the quality of the evidence in support of the use of anti-TNF therapies is moderate and the effect size, including the NNT is favourable in patients that fail first line therapies.

In Chron’s disease, the quality of evidence and effect size are also positive both for induction therapy and for maintenance of remission.

From the available data, it is not possible to evidence differences among anti-TNF drugs.
(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

The comparative effect size and the certainty of long-term benefit is larger in patients that have failed first line therapies.

(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 application correctly review harms and risks of the medicines in the application. Important risks include serious infections, the development of cancer, tuberculosis reactivation and serious infections.

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

The overall risk/benefit of these drugs is favourable.
ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?  
Yes  X  No  

Please provide brief details:  
*Infliximab requires intravenous infusion that requires adequate hospital facilities. Other drugs are administered subcutaneously. Furthermore, patients require screening for latent tuberculosis, fungine infections, HBV and other infections before starting treatment, as these may worsen with treatment.*  

(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:  

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?  
Yes  No  X  

Please provide brief details:  

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

*Cost of TNF-alpha inhibitors has historically been significant, also in light of the biotechnological nature of the compounds. More recently, the advent of biosimilars for infliximab, adalimumab and etanercept have lowered the net price of purchase and have allowed for competition on the market.*  

(10) Any additional comments?  

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

*The inclusion of the anti-TNF therapies a number of issues should be considered: (i) these auto-immune disorders are highly debilitating; (ii) first line treatments are highly effective in a good proportion of patients but other patients do not respond or*
loose response to these treatments; (iii) there is insufficient evidence that these drugs
differ significantly among them in terms of efficacy and safety; (iv) there is sufficient
evidence for their efficacy in patients that do not respond to first line therapy; (iv) the
availability of a number of alternatives and of biosimilars should boost competition on
the market; (v) most evidence arise from countries with a low level of patients with
HBV or tuberculosis latent infections. Price is an issue that might be tapered by the
competition between active principles and advent of biosimilars. The need for
specialized care allows to consider these drugs solely for the complementary EML list
as a therapeutic class.

(12) References (if required)