ERRATUM

Following the Factual Error Check from the manufacturer, the following pages have been revised:

Page 12: The following sentence has been removed: "However, it should be noted that NICE guidance on etanercept for JIA is for all subtypes of JIA."

Page 24: In section 4.1.1.1 (p. 24), the ERG states that 'conference paper' is not an Embase publication type, hence there is an error in the search term. However, Roche applied the RCT filter used for BMJ clinical evidence, which includes 'conference paper' as an Embase publication type. Therefore, page 24 has been revised by removing the statement.

Page 44: In Table 4.11 the 11th line which reads: 'DMARD and/or biologic agent no. patients', is incorrect for the all tocilizumab group. [redacted] This has been corrected.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem.

Does the ERG believe that the manufacturer's description of the underlying health problem is appropriate and relevant to the decision problem under consideration?

The manufacturer's description of the underlying health problem is in line with NICE guidance [1], and hence seems reasonable and relevant to the decision problem. For completeness the following is reproduced from the MS:

"Juvenile idiopathic arthritis (JIA) is a term that covers a heterogeneous group of syndromes in which the onset of inflammatory arthritis occurs before the age of 16 years and lasts for more than 6 weeks. JIA is characterised by persistent joint swelling, pain and limitation of movement. The cause of JIA is poorly understood, but may relate to genetic and environmental factors" (MS, page 20).

"A classification system for JIA has been developed by the International League of Associations for Rheumatology (ILAR). There are seven categories of JIA: systemic, oligo arthritis (formerly pauciarticular), polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, enthesitis related arthritis, psoriatic arthritis and unclassified (types that do not correspond to any, or to more than one, category) (Petty et al., 2004). The clinical manifestations and severity of the different sub-types varies considerably. sJIA is a multiorgan disease characterised by arthritic symptoms, fever, transient rash, liver and spleen enlargement. It is distinct from other subtypes and is often resistant to treatment. The overall outcome of the disease is poor with a high risk of long-term functional impairment. Macrophage activation syndrome (MAS) is a severe, life threatening complication to sJIA which affects around 7% of children, which is associated with serious morbidity and sometimes death (Yokota et al., 2010)" (MS, page 20).

"JIA is a relatively rare disease, with an estimated incidence in the UK of 0.1 per 1000 children per year, equivalent to 1000 children diagnosed per year. The prevalence is in the order of 1 per 1000 children, and about 10,000 children in the UK are affected. Approximately 10% of children diagnosed with JIA have systemic disease. Of these patients, those who have had an inadequate response to NSAIDs and corticosteroids and are 2 years of age and older will be eligible for Tocilizumab treatment." (MS, page 21).

2.2 Critique of manufacturer's overview of current service provision

Does the ERG believe that the manufacturer's overview of current service provision is appropriate and relevant to the decision problem under consideration?

The ERG broadly agrees with the manufacturer's description of current service provision. The MS states that there are no specific NICE guidance documents or national protocols for the treatment of sJIA and in addition there are no licensed therapies for the treatment of sJIA.

The British Society for Paediatric and Adolescent Rheumatology recommends treatment for JIA within multidisciplinary teams including paediatric rheumatologist, paediatric rheumatology clinical nurse specialist, ophthalmologist, general practitioner, paediatric physiotherapist, paediatric clinical psychologist, paediatric occupational therapist, podiatrist (Davies et al 2010). Drug therapy for sJIA

typically begins with systemic corticosteroids to treat systemic symptoms. Later in the disease, the systemic features can be mild / absent and at that stage steroid joint injections are often helpful (and

Search strategy for section 5.8, Indirect and mixed treatment comparisons

The MS reported searches of all the required databases: Medline, Medline In-Process, Embase and the Cochrane Library. Medline, In-Process and Embase searches were undertaken using the Datastar host, appropriate date spans, the date of searching and the full search strategies were reported in the MS.[10] Details of the Cochrane Library strategy were absent from the MS, and were requested by the ERG as part of the clarification process.[10] The clarification response[7] from the manufacturer stated the original Cochrane search had not been recorded on 28.3.11. The manufacturer ran additional searches of the Cochrane Library on 13.5.11 in order to provide that search strategy in the clarification response.[8]

The Medline, In-Process and Embase searches were presented as individual Datastar strategies which were clearly structured into population and intervention facets with the addition of a study design filter. The comparator interventions were identified as etanercept, anakinra, adalimumab and infliximab. Methotrexate (MTX) was not included in the indirect comparison searches.

The ERG considered methotrexate an important comparator intervention and was concerned that searches were not undertaken for studies of MTX in sJIA to allow for an indirect comparison of tocilizumab with MTX, therefore the ERG carried out additional searches which are described later in this section.

The same intervention search terms were applied to all searches, and consisted of the comparator drug's generic name in combination with the brand name, limited to the title and abstract fields. In order to make the searches more sensitive, additional synonyms, brand names and the CAS registry number could have been included, together with thesaurus index terms where available. As with the clinical effectiveness searches, all strategies would have benefit from the inclusion of more comprehensive synonyms for the intervention and population.

The Embase search strategy was presented first in the MS, and contained comprehensive variations of the disease terms. The first line of the search contained a potential typographical error which did not appear relevant to the topic i.e. ***(juvenile adj arthritis adj c adj '12').ab.*** This error would have impaired retrieval of records with 'juvenile arthritis' in abstract. The Embase search incorporated an RCT search filter and attempted to remove references to books, conference papers, editorials, letters and reviews from the retrieved results. The ERG noted a few areas of weakness in the RCT filter, the most important of which being the inclusion of '***retracted article'*** as a synonym for randomised controlled trial. The ERG was unclear why this term was included, as it did not appear to relate to any aspect of controlled trials or randomisation. The Embase RCT filter employed appeared to be a pragmatic collection of terms, limited solely to the title and abstract fields. The ERG felt that an objectively derived filter which incorporated relevant Emtree terms would have increased the sensitivity and relevance of the search results. Line 15 of the RCT filter attempted to remove various publication types combined Emtree terms from the results, by means of the Boolean operator 'NOT'. Unfortunately this attempt was not entirely successful as it appeared that line 15 was intended to search the Emtree ***Exp randomised controlled trial***, for example:

(book or conference adj paper or editorial or letter or review).p.t. not (exp adj randomised or randomized) adj controlled adj trial

OvidSP syntax was used, which failed to work in Datastar and resulted incorrect parentheses. The correct Datastar syntax should have applied, e.g.

(book or editorial or letter or review).pt. not Randomized-Controlled-Trial#.DE.

Woo et al 2000.[18] In the absence of the requested data from the manufacturer (individual data for tocilizumab without methotrexate and placebo without methotrexate from the TENDER trial) this was not possible. It should also be noted that data from Woo et al.[18] are probably minimal as most data are reported for children with sJIA and extended oligoarticular arthritis combined; in addition, outcomes from both trials may not be comparable.

The ERG have investigated heterogeneity within and across TENDER and ANAJIS trails. Inclusion criteria are similar for both trials. Table 4.11 presents baseline characteristics for TENDER and ANAJIS.

Table 4.11: Patient characteristics at baseline for TENDER and ANAJIS trials

					ANAJIS	
					Placebo n=12	**Anakinra n=12**
					8(67)	7(58)
					7.5 (3.73)	9.5 (5.19)
					3.2 (1.95)	4.2 (3.33)
					84 (65.74)	66 (64.4)
					57 (27.85)	44 (23.37)
					16 (15.84)	16 (13.12)
					17 (14.91)	16 (14.88)
					57 (29.74)	63 (20.57)
					55 (26.51)	50 (24.39)
					1.44 (0.625)	1.67 (0.845)
					11 (91.6)	8 (66.7)
					11 (91.6)	8 (66.7)