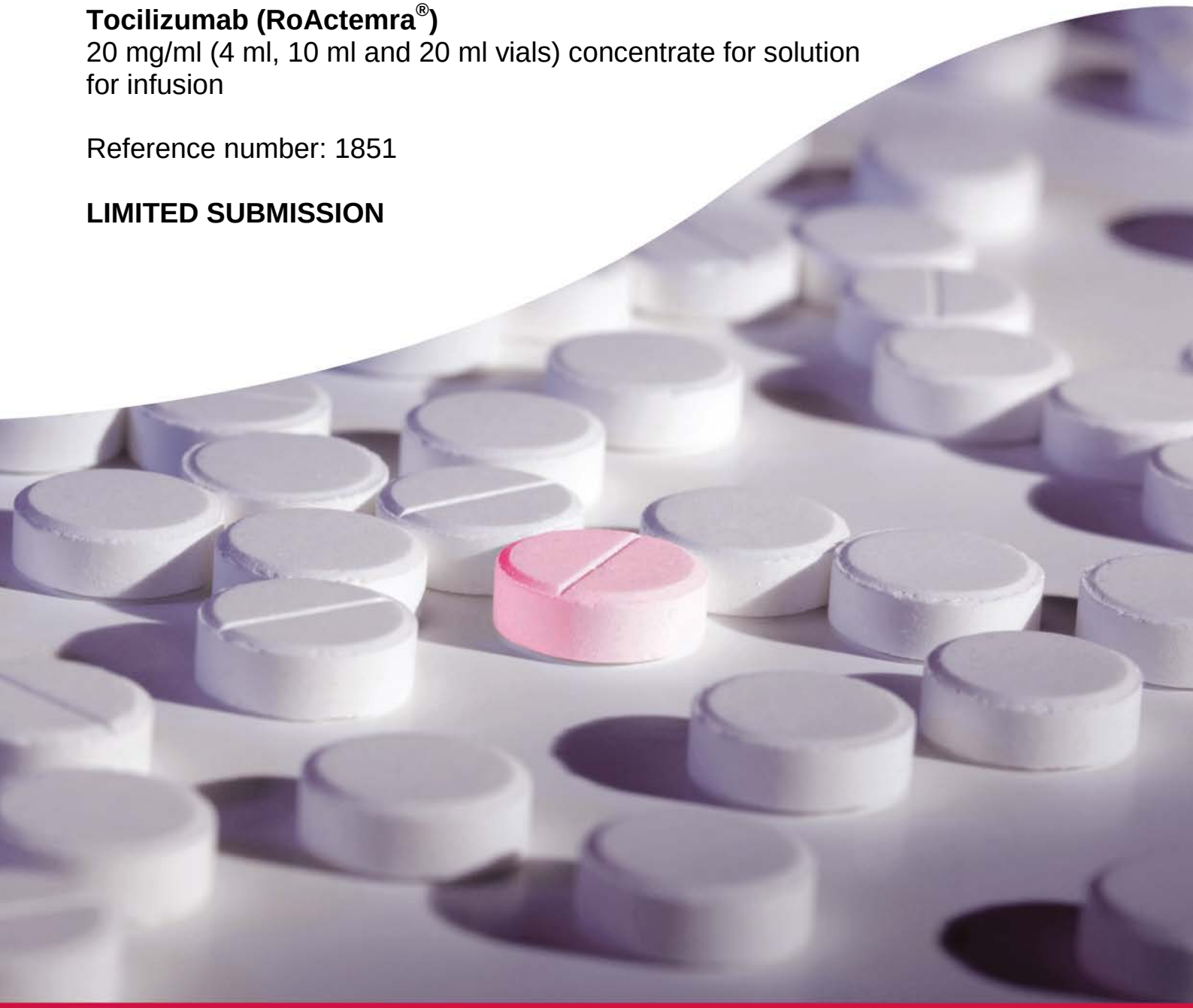
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Tocilizumab (RoActemra®)
20 mg/ml (4 ml, 10 ml and 20 ml vials) concentrate for solution for infusion

Reference number: 1851

LIMITED SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Tocilizumab (RoActemra®) 20 mg/ml (4 ml, 10 ml and 20 ml vials) concentrate for solution for infusion

This assessment report is based on evidence from a limited submission by Roche Products Ltd on 20 September 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Tocilizumab (RoActemra®) 20 mg/ml concentrate for solution for infusion, in combination with methotrexate (MTX), is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate[2].
Dosing	The recommended dose is 8 mg/kg once every four weeks in patients weighing ≥ 30 kg, or 10 mg/kg once every four weeks in patients weighing < 30 kg[2].
Marketing authorisation date	30 May 2013[1,3].
Comparators	The comparators included in the company submission were: • Etanercept (Enbrel®) • Adalimumab (Humira®) • Abatacept (Orencia®)[1]
Limited submission details	Tocilizumab (RoActemra®) for the above indication met the following criteria for eligibility for a limited submission: • A minor licence extension. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparators.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of evidence

The company submission included details of the pivotal phase III multicentre trial, CHERISH (WA19977), to evaluate the efficacy and safety of tocilizumab in patients with active polyarticular juvenile idiopathic arthritis (pJIA; also known as juvenile idiopathic polyarthritis). Patients (n = 188) 2 years of age and older who had documented evidence of at least six months of rheumatoid factor (RF) positive or RF negative pJIA, or of extended oligoarticular arthritis according to International League of Associations for Rheumatology (ILAR) classification criteria, who had an inadequate response to methotrexate (MTX) or inability to tolerate MTX, were enrolled in the study[1,2,4].

The CHERISH trial consisted of three parts, starting with a 16-week open-label lead-in phase (Part I) in which patients ≥ 30 kg received tocilizumab 8 mg/kg as an intravenous (IV) infusion every four weeks for four doses. Patients < 30 kg were randomised 1:1 to

either receive tocilizumab 8 mg/kg or 10 mg/kg as an IV infusion every four weeks for four doses. At week 16, patients (n = 163) with a JIA American College of Rheumatology (ACR)30 response (defined as 3 of any 6 core outcome variables improved by at least 30% from baseline, with no more than 1 of the remaining variables worsened by more than 30%) were eligible to enter Part II of the study. Part II was a 24-week randomised, double-blind, placebo-controlled withdrawal phase in which patients were randomised 1:1 to receive either tocilizumab (same dose as received in Part I) or placebo, stratified by concurrent MTX and corticosteroid use. Part III of the study is an ongoing 64-week open-label extension to examine the long term efficacy and safety of tocilizumab[1,4].

All efficacy analyses were carried out on the intention-to-treat (ITT) population as all enrolled patients received at least one infusion of tocilizumab. The primary endpoint was the proportion of patients with JIA ACR30 flare at week 40 compared to week 16, and this was significantly lower in the tocilizumab group versus the placebo group (25.6% versus 48.1% respectively; p = 0.0024)[1]. The primary endpoint was supported by secondary endpoints[1,4]. The percentage of patients who achieved JIA ACR30/50/70 responses at week 40 relative to baseline was significantly higher in the tocilizumab group versus the placebo group (see Table 1)[1,4].

Table 1. Number and proportion of patients with JIA ACR30/50/70 response rates at week 40 relative to baseline[5,6].

Response Rate	Tocilizumab n = 82	Placebo n = 81
JIA ACR30, n (%)	61 (74.4%)*	44 (54.3%)*
JIA ACR50, n (%)	60 (73.2%)*	42 (51.9%)*
JIA ACR70, n (%)	53 (64.6%)*	34 (42.0%)*

* p < 0.01, tocilizumab versus placebo
JIA ACR30/50/70 responses are defined as 3 of any 6 core outcome variables improved by at least 30/50/70% from baseline, with no more than 1 of the remaining variables worsened by more than 30/50/70%.

In addition to the CHERISH trial, the company provided details of an indirect analysis, comparing tocilizumab, adalimumab and placebo, as monotherapy and as combination therapy with MTX. Based on JIA ACR response rates, the expected efficacy of tocilizumab and adalimumab in pJIA appears to be comparable[7].

Safety data are available for all 188 patients recruited into the CHERISH trial. At the time of the data cut, the median exposure to tocilizumab across Parts I-III of the trial was 48 weeks. The most commonly reported adverse events (AEs) in patients receiving tocilizumab therapy were nasopharyngitis, headache and upper respiratory tract infections. Serious AEs (SAEs) were reported in 9.0% of patients. Five SAEs that occurred in five patients were considered to be remotely possibly or probably related to tocilizumab therapy. There were no deaths during the study[4].

2.2 Points to note

- At the time of writing, three other biologics are approved for use in pJIA in the European Union: adalimumab, etanercept and abatacept[8–10], all of which have been recommended by AWMSG as an option for use in NHS Wales[11–13]. However, there are no direct head-to-head data available to inform a comparison between tocilizumab and these medicines. An indirect treatment comparison for all biologics for the treatment of pJIA is not possible, as the exchangeability assumption necessary to perform a network meta-analysis is violated because of study differences. Furthermore, results from the indirect analysis comparing tocilizumab and adalimumab should be interpreted with caution due to differences in the duration of the withdrawal phase and previous exposure to biologics[7]. The Committee for Medicinal Products for Human Use

(CHMP) were, however, satisfied that efficacy in tocilizumab-treated patients was likely to be similar to that of other biologics used for the treatment of pJIA[4].

- Although no new safety signals were identified, long term safety data are limited. The applicant company will initiate the collection of long term efficacy and safety data in pJIA treatment through a registry which will include the efficacy of 10 mg/kg for patients < 30 kg[4].
- Overall safety data were similar for pJIA patients and that observed in adult rheumatoid arthritis patients. The rate of serious infections was numerically higher in paediatric patients treated with tocilizumab; however, CHMP acknowledge that younger patients are more prone to infection. CHMP concluded that post-marketing data suggests that the safety profile of tocilizumab in patients with pJIA is consistent with that expected for a biologic agent in the pJIA population[4].
- The licensed dosing schedule for tocilizumab is an IV infusion over one hour every four weeks. Etanercept is administered as a subcutaneous injection once or twice weekly and adalimumab is given as a subcutaneous injection every other week. Abatacept is administered as a 30 minute infusion repeated at week two and four, and every four weeks thereafter[8–10]. Differences in the preparation, frequency and route of administration and whether this is likely to be administered in the home or healthcare setting may influence patient/carer and prescriber preference.
- At week 40, JIA ACR30 flare rate was higher for patients not receiving concurrent MTX and for those with previous biologic exposure. However, the incidence of flare was lower for the tocilizumab arm compared to the placebo arm, regardless of MTX use or prior use of a biologic. There was no consistent trend in JIA ACR30 flare rate based on concurrent corticosteroid use, although the sample size was considered to be too small to draw firm conclusions[1,4].
- The Summary of Product Characteristics (SPC) states that full blood count and liver enzymes should be monitored at the time of the second infusion and thereafter according to good clinical practice. Lipid profile is recommended four to eight weeks following tocilizumab initiation[2].
- The SPC states that data suggests that clinical improvement is observed within 12 weeks of initiation of treatment with tocilizumab and that continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe[2].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence[1]

The budget impact evidence presented by the company includes a simple comparison of the annual costs associated with the use of tocilizumab, adalimumab, etanercept, and abatacept for the treatment of pJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. The company estimates that 129 patients in Wales would be eligible for tocilizumab therapy, based on a JIA prevalence of 1 per 1,000, with 23% estimated to have pJIA[1]. Based on market research, the company assumes that only two patients will receive tocilizumab therapy in year one, increasing to five patients in year five. The estimated maximum annual costs associated with tocilizumab and the comparators includes the cost of administration and nursing time, and has been based on the treatment of a 59.5 kg 17 year old patient. The cost of displaced biologics is based on an average cost of adalimumab, etanercept and abatacept. The estimated numbers of patients and the associated costs are summarised in Table 2.

Table 2. Company-reported comparative annual costs for the treatment of polyarticular juvenile idiopathic arthritis.

	2014	2015	2016	2017	2018
Patients with pJIA*	129	131	133	135	137
Patients treated for pJIA*	115	116	118	119	121
Treated with a biologic	17	18	19	20	21
Treated with RoActemra*	2	3	3	4	5
Total cost of RoActemra†	¶	¶	¶	¶	¶
Total cost of displaced biologics§	£20,182	£30,273	£30,273	£40,364	£50,455
Net resource implications to Wales	¶	¶	¶	¶	¶

*Roche market research assumptions
†Based on a 59.5 kg 17 year old patient (includes confidential discounted price as part of Department of Health-agreed Patient Access Schemes, administration costs and nursing time)[1].
§Based on average cost of other biologics for 59.5 kg, 17 year old patients: £10,091(Enbrel®: £9,613; Humira®: £9,235; Orencia®: £11,424), includes cost of administration and nursing time[1].
¶Commercial in confidence data removed.

3.2 AWTTC critique of the budget impact analysis

- The company has made reasonable efforts to characterise the epidemiology of pJIA in Wales and has used Wales-specific data to do so. However, the anticipated market uptake is based on market research assumptions. This is a key component of the estimated cost savings and is a source of uncertainty.
- Costs are based on treatment of a 17 year old patient weighing 59.5 kg. No information on alternative doses has been provided by the company.
- The total cost of displaced biologics is based on an average cost of the treatments used for the stated indication. The anticipated savings are dependent on the validity of the usage levels of the different comparators, given that comparator costs are calculated as weighted average cost based on these estimates.
- Abatacept (Orencia®) has a Wales Patient Access Scheme (WPAS). The confidential WPAS-agreed price for abatacept has not been considered in the budget impact evidence. AWMSG recommended abatacept as an option for use in NHS Wales for the treatment of moderate to severe active pJIA in January 2014[13].
- No sensitivity analyses to address uncertainty in the budget impact estimates have been reported in the company submission.
- Collectively, the analysis provided by the company to determine the net budget impact of tocilizumab is subject to uncertainty.

3.3 Comparative unit costs

Table 3 provides example comparative acquisition costs for tocilizumab and potential comparators, excluding administrative costs. These biologic agents are individually dosed according to patient body weight or surface area. Therefore, Table 3 reflects only illustrative examples of the range of possible costs for patients aged 2 years (assumed body weight 12 kg) to 17 years (assumed body weight with 75 kg the maximum), as covered by the tocilizumab licensed indication, and is based on current list prices in the first year of treatment.

Table 3. Examples of acquisition costs for tocilizumab and comparators in polyarticular juvenile idiopathic arthritis.

Drug	Example prescribing requirements*†	Approximate first year cost§
Tocilizumab (RoActemra®) for IV infusion, 80 mg, 200 mg or 400 mg vial	(1 x 200 mg vial) to (1 x 200 mg plus 1 x 400 mg vials) by IV infusion every 4 weeks	£3,328 to £9,984
Adalimumab (Humira®) for subcutaneous injection, 40 mg prefilled pen/syringe	1 x 40 mg single-use, prefilled pen/syringe for subcutaneous injection every other week	£9,156
Etanercept (Enbrel®) for subcutaneous injection, 10 mg or 25 mg prefilled pen/syringe	1 x 25 mg single use, prefilled syringe for subcutaneous injection twice weekly	£3,718 to £9,296
Abatacept (Orencia®) for IV infusion, 250 mg vial	1–3 x 250 mg vials by IV infusion on week 0,2 and 4, and then every 4 weeks	£4,234 to £12,701

***** Note that doses need to be individually tailored for body weight or surface area. Prescribing requirements relate to number of prescribing units required to provide required dose for patients aged 2–17 years (maximum assumed weight 75 kg).
† Note that abatacept (Orencia®) is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (pJIA) in paediatric patients 6 years of age. See relevant SPCs for full dosing details[2,8–10].
§ Costs based on MIMS list prices as of 10 October 2013[14], assuming vial wastage where applicable. Note that abatacept and tocilizumab are available in NHS Wales with an associated Wales Patient Access Scheme (WPAS)/Department of Health PAS. This WPAS/PAS-agreed price is confidential and has not been used to calculate comparative costs. Costs exclude administration costs which would differ markedly for subcutaneous and IV routes of administration.
This table does not imply therapeutic equivalence of the medicines and doses listed.

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, tocilizumab (RoActemra®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that tocilizumab (RoActemra®) will be supplied by a home healthcare provider[1].

4.2 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

4.3 Evidence search

Date of evidence search: 27/09/2013
Date range of evidence search: No date limits were applied to database searches.

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