Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Anakinra

Proprietary Product Name: Kineret

Sponsor: A Menarini Australia Pty Ltd

October 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.

- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

- AusPARs are prepared and published by the TGA.

- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.

- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.

- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACR	American College of Rheumatology
ACRpaed	American College of Rheumatology paediatric
ACRpaed 30	American College of Rheumatology paediatric 30
AE	Adverse event
AUC	area under the concentration time curve
CINCA	Chronic Infantile Neurological Cutaneous and Articularsyndrome
CAPS	Cryopyrin-associated periodic syndromes
CHMP	(EMA) committee for medicinal products for human use
CRP	C-reactive protein
DAE	Adverse event leading to discontinuation
DMARD	Disease modifying anti rheumatic drug
EMA	European medicines agency
ESR	Erythrocyte sedimentation rate
GCP	good clinical practice
IL-1	Interleukin-1
IL-1Ra	Interleukin-1 receptor antagonist
JCA	Juvenile Chronic Arthritis
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
MAS	macrophage activation syndrome
MTX	Methotrexate
NOMID	Neonatal Onset Multi-system Inflammatory Disease
NSAID	Non-steroidal anti-inflammatory drug
PD	pharmacodynamics

Abbreviation	Meaning
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
RA	Rheumatoid arthritis
RMP	Risk management plan
SAA	Serum amyloid A
SAE	Serious adverse event
SC	Subcutaneous
SJIA	Systemic-onset juvenile idiopathic arthritis
TNF	Tumour necrosis factor

I. Introduction to product submission

Submission details

Type of submission:	Major variation (extension of indications)
Decision:	Approved
Date of decision:	13 March 2015
Active ingredient:	Anakinra (rbe)
Product name:	Kineret
Sponsor's name and address:	A. Menarini Australia Pty Ltd Level 8, 67 Albert Avenue Chatswood NSW 2067
Dose form:	Solution for injection
Strength:	100 mg/0.67 mL
Container:	Prefilled syringe
Pack size:	4 x 7 syringes
Approved therapeutic use:	*For the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years and above who have failed to respond adequately to non-biological DMARDs.*
Route of administration:	Subcutaneous (SC)
Dosage:	The recommended starting dose is 2 mg/kg/day up to 100 mg/day by SC injection. Dose adjustments should be based on clinical outcome and will thus be individualised based on the response and the severity of the disease. Dose adjustments are performed in steps of 0.5 to 1.0mg/kg. Patients with inadequate response may require a maintenance dose of up to 4 mg/kg/day.
ARTG number (s):	82872

Product background

This AusPAR describes the application by A. Menarini Australia Pty Ltd (the sponsor) to extend the indication for kineret to include the following indication;

> *For the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA). Anakinra may be used alone or in combination with DMARDs'.*

During the process of the evaluation of this submission the proposed indication was modified to:

> *'For the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years and above who have failed to respond adequately to non-biological DMARDs.'*

The initial proposal for dosing regimen recommended a 'starting dose of 1 to 2 mg/kg'. This proposal was modified during the course of the evaluation to '2 mg/kg/day up to a

maximum of 100 mg/day by SC injection. Treatment should be undertaken by physicians experienced in the treatment of SJIA. Decisions should be guided by clinical outcomes including laboratory measures. The treating physician should consider whether patients without clinical improvement should continue treatment with anakinra'.

Juvenile idiopathic arthritis (JIA) is a term that encompasses all forms of arthritis that begin before a patient is aged 16 years that persist for more than 6 weeks and are of unknown origin.[1] Systemic juvenile idiopathic arthritis (SJIA) is a subgroup characterised by prominent systemic features, such as fever, rash, and serositis. The peak onset of SJIA, is between the ages of 18 months and 2 years, but the condition commonly persists as a chronic rheumatic condition.

In Australia, two biological agents are currently approved in SJIA. These are tocilizumab (IL-6 Ra; administered IV once every 2 weeks; used alone or in combination with methtrexate) and canakinumab (IL-1β Ra; administered SC once every 4 weeks).

Anakinra is a recombinant human Interleukin-1 receptor antagonist (IL-1Ra) produced in Esherichia coli. It is currently approved for use in RA and Cryopyrin Associated Periodic Syndromes (CAPS). The CAPS indication was recently approved and was not referred to the Advisory Committee for Prescription Medicines (ACPM) for advice.

Interleukin-1 (IL-1) production is induced in response to inflammatory stimuli and mediates various physiological responses including inflammatory and immunological responses. IL-1 has a broad range of activities including cartilage degradation by its induction of the rapid loss of proteoglycans as well as stimulation of bone resorption. The levels of the naturally occurring Interleukin-1 receptor antagonist (IL-1Ra) in synovium and synovial fluid from rheumatoid arthritis (RA) patients are not sufficient to compete with the elevated amount of locally produced IL-1.

A nonclincial dossier was not required, given earlier approval of a similar agent (IL-1β blocker canakinumab), recent approval of anakinra in CAPS and potential limitations of nonclinical data for a biologicial agent.

There are no changes to the product manufacture/formulation, thus a quality dossier was also not required. The submission is supported by clinical data only and includes mainly literature based evidence with an accompanying risk management plan (RMP).

According to the sponsor's letter of application, the submission in Australia was prompted by a request from the Chair of the Paediatric Medicines Advisory Group (PMAG) in Australia.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 17 June 2003.

The approved indication at the time of the submission was:

> *Kineret (anakinra) is indicated for the treatment of active adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more other Disease Modifying Anti Rheumatic Drugs (DMARDs). Kineret should be given in combination with methotrexate.*

During the time of this submission, an additional indication was approved (on 9 September 2014) for:

> *Kinaret (anakinra) is indicated in adult and paediatric patients aged 8 months and older with a body weight of 10 kg or above for the treatment of Cryopyrin-Associated*

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[1] Prakken B et al. Juvenile Idiopathic Arthritis. *Lancet* 2011; 377: 2138-2149.

Periodic Syndromes (CAPS) including Neonatal-Onset Multisystem Inflammatory Disease (NOMID) I Chronic Infantile Neurological, Cutaneous, Articular Syndrome ICINCA), Muckle-Wells Syndrome (MWS), and Familial Cold Autoinfiammatory Syndrome (FCAS).

Overseas approval status

Anakinra is not approved for use in SJIA in the USA, Canada or EU and the sponsor has confirmed that there is no intent to apply for approval in these jurisdictions.

Orphan drug designation

Kineret has been designated an Orphan Drug for the indication:

For the treatment of active systemic onset juvenile idiopathic arthritis (SoJIA) in children.

But not for the broader indication applied for in this application.

The Orphan Drug Designation does not include use in adults and does not refer to monotherapy or combination therapy with other disease modifying anti rheumatic drug (DMARDs).

An Orphan Drug Designation was also granted (on 24 April 2013) for the use of Kineret for the indication:

for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in adults and children including Muckle-Wells Syndrome (MWS), Familial Cold-induced Autoinflammatory syndrome (FACS) / Familial Cold Urticaria (FUC), and Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological Cutaneous and Articular Syndrome (CINCA).

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

Juvenile idiopathic arthritis (JIA) is a term that encompasses all forms of arthritis that begin before a patient is aged 16 years that persist for more than 6 weeks and are of unknown origin[1]. Systemic juvenile idiopathic arthritis (SJIA) is a subgroup characterised by prominent systemic features, such as fever, rash and serositis, and is much like adult onset Still's disease. SJIA can be further stratified into at least two subgroups on the basis of responsiveness to inhibition of, and therefore implying the possible pathogenic relevance of, inteleukin-1. SJIA accounts for 10 to 20% of JIA and affects males and females equally. The peak onset of SJIA is between the ages of 18 months and 2 years but the condition commonly persists as a chronic rheumatic condition.

SJIA is also known as known as juvenile rheumatoid arthritis (SJRA), which is an older term for the same disease. The condition has also been previously known as Still's disease. The term juvenile chronic arthritis (JCA) is broader than the terms JIA or juvenile rheumatoid arthritis (JRA) as it encompasses all chronic arthritides of childhood but the term systemic juvenile chronic arthritis (SJCA) refers to the same condition as SJIA. In order to avoid confusion in this report the term SJIA will be used to refer to this condition.

Guidance

The sponsor states adherence to the TGA's Literature Based Submission guideline.

Contents of the clinical dossier

The submission contained the following clinical information:

- One pivotal literature based study: Quartier et a.l[2]

- Two company sponsored studies of efficacy and safety: Study 990758 (conducted in subjects with polyarticular juvenile rheumatoid arthritis) and its extension Study 990779. Limited pharmacokinetic (PK) data was also available from Study 990758.

- Two other literature reports in support of efficacy and safety, one of which described the company sponsored studies.

- 17 literature reports in support of safety. These reports were all of poor quality but some safety data were extractable and are commented upon in the relevant sections.

- One periodic safety update report (PSUR) that covered the time period 14 May 2010 to 1 May 2013.

Paediatric data

The submission included paediatric pharmacokinetic, efficacy and safety data relating to the proposed new indication.

Good clinical practice

The company sponsored studies were stated to be compliant with GCP. This information was generally not available for the literature based studies.

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[2] Quartier P et al. A multicentre randomised, double blind, placebo controlled, trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis* 2011; 70: 747-754.

Pharmacokinetics

Studies providing pharmacokinetic data

There were no new pharmacokinetic (PK) data in healthy subjects.

Pharmacokinetics in the target population

In Study 990758 PK data were available for 80 subjects aged 3 to 17 years with JIA. There was a high degree of variability in plasma concentrations. The mean plasma concentrations by age grouping suggest decreased exposure in the younger age groups.

Evaluator's conclusions on pharmacokinetics

The analysis of the plasma concentration data from Study 990758 was inadequate. The data appear to be suitable for use in a population PK analysis which would have enabled assessment of covariate data such as age, weight, gender, renal function and disease severity. This analysis should use all the available PK data. The structural model could be informed by PK data from adult studies. The error model could be informed by the data. The covariate model should explore allometric scaling models for weight on the PK parameters clearance and volume of distribution. Using simulations, a dosing strategy could be developed to produce similar exposure to anakinra, represented by area under the concentration time curve (AUC), for children by age groupings and adults.

There were no PK data available from the Pivotal study: Quartier et al.[2]

The data as presented are insufficient to support the proposed dosing regimen.

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamic (PD) data were included in the submission.

Evaluator's conclusions on pharmacodynamics

The analysis of the plasma concentration data from Study 990758 in combination with response data from the same study appear to be suitable for analysis in a population PK/PD model. As there is a discrepancy between the proposed dosing regimen and that used in the pivotal study, a population PK/PD study would be important in informing the dosing regimen.

The population PK/PD model could use the final population PK model, as proposed to generate individual estimates of the PK parameters (for example, AUC, C_{max} and C_{min}). These could then be used in a logistic regression model to examine the relationship between the PK variables and disease flare. Time to disease flare could be examined using a proportional hazards model.

Dosage selection for the pivotal studies

It is not stated how the dose regimen used in the pivotal study was selected. This is an important omission because the proposed dosing regimen differs from that used in the pivotal study.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies

Quartier et al[2]

This study was an investigator sponsored, multicentre, randomised, double blind, and placebo controlled study of anakinra in subjects with SJIA. For a full description of the study please see Attachment 2.

Other efficacy studies

Study 990758

Study 990758 was a randomised, blinded, placebo controlled study of the PK, efficacy and safety of anakinra in polyarticular juvenile rheumatoid arthritis. The data were also published.[3] For a full description of the study please see Attachment 2.

Evaluator's conclusions on efficacy

The efficacy conclusions are based on the results of a single pivotal study of anakinra as monotherapy. This study was performed in 24 subjects, 12 of whom were treated with anakinra. To conclude efficacy from a single pivotal study the results would need to be both clinically and statistically compelling.

In the pivotal study the response rate was clinically significant and highly statistically significant. There were eight (67%) responders in the anakinra group and one (8%) in the placebo (p = 0.003). However, the initial response was not maintained long term. The data presentation indicated considerable crossover between response and non response and it was not possible to account for concurrent treatments that may have modulated the response.

In addition to the primary efficacy outcome variable, the secondary efficacy outcome variables were supportive of efficacy. There were more American College of Rheumatology paediatric (ACRpaed) 50 and ACRpaed 70[4] responders in the anakinra group than in the placebo. There were greater improvements in the anakinra group for most of the remaining efficacy outcome measures, although these were not statistically significant.

The age range and distribution of ages, for the study subjects included in Quartier et al was not provided. Hence it is not possible to determine whether the age range represented by the proposed indication was studied in the pivotal study. Other than this it appears that the population studied in the pivotal study is similar to those intended for treatment in the proposed indication, noting that the efficacy data relate only to active disease.

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[3] Ilowite N, et al Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and primary efficacy results of a randomised multicentre study. *Clin Rheumatol* 2009; 28: 129-137.
[4] The American College of Rheumatology (ACR) Paediatric 30 criteria are a set of criteria that are used as a primary outcome measure for trials It is defined as a minimum of 30% improvement in at least 3 of the core set criteria and no more than one component worsening by >30%. The ACR Paediatric 20, 50, 70 and 90 are also defined as 20%, 50%, 70%, and 90% improvement respectively in a minimum of three core set criteria with worsening of one variable by no more than 30%. The core set criteria are;
Physician global assessment of disease activity
Parent/patient assessment of overall well-being
Functional ability.
Number of joints with active arthritis.
Number of joints with limited range of motion, and
Erythrocyte sedimentation rate.

The data from the pivotal study were pertinent to the indication of SJIA as opposed to other types of JIA/JCA/JRA. The study appears to have been well conducted and is reported in sufficient detail to be acceptable for evaluation. The pivotal study appears to be in accordance with the CHMP Guideline.[5]

However there are a number of deficiencies in the clinical efficacy data. These are:

- The dose regimen used in the pivotal study is different from that proposed by the sponsor. In the opinion of the evaluator, the regimen used in the pivotal study is supported to a greater extent by the data and should replace that proposed by the sponsor

- The efficacy data are primarily literature based and are not reported in detail

- There were insufficient data to support a maximum dose, specifically a maximum dose of 4 mg/kg/day

- There were insufficient data to support efficacy in combination therapy

- There were inadequate data to support an independent evaluation of combination therapy with DMARDs as a group, or as individual agents

- There were insufficient data to support sustained efficacy over the long term (that is, 6 months or longer).

The intended indication is rare and Orphan Drug Designation applies to the paediatric age groups (but not to the adult). Recruitment for clinical trials for this condition is difficult and would require collaboration between many large centres for paediatric rheumatology.

Safety

Studies providing safety data

Pivotal efficacy study

In the pivotal efficacy study, the following safety data were collected: adverse events (AEs).

Dose-response and non pivotal efficacy studies

The non-pivotal safety study reported AEs and laboratory tests.

Other studies evaluable for safety only

Study 990779.

Studies were identified from the literature search performed by the sponsor

Although these studies were of poor quality, some safety data were extractable. For further detail please see Attachment 2.

Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

Patient exposure

In Study 990758 a total of 80 subjects aged 3 to 17 years with JRA were treated with anakinra 10 mg/kg, up to 100 mg, daily for up to 28 weeks. During the open label phase 86

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[5] CHMP Guideline on Clinical Investigation of Medicinal Products for The Treatment Of Juvenile Idiopathic Arthritis. (CPMP/EWP/422/04).

subjects were treated for a median (range) of 84 (2 to 106) days. During the blinded phase, 25 subjects were treated for a median (range) of 112 (9 to 126) days. There were 15 subjects with systemic JCA.

In Study 990779 there were 44 subjects exposed to anakinra for up to 363 days, mean (SD) duration of treatment 162.68 (54.48) days.

In Quartier et al there were 24 subjects with systemic onset JRA treated with anakinra 2 mg/kg (up to 100 mg) with nine treated for 11 months and seven treated for 12 months.

Post-marketing data

Post-marketing data were provided from one PSUR that covered the time period 14 May 2010 to 1 May 2013. The recommended starting dose over that time period was 1 to 2 mg/kg day up to 8 mg/kg/day in patients with Neonatal Onset Multi system Inflammatory Disease (NOMID)/ Chronic Infantile Neurological Cutaneous and Articular Syndrome (CINCA). Clinical exposure in company sponsored clinical trials was estimated at 6404 subject-years. Cumulative post-marketing exposure was estimated to be 63,748 patient-years since first registration in November 2001. The sponsor has identified an investigator sponsored clinical trial where doses up to 20,900 mg/24 hours were administered intravenously in 13 subjects with no reported serious adverse events (SAEs).

The sponsor identified extensive off label use of anakinra. In the USA the indications for treatment with anakinra were systemic onset JRA for 21% of the patients treated. In Sweden the most common indication for anakinra use in children was systemic onset JRA.

There were no new safety concerns identified in the PSUR.

Evaluator's conclusions on safety

The safety data presented in the submission reflected the known safety profile of anakinra and were consistent with the safety specification stated in the RMP. Injection site AEs were common but were of minor severity and are to be expected with the SC route of administration. Serious infections were reported but it was not possible from the data to determine whether the risk was increased by anakinra or reflected the background risk in the treated population. Similarly, macrophage activation syndrome (MAS) and liver toxicity was also reported in subjects treated with anakinra. The data did not identify any specific issue with regard to neutralising antibodies. There do not appear to be any additional monitoring requirements other than those normally required for patients with systemic JCA.

There is clearly an extensive off label usage of anakinra in subjects with systemic onset JIA and the post-marketing reports of MAS, serious infections and liver toxicity should be interpreted in this context. These events are also associated with the population of patients with systemic onset JIA and may reflect the underlying condition and the medicines used to treat it.

However, there were inadequate data with regard to growth and development in the paediatric population.

First round benefit-risk assessment

First round assessment of benefits

The efficacy conclusions are based on the results of a single pivotal study of anakinra as monotherapy. This study was performed in 24 subjects, 12 of whom were treated with

anakinra. To conclude efficacy from a single pivotal study the results would need to be both clinically and statistically compelling.

In the pivotal study the response rate was clinically significant and highly statistically significant. There were eight (67%) responders in the anakinra group and one (8%) in the placebo (p = 0.003). However the initial response was not maintained long term. The data presentation indicated considerable crossover between response and non-response and it was not possible to account for concurrent treatments that may have modulated response.

In addition to the primary efficacy outcome variable, the secondary efficacy outcome variables were supportive of efficacy. There were more ACRpaed 50 and 70 responders in the anakinra group than in the placebo. There were greater improvements in the anakinra group for most of the remaining efficacy outcome measures, although these were not statistically significant.

The age range and distribution of ages, for the study subjects included in Quartier et al. was not provided. Hence it is not possible to determine whether the age range represented by the proposed indication was studied in the pivotal study. Other than this, it appears that the population studied in the pivotal study is similar to those intended for treatment in the proposed indication, noting that the efficacy data relate only to active disease.

The data from the pivotal study were pertinent to the indication of SJIA as opposed to other types of JIA/JCA/JRA. The study appears to have been well conducted and is reported in sufficient detail to be acceptable for evaluation. The pivotal study appears to be in accordance with the committee for medicinal products for human use (CHMP) guideline.[6]

However, there are a number of deficiencies in the clinical efficacy data. These are:

- The dose regimen used in the pivotal study is different to that proposed by the sponsor. In the opinion of the evaluator, the regimen used in the pivotal study is supported by the data and should replace that proposed by the sponsor.

- The efficacy data are primarily literature based and are not reported in detail.

- There were insufficient data to support a maximum dose, specifically a maximum dose of 4 mg/kg/day.

- There were insufficient data to support efficacy in combination therapy.

- There were inadequate data to support an independent evaluation of combination therapy with DMARDs as a group or as individual agents.

- There were insufficient data to support sustained efficacy over the long term (that is 6 months or longer).

The intended indication is rare and Orphan Drug Designation applies to the paediatric age groups (but not to the adult). Recruitment for clinical trials for this condition is difficult and would require collaboration between many large centres for paediatric rheumatology.

As stated above, the dose regimen used in the pivotal study is different to that proposed by the sponsor and in the opinion of the evaluator, the regimen used in the pivotal study is supported by the data and should replace that proposed by the sponsor. However the PK data available to the sponsor could be explored using population PK/PD methods in order to support a dosing regimen.

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[6] CHMP Guideline On Clinical Investigation Of Medicinal Products For The Treatment Of Juvenile Idiopathic Arthritis (CPMP/EWP/422/04).

First round assessment of risks

The first round assessment of risks is the same as those stated in the clinical evaluator's conclusions of safety.

First round assessment of benefit-risk balance

The benefit-risk balance of anakinra is unfavourable given the proposed usage because of there not being sufficient data supporting sustained efficacy.

First round recommendation regarding authorisation

The evaluator recommends rejection of the application for the extension of indications for Kineret (anakinra) to:

Kineret (anakinra) is indicated

- *for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA). Kineret may be used alone or in combination with other DMARDs.*

The reasons for recommending rejection of the application are:

- In the opinion of the evaluator the pivotal study only relates to the efficacy of anakinra in SJIA as monotherapy and not in combination with other DMARDs.

- The age distribution of the subjects studied in the pivotal study is not presented in sufficient detail to demonstrate efficacy across the age range sought in the application.

- There is no compelling evidence of sustained long term benefit.

- The size of the population studied in the pivotal study was small (24 subjects).

- In the opinion of the evaluator there is inconsistency between the dose recommended by the sponsor and that used in the pivotal study. In addition, there has been inadequate analysis of the PK and PD data available to the sponsor. In the opinion of the evaluator the sponsor should conduct further analysis of these data using a population PK/PD approach, and reconsider the dosing regimen using all the data available.

Clinical questions

Pharmacokinetics

1. Does the sponsor have results from a population PK study using the PK data from the paediatric subjects?

Pharmacodynamics

2. Does the sponsor have results from a population PK/PD study using the PK and outcome data from the paediatric subjects?

Efficacy

3. What is the justification for the 1 mg/kg/day starting dose proposed by the sponsor, given that the starting dose in the pivotal study was 2 mg/kg/day?

4. In the report pivotal study, Quartier et al, the age range of the subjects at baseline was not reported. The sponsor should provide a tabulation of the number of subjects for each year of age that were included in the study.

5. What was the definition of SJIA that was used in the inclusion criteria for Study 990758?

Safety

6. In Study 990779 how many of the subjects included in the study had been diagnosed with SJIA? What was the outcome for these subjects (efficacy and safety)?

7. Does the sponsor have any additional information about the trial described in the PSUR that used doses up to 20,900 mg/24 hours? What was the indication studied?

8. Of the subjects treated with anakinra who developed MAS, did their SJIA initially respond to anakinra?

Second round evaluation of clinical data submitted in response to questions

The sponsor has submitted a detailed response to the clinical questions. The response also includes three new references (two of which are recent publications) which provide substantial additional data. In summary these references are:

- Singh et al. (2014)[7] describes a double blind, randomised controlled trial of high dose anakinra as a neuro protective agent in adult subjects with aneurysmal subarachnoid haemorrhage. For further details see Attachment 2.

- Urien et al. (2013)[8] is a report of a population PK/PD analysis of anakinra conducted in children and adolescents with SJIA and auto inflammatory syndromes. The study included data from 87 subjects aged 8 months to 21 years. There were 22 subjects with SJIA with an age range of 2.26 to 16.8 years. For further details see Attachment 2.

- Vastert et al. (2014)[9] is a report of a prospective cohort study of recombinant Interleukin-1 receptor antagonist (IL-1Ra) (anakinra) in treatment naïve subjects (except for indomethacin) with SJIA. For further details see Attachment 2.

Sponsor's responses to clinical questions

For details of the sponsor's response to the clinical questions and the evaluation of the response please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

The sponsor has provided additional data that have satisfactorily addressed the following concerns:

- The dose regimen used in the pivotal study is different to that proposed by the sponsor. In the opinion of the evaluator, the regimen used in the pivotal study is supported by the data and should replace that proposed by the sponsor

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[7]Singh N et al. The effect of intravenous interleukin-1 receptor antagonist on inflammatory mediators in cerebrospinal fluid after subarachnoid haemorrhage: a phase II randomised controlled trial. *J Neuroinflammation* 2014;11 (doi: 10.1186/1742-2094-11-1).

[8] Urien S et al. Anakinra pharmacokinetics in children and adolescents with systemic-onset juvenile idiopathic arthritis and autoinflammatory syndromes. *BMC Pharmacology and Toxicology* 2013, 14:40.

[9] Vastert S et al. Effectiveness of First-Line Treatment with Recombinant Interleukin-1 Receptor Antagonist in Steroid-Naive Patients with New-Onset Systemic Juvenile Idiopathic Arthritis Results of a Prospective Cohort Study. *Arthritis & rheumatology* 2014; 66: 1034–1043.

- The efficacy data are primarily literature based and are not reported in detail

- There were insufficient data to support efficacy as combination therapy

- There were inadequate data to support an independent evaluation of combination therapy with DMARDs as a group or as individual agents

- There were insufficient data to support sustained efficacy over the long term (that is 6 months or longer).

Specifically the sponsor has provided data from a population PK/PD study, a long-term efficacy study and further detail from studies included in the original application.

However despite having sourced a population PK/PD study that provides dosing recommendations, the sponsor has not adopted those recommendations. Urien et al. (2013), supports a dose of 3 mg/kg/day at body weight < 10 kg and 2 mg/kg/day up to 100 mg/day at body weight ≥ 10 kg. In addition, there are insufficient data to support a maximum dose of 4 mg/kg/day, particularly when a maximum dose of 10 mg/kg/day has been used in this population and there does not appear to be dose-dependent toxicity for anakinra.

As discussed, the simulations of dose effect reported in Urien et al. (2013) did not display the 5th or 95th centiles for each plasma concentration that was simulated (see Figure 1). The simulations only used the typical values of the parameter estimates, and did not use the estimates for inter-individual and residual error displayed in Table 1 and Table 2. Hence there may be considerable variability between subjects in the dose required to produce a steady-state plasma concentration of 0.4 mg/L. There may also be considerable variation in the effect at 0.4 mg/L.

Hence, in the opinion of the evaluator the dosing recommendations should not preclude dosing up to 10 mg/kg/day, a dose that appears to be tolerated by subjects in the data submitted.

Figure 1. Simulations of CRP response by plasma anakinra steady state concentration (from Urien et al 2013).

Figure 3 Model-predicted effect of anakinra on the C-reactive concentration-time courses assuming 0.02 to 0.40 mg/L mean steady-state anakinra concentrations in the 2 subgroups of patients. Left, high base level with large CRP decrease. right, moderate base CRP with initial decrease followed by a re-increase in CRP concentrations.
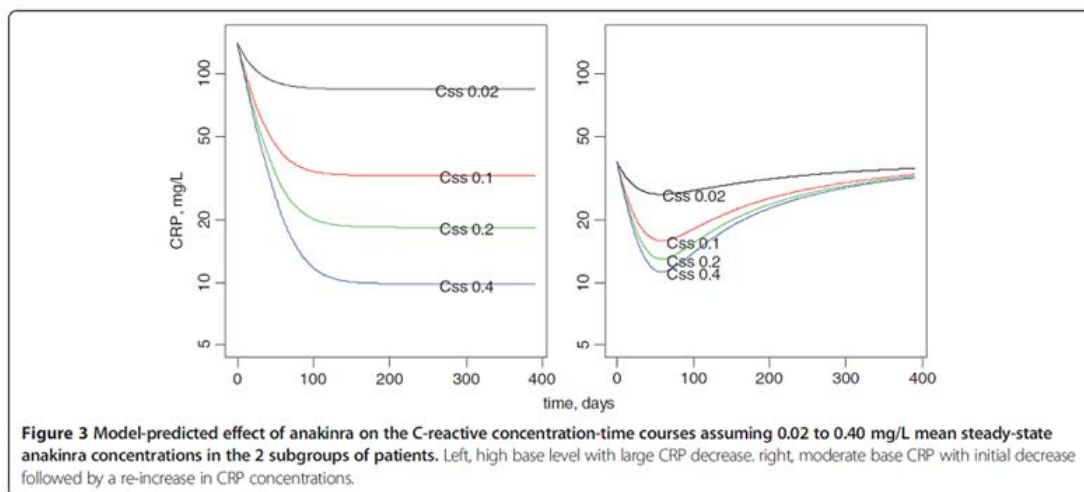
Table 1 Parameter estimates of the final anakinra population pharmacokinetic model in 87 pediatric patients (from Urien et. al. 2013).

Parameter	Estimate	Relative standard error (%)
CL/F (L h^{-1} 70 kg^{-1})	6.24	8
β_{CL}, TV(CL)·(BW/70)$^{\beta CL}$	0.47	14
V/F (L)	65.2	12
β_V, TV(V)·(BW/70)$^{\beta V}$	0.76	16
Ka (h^{-1})	0.38	19
$\eta_{CL/F}$	0.28	15
$\gamma_{V/F}$	0.47	17
ε, mg/L	0.072	10

Key: *CL/F*, apparent elimination clearance; *V/F*, apparent volume of distribution; *Ka*, absorption rate constant; *F*, unknown bioavailability; *TV()*, typical value for the mean covariate value; *β*, covariate effect parameter; *η*, between-subject variability; *γ*, between occasion variability; *ε*, constant residual variability; *BW*, bodyweight (CL/F and V/F estimates are normalized to a 70 kg BW).

Table 2. Parameter estimates of the anakinra effect on c-reactive protein concentrations in 22 SJIA patients (RESP = responders and RESI = patients with onset of 'resistance' to treatment) (from Urien et. al. 2013).

Parameter	Estimate	Relative standard error (%)
Baseline (mg/L)		
RESP	141	27
RESI	37.9	29
k_{TR} (day^{-1})	0.042	27
C_{50} (mg/L)	0.03	37
k_{RESI} (day^{-1})	0.0048	0.0018
Proportion of RESP	0.37	31
$\eta_{BASELINE,RESI}$	0.79	24
η_{KTR}	081	25
ε, mg/L (*)	0.39	6

Key: *Baseline*, CRP level before treatment; *k$_{TR}$*, transit time rate constant; *C$_{50}$*, anakinra concentration that induces a 50% decrease of CRP level; *k$_{RESI}$*, time rate constant of resistance appearance; *η*, between-subject variability; *ε*, constant residual variability, *log-additive model.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of anakinra in the proposed usage are unchanged from those identified in the first round assessment of risks.

Second round assessment of benefit-risk balance

The benefit-risk balance of anakinra, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

The evaluator had no objection to the authorisation of Kineret (anakinra) for the following indication:

> *Kineret (anakinra) is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA).*

The reasons for the change in recommendation from that in the first round evaluation are:

- The sponsor has amended the proposed indication by removing the sentence: '*Kineret may be used alone or in combination with other DMARDs*'

- The sponsor has clarified the age distribution of the subjects studied in the pivotal study in sufficient detail to justify the age range sought in the application

- The sponsor has provided support for sustained long term benefit[9]

- The sponsor has provided data from an additional 20 subjects.[9] Although the size of the population studied in the pivotal study was small (24 subjects) and the population studied in Vastert et al. (2014) is also small (20 subjects), SJIA is an uncommon condition and there would be difficulties in recruiting a larger sample of subjects in any clinical trial for this condition. Consistent with this, Kineret has been designated an Orphan Drug for the indication: *for the treatment of active systemic onset juvenile idiopathic arthritis (SoJIA) in children.* The populations included in the studies included in the submission are predominantly children

- The sponsor has provided further analysis using a population PK/PD approach, which provides support for a rational dosing regimen.

However the dosing regimen proposed by the sponsor is not consistent with the data presented in the application. Urien et al. (2013), supports a dose of 3 mg/kg/day at body weight < 10 kg and 2 mg/kg/day up to 100 mg/day at body weight ≥ 10 kg. In the opinion of the evaluator this dosing regimen should be adopted as the starting dose.

As discussed the simulations of dose effect reported in Urien et al. (2013) did not display the 5th or 95th centiles for each plasma concentration that was simulated (Figure 7, Attachment 2). The simulations only used the typical values of the parameter estimates and did not use the estimates for inter-individual and residual variability displayed in Table 11 and Table 12, Attachment 2. Hence there may be considerable variability between subjects in the dose required to produce a steady-state plasma concentration of 0.4 mg/L. There may also be considerable variation in the effect at 0.4 mg/L.

Hence, in the opinion of the evaluator, the dosing recommendations should not preclude dosing up to 10 mg/kg/day, a dose that appears to be tolerated by subjects in the data submitted. In those patients who do not respond to the starting dose, the recommendation with regard to maximum dose should include the dose range studied in this population, which was not associated with an increase in adverse effects, that is up to 10 mg/kg/day. In the opinion of the evaluator the maximum dose should be increased from 4 mg/kg/day up to 10 mg/kg/day.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan Anakinra EU-RMP (version 3.2 September 2013) and Australian specific Annex (dated February 2014) which was reviewed by the TGA.

Summary of ongoing safety concerns

Table 3 provides a summary of the Ongoing Safety Concerns as specified by the sponsor.

Table 3. Summary of ongoing safety concerns.

Important identified risks	Injection site reactions (ISR)
	Immunogenicity
	Serious infections
	Neutropenia
	Allergic conditions
	Hepatic disorders
	Interaction with tumour necrosis factor (TNF) antagonists
Important potential risks	Malignancies
	Macrophage activation syndrome (MAS)
	Medication errors including re-use of syringe
	Safety in off-label use
Important missing information	Pregnant women
	Lactating women
	Patients with cardiac impairment
	Use in patients with chronic infections
	Use in patients with pre-existing cancers
	Interactions with living vaccines

Pharmacovigilance plan

Routine pharmacovigilance is proposed by the sponsor to monitor all specified safety concerns.

Targeted questionnaires are proposed for the important identified risks 'serious infections', 'neutropenia' and 'hepatic disorders' and important missing information 'pregnant women'.

The pharmacovigilance plan includes 4 patient registries (3 ongoing, 1 planned):

- British Society of Rheumatism Biologics Register (BSRBR) (ongoing)

- German Rheumatism Research Center Berlin Deutsches Rheuma-Forschungszentrum (DRFZ) RABBIT Registry (ongoing)

- Swedish Biologics Registry (ARTIS) (ongoing)

- Pediatric Rheumatology International Trials Organisation (PRINTO)/Eurofever Registry (planned).

OPR reviewer comment

The PRINTO/Eurofever Registry is a post-authorisation safety study of Kineret in CAPS patients. Prospective data collection is planned in the third quarter (Q3) 2014 with follow

up until 2018. Data will be reported annually. Although not specific to the proposed indication it is accepted that safety data gained from this study will be generally informative to the safety profile.

Risk minimisation activities

According to the RMP routine risk minimisation activities are proposed for Australia. No additional risk minimisation activities are proposed in the ASA provided however the EU-RMP does propose additional risk minimisation activities in the form of educational materials.

Reconciliation of issues outlined in the RMP report

Table 4 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and an evaluation of the sponsor's responses.

Table 4. Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the TGAs consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor agrees that for any safety considerations raised by the nonclinical and clinical evaluator, the information provided in response to the issues will include consideration of the relevance for the RMP.

The RMP ASA has been updated with relevant information for SJIA. | This is acceptable. |
| 2. The protocols of ongoing activities have not been reviewed as part of this evaluation. The ongoing studies will either generate safety data that will simply support the known safety profile of the medicine or generate data that will provoke applications to amend the Australian registration details. It is | The sponsor agrees to provide all interim reports and final reports for each activity to the TGA as they become available. | This is acceptable. |

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
recommended that all interim reports and final reports for each activity are provided to the TGA accordingly.		
3. The sponsor is requested to provide in their response to the TGAs request for information the most recent version of the ASA and RMP which should accommodate the changes previously negotiated including the additional pharmacovigilance activities (and their associated milestones) as they apply in the Australian context. The updated ASA should also include information regarding the proposed SJIA indication as appropriate.	The most recent version of the ASA (Version No. 3.1.2) which accommodates the changes previously negotiated includes the additional pharmacovigilance activities and their associate milestones as they apply in the Australian context. The updated ASA also includes information regarding the proposed SJIA indication as appropriate.	The updated ASA submitted is labelled version 3.2 not 3.1.2. The sponsor's response is acceptable.
4. The sponsor is requested to provide in their response to TGAs request for information the most recent version of the ASA and RMP which should accommodate the changes previously negotiated including the summary table of product labelling statements as they apply in Australia.	The most recent version of the ASA (Version No. 3.1.2) which accommodate the changes previously negotiated including the summary table of product labelling statements as they apply in Australia is attached in Module 1.13, Risk management plan for Australia. The RMP Version 3.2 included with the submission is the latest version.	The updated ASA submitted is labelled version 3.2 not 3.1.2. The sponsor's response is acceptable.
5. In the response to the TGAs request for information for a previous application, the	The updated ASA (Version No. 3.1.2) provided in Module	The updated ASA submitted is labelled version 3.2 not 3.1.2.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
sponsor agreed to provide healthcare and patient educational materials as additional risk minimisation activities to ensure consistency with activities in the European Union (EU). The sponsor should update the ASA regarding the educational materials with consideration of the following: Educational materials are considered additional risk minimisation and should be presented as such in the ASA. The ASA should detail a distribution strategy for the educational materials. The ASA should detail a strategy for the assessment of the effectiveness of the educational materials. The ASA should include at least draft educational materials proposed for Australia. The TGA expects that the educational materials will be updated with information specific to the SJIA indication if approved.	1.13, Risk management plan for Australia. The ASA has been updated to include the following: Educational materials are included as additional risk minimisation. Details on the distribution strategy for the educational materials. Detail a strategy for the assessment of the effectiveness of the educational materials. As presented in the ASA, Section 3, Risk Minimisation Plan, the number and change in numbers of reports describing injection site reactions and medication errors including re-use of syringe will be followed. This will be done by monitoring and evaluating individual case safety reports (ICSRs) and comparing the frequency of events to frequencies for previous years. The results of the assessments will be reported to TGA in future PSURs. Draft educational materials proposed	The evaluator has no objection to the content of the draft educational materials. The sponsor's approach to implementing the educational program is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	for Australia. The educational materials have been updated with information specific to the SJIA indication if approved.	
6. The incidence of medication errors seen in the clinical trial programme and in post-marketing experience for the available and proposed indications is not appropriately detailed in the RMP or ASA. This should be corrected. Characterisation of medication errors is considered a requirement of the RMP.	The incidence of medication errors seen in the clinical trial programme and in post-marketing experience for the available and proposed indications is further detailed in the updated ASA (Version No. 3.1.2), Section 2.2.2, Safety concerns – Important potential risks. Medication errors are followed by Sobi[10] as part of regular safety surveillance. Currently the new graduated syringe, which has not been used either in RA or in CAPS studies, is being introduced worldwide. Sobi will continue to follow medication errors and search for any changes in frequency and/or types of medication errors when the new graduated syringe is introduced. Sobi	The updated ASA submitted is labelled version 3.2 not 3.1.2. The sponsor's approach to pharmacovigilance and risk minimisation for the risk of medication errors is considered acceptable.

[10] Sobi is an international specialty healthcare company dedicated to rare diseases.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	will also, as agreed with European medicines agency (EMA), conduct a PASS in CAPS patients in Europe. One of the primary objectives of this PASS is to monitor types and incidence of medication errors. As mentioned in the response above, since EU has a similar demographic to Australia, the company considers that the results from the PASS conducted in EU are also relevant for Australia. The results of the PASS will be provided to TGA when they are available.	

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

The statement in section 3.2 of the ASA that '*no additional risk minimisation activities are planned for Australia*' is incorrect and should be deleted. An educational program is proposed as additional risk minimisation for the risks of injection site reactions and medication error.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Implement Anakinra EU-RMP (version 3.2 dated 13 September 2013) with Australian Specific Annex (version 3.2 dated September 2014) to be revised as recommended in section 1 and any future updates as a condition of registration.

Key changes to the updated RMP

The ASA evaluated in the first round has been superseded by the ASA to EU-RMP version 3.2 (dated September 2014).

Table 5. Key changes to the updated RMP.

Safety specification	Information relating to Systemic Juvenile Idiopathic Arthritis (SJIA) has been included throughout the ASA.
Pharmacovigilance activities	Updated with additional information regarding the Post-authorisation Safety Study to be conducted in CAPS patients.
Risk minimisation activities	Additional information regarding the educational program has been included.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Supporting clinical data

The clinical data underlying this submission consist of published reports of 2 trials for assessment of efficacy and a number of literature reports in support of clinical safety. One PSUR (14/5/2010 to 01/5/2013) was also included. Further significant information was provided at the time of the response to questions raised by the TGA.

Pharmacokinetics and dose selection

The dose regimen used in the nominated efficacy studies was not based on prior dose investigation.

Limited PK data were collected in Study 990758 (see Table 6) in JRA patients aged 3 to 17 years. The dose normalised results, by age groupings including historical comparison with data in adults were as follows (see Figure 2).

Table 6. Study 990758 Pharmacokinetic data.

	1 mg/kg SC Normalized Concentration (ng/mL)			
Study (Age)	990758 (3 to 6)	990758 (7 to 12)	990758 (13 to 17)[a]	560 (Adult)
n	21	98[b]	85	1475[b]
Mean	182	259	194	221
SD	161	304	185	152
%CV	88.2	117	95.5	68.9
Min	24.4	20.4	24.4	0.397
Median	95.8	167	145	192
Max	514	1840	1360	1100

[a] One unadjusted value of 3354.16 ng/mL (subject 71001, day 84) was excluded as an outlier from the 1 mg/kg and 100 mg dose normalizations.
[b] The sample size for the 1 mg/kg and the 100 mg/kg normalized concentrations differ because a mg/kg dose normalization could not be calculated because of missing body weight data for subjects 71902 (study 990758, 11 yrs) and 141521 (study 0560, adult).

Figure 2 Normalised PK data.

Note: tp = time point
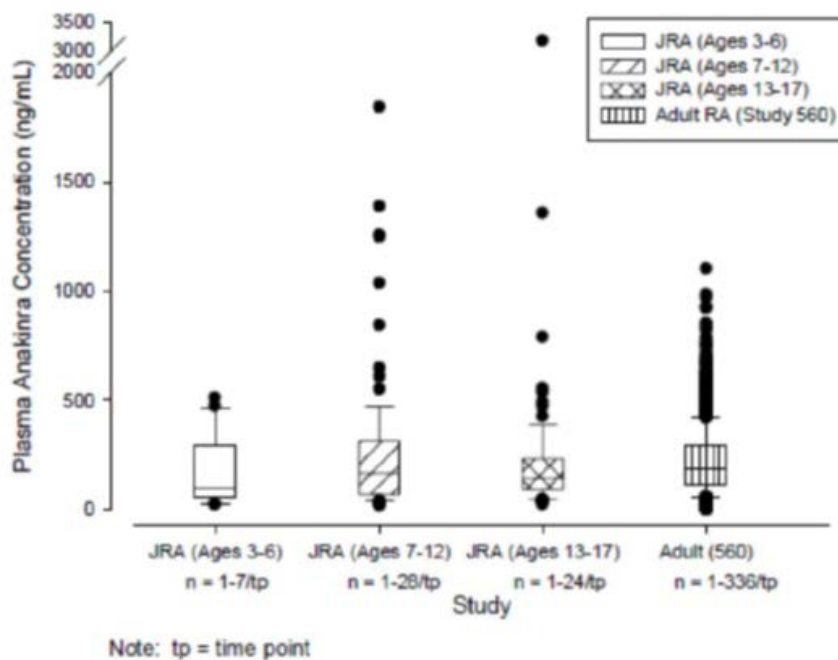
Analysis of PK data at Month 2 and Month 6 indicated a trend towards lower anakinra concentration (45.5 ng/mL (SD 51), range 20 to 122 ng/mL) in patients with lower body weight and patients who were non responders to anakinra at Month 1 compared to patients who were responders to anakinra at Month 1 (136.5 ng/mL (SD 106), range 20 to353 ng/mL). However, the overall difference was not significant.

Clinical efficacy

Quartier et al (2011)[2]

This was an investigator sponsored, trial in SJIA patients (> 6 months disease duration) consisting of 1 month double blind placebo controlled treatment (anakinra 2 mg/kg/day SC to a maximum of 100 mg/day versus placebo) followed by 11 month open label single arm anakinra treatment. This constitutes the pivotal trial for this submission.

The inclusion criteria were age 2 to 20 years, active systemic disease (disease related fever and/or C-reactive protein (CRP) > 20 mg/L and/or first hour erythrocyte sedimentation

rate (ESR) > 20) and significant overall disease activity on Day 1 (at least 3 of the 6) as follows:

1. Physician global assessment of disease activity ≥ 20/100

2. Parent/patient assessment of disease on overall wellbeing ≥ 20/100

3. Childhood Health Assessment Questionnaire score ≥ 0.375/3

4. ≥ 2 joints with active arthritis.

5. ≥ 2 joints with non-irreversible limited range of motion

6. ESR ≥ 30 despite oral prednisone or prednisolone ≥ 0.3 mg/kg or 10 mg/day whichever was lower.

Intravenous or intra articular steroids, immunosuppressive drugs and DMARDs had to be stopped at least 1 month before study or longer depending on half-life.

A total of 24 patients were randomised (12 in each group). The mean age was 9.5 years (SD 5.19) in anakinra group versus 7.5 years (SD 3.73) in placebo group. The age range was 2 to 16 years. The mean duration of disease was 4.2 years (SD 3.3) in anakinra versus 3.2 years (SD 1.95) in placebo group. The mean daily steroid dose was 0.52 mg/kg (SD 0.237) in anakinra group versus 0.66 mg/kg (SD 0.373) in placebo group. A total of 8/12 patients in anakinra group and 11/12 patients in placebo group were on methotrexate (MTX) at baseline. All patients completed Month 1 and 16 patients completed Month 12.

The primary efficacy outcome was proportion of responders (patients fulfilling 3 criteria as follows:

1. Modified American College of Rheumatology Paediatric (ACRpaed 30) score

2. Absence of disease related fever (body temperature < 38°C for > 7 days)

3. Normalisation or ≥ 50% decrease compared with Day 1 in CRP and ESR)

There were a number of secondary outcomes.

Results

The results were as follows:

Results at Month 1

There were 8/12 (67%) responders in anakinra group versus 1/12 (8%) responder in placebo group. The treatment difference was statistically significant (p = 0.003). Same proportion of patients responded with resolution of systemic symptoms (body temperature < 38°C for > 7 days, CRP and ESR normalised or decrease ≥ 50%) in the two groups respectively.

- ACRpaed 30 responders: 11/12 (92%) in anakinra versus 7/12 (58%) in placebo group

- ACRpaed 50 responders: 7/12 (58%) in anakinra versus none in placebo group

- ACRpaed 70 responders: 5/12 (42%) in anakinra versus none in placebo group

- There were no ACRpaed 100 responders in either group.

ACRpaed 30 response, no fever (> 7 days) and CRP < 15 mg/L was attained by 10/12 (83%) anakinra patients compared to 3/12 (25%) placebo patients.

Erythrocyte sedimentation rate, CRP and serum amyloid A (SAA) decreased to a statistically greater extent in the anakinra group compared to placebo group. No increase was reported in either group.

Physician's disease activity assessment, parent/patient global assessment, parent/patient assessment of pain and CHAQ all decreased to a greater extent in anakinra group compared to placebo but the differences were not statistically significant.

Open label results (Month 2 to 12)

A total of 22 patients entered the single arm phase at the end of Month 1.

A total 9/10 (90%) placebo patients who switched to anakinra were responders at Month 2, that is, after one month of active treatment. A total of 17 patients continued treatment until Month 6 with 6 responders and 11 non responders at Month 6. Among responders, the daily prednisolone dose was < 10 mg or 0.3 mg/kg. A total of 16 patients continued treatment to Month 12 with 7 responders and 9 non responders by Month 12. Among the responders 6 had stopped corticosteroid treatment and 5 had inactive disease.

Comment: How the patient counts at the various time points (Months 1, 2, 6 12) were derived was not clear. The sponsor is requested to clarify this. Please also comment whether 'disease flare' was examined in this study and include summary of results.

Study 990758 and extension Study 990779

This supportive trial was a randomised, double blind, placebo controlled study in polyarticular JRA. The study consisted of a run in phase (12 weeks; n = 86 included 15 SJIA patients) with responders randomised to anakinra or placebo for the blinded phase (16 weeks; n = 50) followed by an open label extension study (12 months; n = 44 included 10 SJIA patients). The 50 patients randomised to the blinded treatment included 11 SJIA patients (9/25 in anakinra and 2/25 in placebo group).

The study population was 2 to 17 years old patients presenting with polyarticular JRA independent of onset. The study treatments were anakinra 1.0 mg/kg/day up to 100 mg/day or placebo, administered SC once daily. The intended sample size of 200 was not achieved and the study objectives were amended to safety.

A total of 31/50 (62%) completed the blinded phase. The available efficacy data in SJIA patients in blinded phase were limited to two patients (one in each group that is one anakinra treated SJIA patient). This patient had an increase in affected joints of 2 during the blinded treatment. In the published report of this trial,[3] disease flares were reported in 2/9 SJIA patients in anakinra group and 1/2 SJIA patient in placebo group.

Study 990779 was an open label extension study to Study 990758. The study included patients who entered Study 990758, including non-responders during the run in phase. The patients received anakinra 1 mg/kg/day up to a maximum of 100 mg/day for up to one year. A total of 44 patients entered the open label phase. The age range was 4 to 18 years. A total of 29/44 patients completed the study. No efficacy data were collected during the extension study. As such the Study 990758 and its extension 990779 do not provide meaningful data for assessment of anakinra efficacy in SJIA.

Other studies

A number of published articles provided very limited observational data for efficacy as well as safety. Overall these are not considered useful for regulatory decision making with respect to efficacy. The published papers submitted included Canna et al. (2009) (3 patients)[11], De Jager et al. (2009)[12], (2010)[13], (2011)[14] (8 to 16 patients), Gattorno et al.

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[11] Canna S et al Acute hepatitis in three patients with systemic juvenile idiopathic arthritis taking interleukin-1 receptor antagonist. *Pediatr Rheumatol.* 2009; 7: 21.

[12] de Jager, W et al Early treatment of newly diagnosed systemic onset juvenile idiopathic arthritis patients with anakinra restores the IL-18 response of NK cells. 2009; *10th Annual Congress of the European League Against Rheumatism.* Copenhagen OP-0208.

(2008) (22 patients)[15], Hedrich et al. (2011) (4 patients)[16], Henrickson (2004) (4 patients)[17], Irigoyen et al. (2006) (14 patients)[18], Lequerre et al. (2008) (35 patients)[19], Livermore and Woo (2008) (10 patients)[20], Lurati et al. (2005) (one patient)[21], Nigrovic et al. (2011) (46 patients)[22], Ohlson et al. (2008) (7 patients)[23], Pascual et al. (2005) (9 patients)[24], Pontitaki et al. (2008) (16 patients)[25], Verbsky and White (2004) (2 patients)[26] and Zeft et al. (2009) (33 patients)[27].

De Jager et al. (2010)[13] was a report of 13 patients with systemic onset JRA. There was 'a fast response' in all patients and 75% were described as having achieved an ACR90pedi response after 3 weeks. After 1 year, 6 patients were in remission off treatment, 4 patients were in remission on anakinra and 3 patients required addition of steroid treatment.

Nigrovic et al (2011)[22] was a report of 46 anakinra treated patients with systemic JRA. Ten (22%) patients received anakinra as monotherapy, 67% received corticosteroids and 33% received additional DMARDs. Nearly 60% patients attained complete response. The median starting dose was 1.5 mg/kg/day (range 0.93 to 11.2 mg/kg/day). The median duration of follow up was 14.5 months (range 7.5 to 26 months); 11 MAS episodes were reported of which 6 were prior to anakinra treatment. Injection site reactions were reported in 44% patients with evaluable data. Three serious infections were reported (pneumococcal bacteraemia, infected gastric feeding tube site and pneumonia). One case of eosinophilic hepatitis, two patients with elevated transaminases and one patient with neutropenia were reported.

Additional data in response to TGAs request for information

Three new references were provided for the second round evaluation. Among these Singh et al. (2014)[7] is not relevant to this submission.

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[13] de Jager, W et al Anakinra treatment prior to steroids in newly diagnosed systemic onset JIA: Changing the biology? *Ann Rheum Dis* 2010; 69: 624.

[14] de Jager, W et al. Anakinra restores the defective IL-18 NK cell axis in steroid naïve systemic onset JIA patients. *Pediatr Rheumatol* 2011; 9: O33.

[15] Gattorno, M. et al The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 2008; 58: 1505-1015.

[16] Hedrich, C. M et al Anakinra: A safe and effective first-line treatment in systemic onset juvenile idiopathic arthritis (SoJIA). *Rheumatol Int: 2*011; 32:3525–3530.

[17] Henrickson M. Efficacy of anakinra in refractory systemic arthritis. *Arthritis & Rheumatism* 2004; 50: S438

[18] Irigoyen, P. Treatment of systemic onset juvenile idiopathic arthritis with anakinra - Case series. *Pediatr Rheumatol* 2006 Online J.

[19] Lequerré, T, et al Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. *Ann Rheum Dis* 2008; 67: 302-308.

[20] Livermore, P. and P. Woo. Experience of one UK site presenting a closer examination of safety and efficacy of Anakinra (Kineret) in systemic juvenile idiopathic arthritis. *Pediatr Rheumatol* 2008; 6: 32.

[21] Lurati, A et al Macrophage activation syndrome (MAS) during anti-IL1 receptor therapy (anakinra) in a patient affected by systemic onset idiopathic juvenile arthritis (soJIA): A report and review of the literature. *Pediatric Rheumatology Online Journal* 2005, 3:79-85.

[22] Nigrovic, P. A. et al Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicentre series. *Arthritis Rheum* 2011; 63: 545-555.

[23] Ohlsson, V. et al Anakinra treatment for systemic onset juvenile idiopathic arthritis (SOJIA). *Rheumatology* (Oxford) 2008; 47: 555-556.

[24] Pascual, V. et al Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005; 201: 1479-1486.

[25] Pontikaki, I.et al (2008). Anakinra in systemic juvenile idiopathic arthritis (soJIA) non responsive to antiTNF. *Pediatr Rheumatol* 2008; 6:30.

[26] Verbsky JW, White AJ. Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. *J Rheumatol*. 2004; 31:2071-2075.

[27] Zeft, A. et al Anakinra for systemic juvenile arthritis: the Rocky Mountain experience. *J Clin Rheumatol* 2009; 15: 161-164.

Vastert et al. (2014)

Vastert et al. (2014)[9] was a report of a prospective uncontrolled anakinra treatment in treatment naïve patients (indomethacin excepted) with SJIA (n = 20; age range 1 to 15 years). The treatment was commenced as anakinra 2 mg/kg/day and was tapered if patient had inactive disease after 3 months of treatment (every second day for a month then ceasing treatment). Clinical remission was defined as inactive disease for at least 6 months.

After 1 year of treatment, 11/20 (55%) patients had inactive disease off treatment, two had inactive disease on treatment, one had inactive disease off treatment following combined therapy with anakinra and MTX and/or corticosteroids, one had inactive disease with ongoing combined therapy with anakinra and MTX and/or corticosteroids, and five had varying response on concomitant treatment with MTX and/or corticosteroids.

Over a 3 year follow up period, 90% patients had sustained ACRpaed 70 and 80% had sustained ACRpaed 90. There were 60% patients with sustained ACRpaed 90 on monotherapy. One patient died of MAS and pulmonary hypertension 2 years into the study. No serious invasive infection was reported. Reactivation of herpes simplex virus type 1 infection was reported in several patients.

Urien et al.(2013)

Urien et al. (2013)[8] was a report of a population PK/PD analysis in patients with SJIA and auto inflammatory syndromes. The study included data from 87 patients aged 8 months to 21 years and included 22 patients with SJIA (age range 2 to 16 years; all from pivotal study Quartier et al). Anakinra was administered in the dose range 2 mg/kg/day to 10 mg/kg/day up to 100 mg daily. The only significant covariate was body weight. The predicted dose as function of body weight was as shown in Figure 3.

Figure 3. Daily dose of anakinra (mg/kg, thick curve) as a function of bodyweight in order to reach the mean anakinra steady state concentration of 0.4 mg/L.
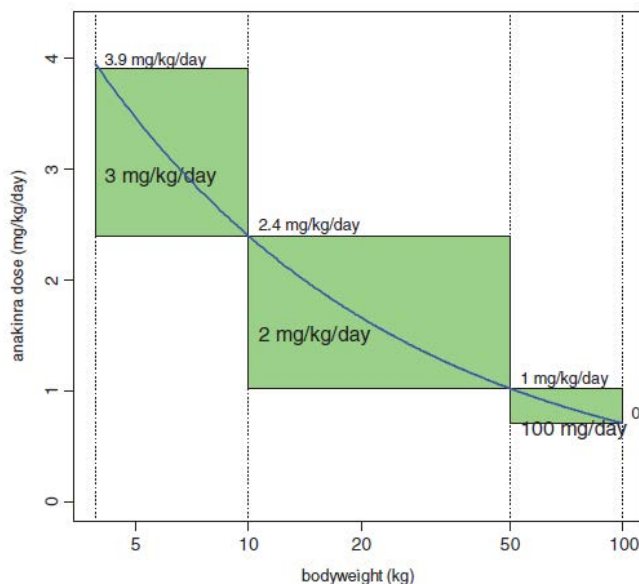
The 0.4 mg/L target corresponds to a maximal effect on the CRP biological marker of inflammation. Bold text in rectangles defines possible mean dosage recommendation for 3 bodyweight ranges. Text on top side stands for the maximal dosage in the corresponding bodyweight range.

The PD measure for PK/PD modelling was CRP. Based on a steady state anakinra plasma concentration of 0.4 mg/L required to obtain plasma CRP ≤ 10 mg/L, the model indicated mean anakinra dose of 3 mg/kg/day for body weight < 10 kg and 2 mg/kg/day for body weight 10 to 50 kg and 1 mg/kg up to a maximum of 100 mg/day for body weight > 50 kg.

For further details of sponsor's response to questions raised in the first round clinical evaluation please see Attachment 2.

Clinical safety

The safety information in this dossier was consistent with the known adverse effects profile of anakinra. Currently there are no data with regard to growth and development in children.

Clinical evaluator's recommendation

The clinical evaluator had no objection to the authorisation of Kineret (anakinra) for the following (modified) indication:

Kineret (anakinra) is indicated for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA).

Risk management plan

The submission is subject to a Risk Management Plan (RMP) to the satisfaction of RMP evaluation area and this will be a condition of registration.

Delegate's comment and recommendation

Delegate's considerations

1. The supporting evidence of efficacy is based on the results of a single placebo controlled pivotal trial (Quartier et al) in 24 patients with SJIA. The patients had disease for at least 6 months and had active disease at the time of entry into the study. The age of participants was 2 to 16 years. The patients were variously on treatment but DMARDs were discontinued prior to the study. The patients remained on steroids although tapering was allowed on clinical basis in responders after one month of double blind treatment. The uncontrolled single arm treatment continued from Months 2 to 12.

   The response rate was clinically meaningful (8/12 (67%) responders (anakinra) versus 1/12 (8%) responder (placebo)) and statistically significant (p = 0.003) at Month 1. The evidence of sustained long term benefit over 12 months was inconsistent with considerable crossover between responders and non responders throughout the study.

   Additional evidence of benefit was either anecdotal or observational from a number of published articles.

   Overall, treatment with anakinra in SJIA resulted in rapid (3 to 4 weeks) amelioration of systemic signs and symptoms but the evidence of maintenance of effect was less compelling. The report by Vastert et al. (2014)[9] (provided at the time of response to questions) included follow up of up to 3 years.

   Overall, the adverse effects profile in children was generally consistent with the known adverse effects data in adults.

   Based on post-market data the sponsor identified extensive off label use of anakinra. In the US the indications for treatment with anakinra for systemic onset JRA were 21% of the patients treated. In Sweden the most common indication for anakinra use in children was systemic onset JRA.

Comment: The sponsor is requested to include a summary of Australian specific data of off-label anakinra use in SJIA.

2. The dataset is very small. Tocilizumab (IL-6Ra) and canakinumab (IL-1 Ra) are currently approved biological agents for use in SJIA. In particular, the dataset supporting canakinumab was larger and more organised than presented here for anakinra. In addition, canakinumab provides distinct advantage in terms of administration regime (SC every 4 weeks) compared to anakinra (SC every day).

Comment: The sponsor is requested to comment whether every day administration regime of anakinra has been re-examined since its first worldwide approval, in particular whether sponsor is in possession of any data indicating that a less frequent administration may or may not be effective given its biological effect.

3. SJIA is most often diagnosed at or after 2 years of age. This was reflected in the pivotal trial where the age of participating patients was 2 to 16 years. This age limitation is also reflected in the previously approved agents for SJIA in Australia. Hence a restriction to age 2 years and above is considered appropriate.

4. The data were inadequate for evaluation of combination therapy with DMARDs including methotrexate. However, qualification of use as second line therapy (inadequate response to DMARDs) may be appropriate. Similarly, withdrawal or interruption of treatment was not studied but recommendations on theoretical grounds may be justified.

5. The dose regimen used in the pivotal study (2 mg/kg/day SC to a maximum of 100 mg/day) was not based on prior dose finding. The proposed maximum dose (4 mg/kg/day) was also not used in this study.

    The PK/PD model (Urien et al. (2013)) supports anakinra 3 mg/kg/day for body weight < 10 kg, 2 mg/kg/day for body weight 10 to 50 kg and 1 mg/kg up to a maximum of 100 mg/day for body weight > 50 kg. The use of CRP (target plasma level ≤ 10 mg/L) as biological marker for correlation with mean plasma anakinra level is considered appropriate for SJIA.

    However, as recommended above if the indication is restricted to SJIA patients aged 2 years and above, the < 10 kg body weight category may not be relevant. Hence, the proposed dose ('2 mg/kg/day up to 100 mg/day by SC injection') is considered consistent with the model both as starting and maintenance dose.

6. The higher doses, 4 mg/kg proposed by sponsor and up to 10 mg/kg proposed by the clinical evaluator, are not supported in SJIA. The reasons are

    a. these doses were not used in the pivotal study which contributed all SJIA patients to the PK/PD model

    b. higher doses in the model were contributed by patients with other auto inflammatory syndromes (note higher dose is approved in CAPS)

    c. the model predictions (mean doses) do not support these higher doses, and

    d. in some patients these will lead to absolute drug amount higher than the adult approved dose (100 mg/kg/day) in RA.

    It is argued that failure of response at the predicted mean dose levels should be considered non response and grounds for discontinuation of treatment.

7. Pending advice from the ACPM, the following indication is supported:

    For the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years and above who have failed to respond adequately to non-biological DMARDs.

    The recommended dose in SJIA is 2 mg/kg/day up to a maximum of 100 mg/day by SC injection.

Treatment should be undertaken by physicians experienced in the treatment of SJIA. Decisions should be guided by clinical outcomes including laboratory measures. The treating physician should consider whether patients without clinical improvement should continue treatment with anakinra.

Proposed action

The Delegate had no reason to say, at the time, that the application for Kineret (anakinra 100 mg/0.67 mL) should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the committee consider the supporting dataset sufficient for approval of anakinra in SJIA patients aged 2 years and above?

2. Would a second line indication (failed response to non-biological agents) and broad recommendation (without specifying concomitant use with methotrexate) be clinically appropriate?

3. Is the Delegate's recommended restricted dosing regimen (2 mg/kg/day up to 100 mg/day SC) consistent with the data and the PK/PD model?

4. Does the committee have further specific recommendations in regard to treatment withdrawal in case of non-response (such as after 4 weeks of treatment) and cessation of treatment in case of responders (such as at 3 months)? Would tapering (such as once every other day dosing for one month) be appropriate prior to ceasing?

The committee is also requested to provide advice on any other issue that may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor supports the Delegate's preliminary recommendation that there is no reason that the application for Kineret (anakinra 100 mg/0.67 mL) should not be approved for registration.

Delegate's comment and recommendation

1.   The sponsor is requested to include a summary of Australian specific data of off label anakinra use in SJIA.

Sponsor's response:

Menarini only has access to data on off label anakinra use in SJIA in Australia from the compassionate supply program via the special access scheme. The compassionate supply program was ceased at the end of 2012 when Actemra was listed in the pharmaceutical benefits scheme (PBS). Until the end of 2012, there were 10 patients in the program which have been treated with anakinra off label in SJIA, which is aligned with the estimated number of patients quoted by an Australian Paediatric Rheumatologist.

'I, [information redacted]*, am a legally qualified consultant paediatric rheumatologist practicing in the* [information redacted]*. I hold the following qualifications: MBBS* [information redacted]*, FRACP* [information redacted]*. I have been involved with clinical paediatrics for 17 years and been a consultant paediatric rheumatologist for 9 years. I am employed on a full time basis as a consultant paediatric rheumatologist and paediatrician at* [information redacted]*. I have been asked to provide an opinion regarding the utility of Anakinra in the management of systemic Juvenile Idiopathic Arthritis.*

Juvenile idiopathic arthritis (JIA) is the commonest auto-immune paediatric rheumatic disease. It has an estimated prevalence of 1: 1000 children, affecting approximately 4600 Australians under the age of 16 in 2004-05.[28] Systemic JIA (SJIA) is a subtype of JIA comprising approximately 10% of all children with this condition. Its name is derived from the significant constitutional symptoms that may accompany the arthritis. These include debilitating fevers, rash, organ enlargement and abnormalities of blood tests indicating marked systemic inflammation. In the short-term these symptoms result in a significant deterioration in the physical functioning and quality of life of affected children, which persists until the disease is adequately controlled. This has traditionally been achieved using systemic corticosteroid therapy, as until recently there have been no alternative agents effective in controlling this aspect of the disease. For many patients the need for steroid therapy is ongoing as more than 50% of SJIA patients have recurrent or persistent disease.[29] The result of both long-term steroid therapy and active disease has historically been that patients with SJIA have a poor outcome, with almost two thirds reporting severe disability and marked impairment of physical and psychological functioning as adults, the most of any subtype of JIA.[30, 22]

Over the last 2 decades the pathogenesis of JIA has been the subject of intense research. For most subtypes, the cytokine tumour necrosis factor alpha (TNFα) has been found to play a key role in promoting inflammation and its blockade with specific anti-TNF therapy effective in reducing arthritis activity.[31,32,33] The effect of TNFα blockade on the systemic manifestations of sJIA, typically the most disabling aspect of the disease, has never been assessed as sJIA patients with active systemic symptoms were excluded from the pivotal trials of TNF agents in JIA. Instead it is increasingly recognised that the cytokines IL-1 and IL-6 play a central role in promoting systemic inflammation in SJIA.[34, 24] Trials examining the response of sJIA patients to blockade of these cytokines have shown that they are safe and produce clinically relevant improvements in both the arthritis and systemic features, with an associated reduction and even elimination of the need for concurrent steroid therapy.[22, 24, 19, ,35,27,] 2 In the case of anakinra (which blocks IL-1), these reports combined with the experience gained in the off label use of the drug in the management of SJIA in paediatric rheumatology centres around the world, including Australia, have led to its inclusion in both the American College of Rheumatology recommendations for the management of SJIA and in the Consensus Treatment Plans for new-onset SJIA published by the North American Children's Arthritis and Rheumatology Research Alliance.[36,37] It is of note that in the latter, 92.6% (n=133) of North American paediatric rheumatologists who responded to a survey regarding willingness to follow the suggested treatment plans indicated they would use that

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[28] Juvenile Arthritis in Australia. Canberra: Australian Institute of Health and Welfare 2008.

[29] Singh-Grewal D et al. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. *Arthritis Rheum*. 2006;54: 1595-1601.

[30] Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology* (Oxford). 2002;41:1428-1435.

[31] Lovell DJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med*. 2000;342: 763-769.

[32] Lovell DJ et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2006;54:1987-1994.

[33] Lovell DJ, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med*. 2008; 359: 810-820.

[34] de Benedetti F et al. Correlation of serum interleukin-6 levels with joint involvement and thrombocytosis in systemic juvenile rheumatoid arthritis. *Arthritis Rheum.* 1991; 34: 1158-1163.

[35] Yokota S et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase Ill trial. *Lancet*. 2008; 371:998-1006.

[36] Beukelman et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* (Hoboken). 2011; 63: 465-482.

[37] Dewitt EM et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res* (Hoboken). 2012.

suggested for anakinra, establishing it as current standard of care for children for a subset of children with SJIA (15).

In Australia the only disease modifying drug with specific efficacy for SJIA currently available on the PBS is the anti-IL-6 agent, tocilizumab. Children with SJIA may qualify for use of this agent if they have active arthritis poorly responsive to methotrexate or corticosteroid dependent systemic symptoms. The administration of tocilizumab requires the insertion of an intravenous cannula and a day-stay hospital admission for infusion of the drug every two weeks. This imposes a significant burden on the child and his/her parents which may preclude its use in certain situations, for example where families live significant distances from the treatment centre. Even for patients where distance considerations are not an issue, parents must accompany their child during their hospital stay, which requires they take 25 days of leave per year of therapy. For some families this is not easily achievable. In these circumstances the availability of an effective alternate agent which can be administered at home, such as anakinra, can significantly reduce the treatment related burden of disease on affected families. Conversely, the availability of tocilizumab means that only a subset of children with severe SJIA who require DMARD therapy will need anakinra, possibly fewer than 6 to 12 per year Australia wide. It is for this small subset, however, that the availability of anakinra will be the difference between effective therapy with few side effects and the use of heavily corticosteroid dependent and side effect prone treatment approaches that were common in the management of this condition 10 years ago.'

2. *The sponsor is requested to comment whether every day administration regime of anakinra has been re-examined since its first worldwide approval, in particular whether sponsor is in possession of any data indicating that a less frequent administration may or may not be effective, given its biological effect.*

Sponsor's response:

Menarini is not aware of any studies using regimens other than every day administration. Based on the short terminal half-life of anakinra (4 to 6 hours) less frequent administration may not be effective in clinical practice. Sub-cutaneous administration on a daily basis with anakinra, as indicated in the attached letter (above), does represent a significant improvement over the current biological therapy available to patients via the PBS (fortnightly hospital based infusions of tocilizumab).

3. *SJIA is most often diagnosed at or after 2 years of age. This was reflected in the pivotal trial where the age of participating patients was 2 to 16 years. This age limitation is also reflected in the previously approved agents for SJIA in Australia. Hence a restriction to age 2 years and above is considered appropriate.*

Sponsor's response:

Menarini agrees that SJIA is most often diagnosed at or after 2 years of age and that the patients randomised in the pivotal trial were 2 to 16 years of age. On these bases, Menarini agrees with the restriction to age 2 years and above recommended by the Delegate.

4. *The data were inadequate for evaluation of combination therapy with DMARDs including methotrexate. However, qualification of use as second line therapy (inadequate response to DMARDs) may be appropriate. Similarly, withdrawal or interruption of treatment was not studied but recommendations on theoretical grounds may be justified.*

Sponsor's response:

In the pivotal study (Quartier et al) the patients had been treated with DMARDs prior to study initiation. However, in the recent study by Vastert et al[9] anakinra treatment was initiated after failure to respond to indomethacin (non-steroidal anti-inflammatory drug (NSAID)) but before the use of other DMARDs, systemic corticosteroids, or other biologic agents. The authors conclude that the strategy of using anakinra as a first line therapy in

SJIA patients and adding additional treatment only when full remission is not achieved results in very high and sustained rates of adapted ACRpaed 90 responses or inactive disease. Based on these data, Menarini consider the use of anakinra as a first line treatment option clinically appropriate, consistent with Actemra and Ilaris.

Furthermore, in the study by Vastert et al the anakinra treatment could be stopped within 1 year in the majority of responding patients, with remission being preserved during follow up. This protocol included a stop strategy, in which anakinra (when given as first line treatment) was tapered at a time point of 3 months in patients achieving at least an adapted ACRpaed 90 response. In this case, the treatment was tapered for 4 weeks and stopped thereafter.

5. *The dose regimen used in the pivotal study (2 mg/kg/day SC to a maximum of 100 mg/day) was not based on prior dose finding. The proposed maximum dose (4 mg/kg/day) was also not used in this study.*

    The PK/PD model (Urien et al) supports anakinra 3 mg/kg/day for body weight < 10 kg, 2 mg/kg/day for body weight 10 to 50 kg and 1 mg/kg up to a maximum of 100 mg/day for body weight > 50 kg. The use of CRP (target plasma level ≤ 10 mg/L) as biological marker for correlation with mean plasma anakinra level is considered appropriate for SJIA.

    However, as recommended above if the indication is restricted to SJIA patients aged 2 years and above, the < 10 kg body weight category may not be relevant. Hence, the proposed dose ('2 mg/kg/day up to l00 mg/day by SC injection') is considered consistent with the model both as starting and maintenance dose.

Sponsor's response:

The sponsor agrees that the proposed dose '2 mg/kg/day up to 100 mg/day by SC injection' is consistent with the PK/PD model both as starting and maintenance dose.

6. *The higher doses, 4 mg/kg proposed by sponsor and up to 10mg/kg proposed by the clinical evaluator, are not supported in SJIA. The reasons are (1) these doses were not used in the pivotal study which contributed all SJIA patients to the PK/PD model, (2) higher doses in the model were contributed by patients with other auto inflammatory syndromes (Note higher approved dose in CAPS), (3) the model predictions (mean doses) do not support these higher doses, and (4) in some patients these will lead to absolute drug amount higher than the adult approved dose (100 mg/kg/day) in RA. It is argued that failure of response at the predicted mean dose levels should be considered non-response and grounds for discontinuation of treatment.*

Sponsor's response:

Menarini agrees that the proposed dose '2 mg/kg/day up to 100 mg/day by SC injection' is consistent with the PK/PD model and with the pivotal study.

7. *Pending advice from the ACPM, the following indication is supported:*

    '*For the treatment of active Systemic Juvenile Idiopathic Arthritis in patients 2 years and above who have failed to respond adequately to non biological DMARDs.*

    The recommended dose in SJIA is 2 mg/kg/day up to a maximum of 100 mg/day by SC injection.

    Treatment should be undertaken by physicians experienced in the treatment of SJIA. Decisions should be guided by clinical outcomes including laboratory measures. The treating physician should consider whether patients without clinical improvement should continue treatment with anakinra.'

Sponsor's response:

As mentioned above, Menarini consider that the data support the use of anakinra as a first line treatment option. The size of treatment difference in the primary endpoint (ACRpaed 30 response) in the pivotal study (Quartier et al) was comparable to the treatment differences seen in the major studies of other products (Actemra and Ilaris). Furthermore, in a newly published study by Vastert et al. (2014) anakinra was used as first-line therapy in patients with new onset SJIA. Patients fulfilled the International League of Associations for Rheumatology criteria for SJIA. Anakinra 2 mg/kg/day was used as a starting dose in all 20 included patients. The 2 mg/kg/day dose was maintained in 18 of the patients and increased to 4 mg/kg/day in 2 patients.

Treatment was stopped if patients met at least the adapted ACRPaed 90 criteria for improvement in JIA after 3 months treatment. The authors concluded than an excellent response was observed in nearly all patients within 3 months, and that more than 80% of the patients achieved persistent disease remission, either on or off medication, during a mean follow up of 2 years and 8 months. Hence, it would seem reasonable to approve the same indication as Ilaris, that is, for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years and above.

The sponsor supports the Delegate's recommended dose.

Additional issue to address

Clinical Efficacy; Quartier et al.(2011) open label results (Month 2 to 12).

'How the patient counts at the various time points (Months 1, 2, 6 12) were derived was not clear. The sponsor is requested to clarify this. Please also comment whether 'disease flare' was examined in this study and include summary of results.'

Sponsor's response:

The patient counts at the various time points (Months 1, 2, 6, 12) are summarised in Table 5 below.

Table 5. Quartier et al patients accounting month 1 to 12.

Time point	Group receiving anakinra since Day 1; number of patients	Group receiving anakinra after Month 1; number of patients
Month 1	12	12
Month 2	12	10
Month 6	8	9
Month 12	7	9

A severe disease flare was considered as a failure and in the case of a flare the patients were allowed to be withdrawn from the study and to receive the best available treatment according to the investigator's judgment. A severe flare was defined as at least one of the following:

- Symptomatic pericarditis or other symptomatic visceral involvement

- At least 3 days of disease related fever equal or superior to 39°C in the preceding 7 days

- A 30% worsening of at least 3 items of Giannini's core set with no more than one item improved by 30% or more.

Severe flares leading to treatment discontinuation were seen in 2 patients after 2 and 3 months of treatment, respectively.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Kineret solution for injection pre-filled syringe containing 100 mg/0.67 mL of anakinra to have an overall positive benefit–risk profile for the Delegate's amended indication;

> *For the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years and above who have failed to respond adequately to non-biological DMARDs.*

The recommended dose in SJIA is 2 mg/kg/day up to a maximum of 100 mg/day by SC injection.

Treatment should be undertaken by physicians experienced in the treatment of SJIA. Decisions should be guided by clinical outcomes including laboratory measures. The treating physician should consider whether patients without clinical improvement should continue treatment with anakinra.

In making this recommendation the ACPM;

- Noted this application was prompted by the Department of Health's Paediatric Medicines Advisory Group (PMAG)

- Noted the limited dataset available including cited references that were frequently abstracts and/or difficult to access

- No meaningful data on dose escalation or on combination therapy

- Noted that for the pivotal trial (Quartier, 2011), patients at entry had mean disease duration which exceeded 3 years; that is, this was clearly not first line therapy

- Noted the PK study submitted was not adequate and provided no dose finding results

- Noted that the PK/PD data suggest that body surface area dosing might be more appropriate than dosing according to body weight strata

- Noted the sponsor has only limited data on off label anakinra use for SJIA in Australia.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- The Immunogenicity section should be rewritten as its meaning and importance is not clear

- Material relating to results of the pivotal study should be presented with the addition of a table and include timing of response and treatment failures

- When describing 'Additional published data in SJIA' the sources should be identified

- The diagram in the CMI of the syringe could be clearer.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the Committee consider the supporting dataset sufficient for approval of anakinra in SJIA patients aged 2 years and above?*

The data are limited but adequate for prescription by experienced clinicians.

2. *Would a second line indication (failed response to non-biological agents) and broad recommendation (without specifying concomitant use with methotrexate) clinically appropriate?*

The ACPM advised that a second line indication was suitable, given the evidence provided by the pivotal study in particular.

3. *Is the Delegate's recommended restricted dosing regimen (2 mg/kg/day up to 100 mg/day SC) consistent with the data and the PK/PD model?*

The ACPM was of the view that the proposed dosing was supported by the trial evidence, but that individualised treatment to target would be the norm. Information regarding benefit of dose escalation is sparse though CAPS experience suggests it would be safe. The ACPM noted that the PK/PD data presented was very limited.

4. *Does the committee have further specific recommendations in regard to treatment withdrawal in case of non-response (such as after 4 weeks of treatment) and cessation of treatment in case of responders (such as at 3 months)? Would tapering (such as once every other day dosing for one month) be appropriate prior to ceasing?*

The informative cessation data are limited to the Vastert open label study which tapered over one month after 3 months of effective therapy and the Quartier study suggests responses may take longer than 1 month to be obtained.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Kineret anankinra (rbe) 100 mg/0.67 mL solution for injection prefilled syringe, indicated:

> *For the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years and above who have failed to respond adequately to non-biological DMARDs.*

Specific conditions of registration applying to these goods

The anakinra EU-Risk Management Plan (EU-RMP), version 3.2, dated 13 September 2013 with Australian Specific Annex (version 3.2 dated September 2014), included with the submission PM-2013-04579-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for Kineret at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration