ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kevzara 150 mg solution for injection in pre-filled syringe
Kevzara 150 mg solution for injection in pre-filled pen
Kevzara 200 mg solution for injection in pre-filled syringe
Kevzara 200 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

150 mg solution for injection
Each single-dose pre-filled syringe contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).
Each single-dose pre-filled pen contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

200 mg solution for injection
Each single-dose pre-filled syringe contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).
Each single-dose pre-filled pen contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

Sarilumab is a human monoclonal antibody selective for the interleukin-6 (IL-6) receptor, produced in Chinese Hamster Ovary cells by recombinant DNA technology.
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear, colourless to pale yellow sterile solution of approximately pH 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by healthcare professionals experienced in the diagnosis and treatment of rheumatoid arthritis. Patients treated with Kevzara should be given the patient alert card.

Posology
The recommended dose of Kevzara is 200 mg once every 2 weeks administered as a subcutaneous injection.

Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations.

Dose modification:
Treatment with Kevzara should be withheld in patients who develop a serious infection until the infection is controlled.

Initiating treatment with Kevzara is not recommended in patients with a low neutrophil count, i.e., absolute neutrophil count (ANC) less than 2 x 10^9/L.

Initiating treatment with Kevzara is not recommended in patients with a platelet count below 150 x 10^3/µL.

Recommended dose modifications in case of neutropenia, thrombocytopenia, or liver enzyme elevations (see sections 4.4 and 4.8):

Low Absolute Neutrophil Count (see section 5.1)	
Lab Value (cells x 10^9/L)	**Recommendation**
ANC greater than 1	Current dose of Kevzara should be maintained.
ANC 0.5-1	Treatment with Kevzara should be withheld until >1 x 10^9/L. Kevzara can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ANC less than 0.5	Treatment with Kevzara should be discontinued.

Low Platelet Count	
Lab Value (cells x 10^3/µL)	**Recommendation**
50 to 100	Treatment with Kevzara should be withheld until >100 x 10^3/µL. Kevzara can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
Less than 50	If confirmed by repeat testing, treatment with Kevzara should be discontinued.

Liver Enzyme Abnormalities	
Lab Value	**Recommendation**
ALT > 1 to 3 x Upper Limit of Normal (ULN)	Clinically appropriate dose modification of concomitant DMARDs should be considered.
ALT > 3 to 5 x ULN	Treatment with Kevzara should be withheld until < 3 x ULN. Kevzara can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ALT > 5 x ULN	Treatment with Kevzara should be discontinued.

Missed dose
If a dose of Kevzara is missed and it has been 3 days or less since the missed dose, the next dose should be administered as soon as possible. The subsequent dose should be administered at the regularly scheduled time. If it has been 4 days or more since the missed dose, the subsequent dose should be administered at the next regularly scheduled time, the dose should not be doubled.

Special Populations
Renal impairment:
No dose adjustment is required in patients with mild to moderate renal impairment. Kevzara has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment:
The safety and efficacy of Kevzara have not been studied in patients with hepatic impairment, including patients with positive hepatitis B virus (HBV) or hepatitis C virus (HCV) serology (see section 4.4).

Elderly:
No dose adjustment is required in patients over 65 years of age (see section 4.4).

Paediatric population:
The safety and efficacy of Kevzara in children up to 18 years of age have not been established. No data are available.

Method of Administration
Subcutaneous use.

The total content (1.14 ml) of the pre-filled syringe/pre-filled pen should be administered as a subcutaneous injection. Injection sites (abdomen, thigh and upper arm) should be rotated with each injection. Kevzara should not be injected into skin that is tender, damaged, or has bruises or scars.

A patient may self-inject Kevzara or the patient's caregiver may administer Kevzara if their healthcare professional determines that it is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of Kevzara prior to use.

For further details on administration of this medicinal product see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability of Kevzara
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Serious infections
Patients should be closely monitored for the development of signs and symptoms of infection during treatment with Kevzara (see sections 4.2 and 4.8). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Kevzara should not be administered in patients with an active infection, including localised infections. Consider the risks and benefits of treatment prior to initiating Kevzara in patients who have:
- chronic or recurrent infection;
- a history of serious or opportunistic infections;
- HIV infection;
- underlying conditions that may predispose them to infection;
- been exposed to tuberculosis; or
- lived in or travelled to areas of endemic tuberculosis or endemic mycoses.

Treatment with Kevzara should be withheld if a patient develops a serious infection or an opportunistic infection.

A patient who develops an infection during treatment with Kevzara should also undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including Kevzara for RA. The most frequently observed serious infections with Kevzara included pneumonia and cellulitis (see section 4.8). Among opportunistic infections, tuberculosis, candidiasis, and pneumocystis were reported with Kevzara. In isolated cases, disseminated rather than localised infections were observed in patients often taking concomitant immunosuppressants such as MTX or corticosteroids, which in addition to RA may predispose them to infections.

Tuberculosis
Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating treatment with Kevzara. Patients with latent or active tuberculosis should be treated with standard antimycobacterial therapy before initiating Kevzara. Consider anti-tuberculosis therapy prior to initiation of Kevzara in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. When considering anti-tuberculosis therapy, consultation with a physician with expertise in tuberculosis may be appropriate.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Viral reactivation
Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with Kevzara. No cases of Hepatitis B reactivation were reported in the clinical studies; however patients who were at risk for reactivation were excluded.

Laboratory parameters
Neutrophil count
Treatment with Kevzara was associated with a higher incidence of decrease in ANC. Decrease in ANC was not associated with higher incidence of infections, including serious infections.

- Initiating treatment with Kevzara is not recommended in patients with a low neutrophil count, i.e., ANC less than 2 x 10^9/L. In patients who develop an ANC less than 0.5 x 10^9/L, treatment with Kevzara should be discontinued.
- Neutrophil count should be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on ANC results see section 4.2.
- Based on the pharmacodynamics of the changes in ANC, use results obtained at the end of the dosing interval when considering dose modification (see section 5.1).

Platelet count
Treatment with Kevzara was associated with a reduction in platelet counts in clinical studies. Reduction in platelets was not associated with bleeding events (see section 4.8).

- Initiating treatment with Kevzara is not recommended in patients with a platelet count below 150 x10^3/µL. In patients who develop a platelet count less than 50 x 10^3/ µL, treatment with Kevzara should be discontinued.
- Platelet count should be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on platelet counts see section 4.2.

Liver enzymes
Treatment with Kevzara was associated with a higher incidence of transaminase elevations. These elevations were transient and did not result in any clinically evident hepatic injury in clinical studies (see section 4.8). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic medicinal products (e.g., MTX) were used in combination with Kevzara.

Initiating treatment with Kevzara is not recommended in patients with elevated transaminases, ALT or AST greater than 1.5 x ULN. In patients who develop elevated ALT greater than 5 x ULN, treatment with Kevzara should be discontinued (see section 4.2).

ALT and AST levels should be monitored 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, consider other liver function tests such as bilirubin. For recommended dose modifications based on transaminase elevations see section 4.2.

Lipid abnormalities
Lipid levels may be reduced in patients with chronic inflammation. Treatment with Kevzara was associated with increases in lipid parameters such as LDL cholesterol, HDL cholesterol, and/or triglycerides (see section 4.8).

Lipid parameters should be assessed approximately 4 to 8 weeks following initiation of treatment with Kevzara, then at approximately 6 month intervals.

Patients should be managed according to clinical guidelines for the management of hyperlipidaemia.

Gastrointestinal perforation
Events of gastrointestinal perforation have been reported in clinical studies, primarily as complications of diverticulitis. Use Kevzara with caution in patients with previous history of intestinal ulceration or diverticulitis. Patients presenting with new onset abdominal symptoms such as persistent pain with fever should be evaluated promptly (see section 4.8).

Malignancies
Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with Kevzara on the development of malignancies is not known but malignancies were reported in clinical studies (see section 4.8).

Hypersensitivity reactions
Hypersensitivity reactions have been reported in association with Kevzara (see section 4.8). Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Patients should be advised to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, administration of Kevzara should be stopped immediately. Kevzara should not be administered to patients with known hypersensitivity to sarilumab (see section 4.3).

Hepatic impairment
Treatment with Kevzara is not recommended in patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8).

Vaccinations
Avoid concurrent use of live vaccines as well as live attenuated vaccines during treatment with Kevzara as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving Kevzara. Prior to initiating Kevzara, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. The interval between live vaccinations and initiation of Kevzara therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents (see section 4.5).

Cardiovascular risk
RA patients have an increased risk for cardiovascular disorders and risk factors (e.g. hypertension, hyperlipidaemia) should be managed as part of usual standard of care.

4.5 Interaction with other medicinal products and other forms of interaction

Sarilumab exposure was not affected when coadministered with MTX based on the population pharmacokinetic analyses and across study comparisons. MTX exposure is not expected to be changed by sarilumab coadministration; however, no clinical data was collected. Kevzara has not been

investigated in combination with Janus kinase (JAK) inhibitors or biological DMARDs such as Tumor Necrosis Factor (TNF) antagonists.

Various *in vitro* and limited *in vivo* human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) and therefore have the potential to alter the pharmacokinetics of concomitantly administered medicinal products that are substrates of these enzymes. Elevated levels of interleukin-6 (IL-6) may down-regulate CYP activity such as in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signalling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered medicinal products concentrations.

The modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of Kevzara in patients being treated with CYP substrate medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., theophylline) should be performed and the individual dose of the medicinal product should be adjusted as needed.

Caution should be exercised in patients who start Kevzara treatment while on therapy with CYP3A4 substrates (e.g., oral contraceptives or statins), as Kevzara may reverse the inhibitory effect of IL-6 and restore CYP3A4 activity, leading to decreased exposure and activity of CYP3A4 substrate. (see section 5.2).Interaction of sarilumab with substrates of other CYPs (CYP2C9, CYP 2C19, CYP2D6) has not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective contraception during and up to 3 months after treatment.

Pregnancy
There are no or limited amount of data from the use of sarilumab in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Kevzara should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab.

Breast-feeding
It is unknown whether sarilumab is excreted in human milk or absorbed systemically after ingestion. The excretion of sarilumab in milk has not been studied in animals (see section 5.3).
Because IgG1 are excreted in human milk**,** a decision should be made whether to discontinue breast-feeding or to discontinue sarilumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No data are available on the effect of sarilumab on human fertility. Animal studies showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Kevzara has no or negligible influence on the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions observed with Kevzara in clinical studies were neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections. The most common serious adverse reactions were infections (see section 4.4).

Tabulated list of adverse reactions

The safety of Kevzara in combination with DMARDs was evaluated based on data from seven clinical studies, of which two were placebo-controlled, consisting of 2887 patients (long- term safety population). Of these, 2170 patients received Kevzara for at least 24 weeks, 1546 for at least 48 weeks, 1020 for at least 96 weeks, and 624 for at least 144 weeks.

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: *ADRs in controlled clinical studies*

System Organ Class	Frequency	Adverse Reaction
Infections and Infestations	Common	Upper respiratory tract infection
		Urinary tract infection
		Nasopharyngitis
		Oral herpes
Blood and Lymphatic System Disorders	Very Common	Neutropenia
	Common	Thrombocytopenia
Metabolism and Nutrition Disorders	Common	Hypercholesterolemia
		Hypertriglyceridemia
Hepatobiliary Disorders	Common	Transaminases increased
General Disorders and Administration Site Conditions	Common	Injection site erythema
		Injection site pruritus

Description of selected adverse reactions

Infections

In the placebo-controlled population, the rates of infections were 84.5, 81.0, and 75.1 events per 100 patient-years, in the 200 mg and 150 mg Kevzara + DMARDs and placebo + DMARDs groups respectively. The most commonly reported infections (5% to 7% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis. The rates of serious infections were 4.3, 3.0, and 3.1 events per 100 patient-years, in the 200 mg, 150 mg Kevzara + DMARDs, and placebo + DMARDs groups, respectively.

In the Kevzara +DMARDs long-term safety population, the rates of infections and serious infection were 57.3 and 3.4 events per 100-patient years, respectively.

The most frequently observed serious infections included pneumonia and cellulitis. Cases of opportunistic infection have been reported (see section 4.4).

The overall rates of infections and serious infections in the Kevzara monotherapy population were consistent with rates in the Kevzara + DMARDs population.

Gastrointestinal perforation
In the placebo-controlled population, one patient on Kevzara therapy experienced a gastrointestinal (GI) perforation (0.11 events per 100 patient-years). In the Kevzara + DMARDs long-term safety population, the rate of GI perforations was 0.14 events per 100 patient-years.

Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including lower GI perforation and abscess. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or methotrexate. The contribution of these concomitant medications relative to Kevzara in the development of gastrointestinal perforations is not known (see section 4.4).

There were no reports of gastrointestinal perforation in the Kevzara monotherapy population.

Hypersensitivity reactions
In the placebo-controlled population, the proportion of patients who discontinued treatment due to hypersensitivity reactions was higher among those treated with Kevzara (0.9% in 200 mg group, 0.5% in 150 mg group) than placebo (0.2%). The rates of discontinuations due to hypersensitivity in the Kevzara + DMARDs long-term safety population and the Kevzara monotherapy population were consistent with the placebo-controlled population. In the placebo-controlled population, 0.2% of the patients treated with Kevzara 200 mg q2w + DMARD reported serious adverse events of hypersensitivity reactions, and none from Kevzara 150 mg q2w + DMARD group.

Injection site reactions
In the placebo-controlled population, injection site reactions were reported in 9.5%, 8%, and 1.4% of patients receiving Kevzara 200 mg, 150 mg, and placebo respectively. These injection site reactions (including erythema and pruritus) were mild in severity for the majority of patients. Two patients on Kevzara (0.2%) discontinued treatment due to injection site reactions.

Laboratory abnormalities
To allow for a direct comparison of frequency of laboratory abnormalities between placebo and active treatment, data from weeks 0-12 were used as this was prior to patients being permitted to switch from placebo to Kevzara.

Neutrophil count
Decreases in neutrophil counts below 1 x 10^9/L occurred in 6.4% and 3.6% of patients in the 200 mg and 150 mg Kevzara + DMARDs group, respectively, compared to no patients in the placebo + DMARDs group. Decreases in neutrophil counts below 0.5 x 10^9/L occurred in 0.8% and 0.6% of patients in the 200 mg and 150 mg Kevzara+ DMARDs groups, respectively. In patients experiencing a decrease in absolute neutrophil count (ANC), modification of treatment regimen such as interruption of Kevzara or reduction in dose resulted in an increase or normalization of ANC (see section 4.2). Decrease in ANC was not associated with higher incidence of infections, including serious infections.

In the Kevzara + DMARDs long-term safety population and the Kevzara monotherapy population, the observations on neutrophil counts were consistent with those seen in the placebo-controlled population (see section 4.4).

Platelet count
Decreases in platelet counts below 100 x 10^3/µL occurred in 1.2% and 0.6% of patients on 200 mg and 150 mg Kevzara + DMARDs, respectively, compared to no patients on placebo + DMARDs**.**

In the Kevzara + DMARDs long-term safety population and the Kevzara monotherapy population, the observations on platelet counts were consistent with those seen in the placebo-controlled population.

There were no bleeding events associated with decreases in platelet count.

Liver enzymes
Liver enzyme abnormalities are summarised in Table 2. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as interruption of Kevzara or reduction in dose, resulted in decrease or normalization of liver enzymes (see section 4.2). These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency (see section 4.4).

Table 2: Incidence of liver enzyme abnormalities in controlled clinical studies

	Placebo + DMARD N = 661	**Kevzara 150 mg + DMARD N = 660**	**Kevzara 200 mg + DMARD N = 661**	**Kevzara Monotherapy Any Dose N = 467**
AST				
>3 x ULN – 5 x ULN	0%	1.2%	1.1%	1.1%
>5 x ULN	0%	0.6%	0.2%	0%
ALT				
>3 x ULN – 5 x ULN	0.6%	3.2%	2.4%	1.9%
>5 x ULN	0%	1.1%	0.8%	0.2%

Lipids
Lipid parameters (LDL, HDL, and triglycerides) were first assessed at 4 weeks following initiation of Kevzara+ DMARDs in the placebo-controlled population. At Week 4 the mean LDL increased by 14 mg/dL; mean triglycerides increased by 23 mg/dL; and mean HDL increased by 3 mg/dL. After Week 4 no additional increases were observed. There were no meaningful differences between doses.

In the Kevzara + DMARDs long-term safety population and the Kevzara monotherapy population, the observations in lipid parameters were consistent with those seen in the placebo-controlled population.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with Kevzara.

In the placebo-controlled population, 4.0%, 5.6%, and 2.0% of patients treated with Kevzara 200 mg + DMARDs, Kevzara 150 mg + DMARDs and placebo + DMARDs respectively, exhibited a positive response in the anti-drug antibody (ADA) assay. Positive responses in the neutralizing antibody (NAb) assay were detected in 1.0%, 1.6%, and 0.2% of patients on Kevzara 200 mg, Kevzara 150 mg, and placebo respectively.

In the Kevzara monotherapy population, observations were consistent with the Kevzara + DMARDs population.

Anti Drug Antibody (ADA) formation may affect pharmacokinetics of Kevzara. No correlation was observed between ADA development and either loss of efficacy or adverse events.

The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used and testing conditions. For these reasons, comparison of the incidence of antibodies to Kevzara with the incidence of antibodies to other products may be misleading.

Malignancies
In the placebo-controlled population, malignancies occurred at the same rate in patients receiving either Kevzara + DMARDs or placebo + DMARDs (1.0 events per 100 patient-years).

In the Kevzara + DMARDs long-term safety population and the Kevzara monotherapy population, the rates of malignancies were consistent with the rate observed in the placebo-controlled population (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are limited data available on overdose with Kevzara. There is no specific treatment for Kevzara overdose. In the event of an overdose, the patient should be closely monitored, treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosupressants, Interleukin inhibitors, ATC code: L04AC14

Mechanism of action
Sarilumab is a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound IL-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling which involves ubiquitous signal-transducing glycoprotein 130 (gp130) and the Signal Transducer and Activator of Transcription-3 (STAT-3).

In functional human cell-based assays, sarilumab was able to block the IL-6 signalling pathway, measured as STAT-3 inhibition, only in the presence of IL-6.

IL-6 is a pleiotropic cytokine that stimulates diverse cellular responses such as proliferation, differentiation, survival, and apoptosis and can activate hepatocytes to release acute-phase proteins, including C-reactive protein (CRP) and serum amyloid A. Elevated levels of IL-6 are found in the synovial fluid of patients with rheumatoid arthritis and play an important role in both the pathologic inflammation and joint destruction which are hallmarks of RA. IL-6 is involved in diverse physiological processes such as migration and activation of T-cells, B-cells, monocytes, and osteoclasts leading to systemic inflammation, synovial inflammation, and bone erosion in patients with RA.

The activity of sarilumab in reducing inflammation is associated with laboratory changes such as decrease in ANC and elevation in lipids (see section 4.4).
Pharmacodynamic effects
Following single-dose subcutaneous (SC) administration of sarilumab 200 mg and 150 mg in patients with RA rapid reduction of CRP levels was observed. Levels were reduced to normal as early as 4 days after treatment initiation. Following single-dose sarilumab administration, in patients with RA, ANC decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline (see section 4.4). Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in haemoglobin and serum albumin.

Clinical efficacy
The efficacy and safety of Kevzara were assessed in three randomised, double-blind, controlled multicentre studies (MOBILITY and TARGET were placebo-controlled studies and MONARCH was an active comparator-controlled study) in patients older than 18 years with moderately to severely active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline.

Placebo-controlled studies
MOBILITY evaluated 1197 patients with RA who had inadequate clinical response to MTX. Patients received Kevzara 200 mg, Kevzara 150 mg, or placebo every 2 weeks with concomitant MTX. The primary endpoints were the proportion of patients who achieved an ACR20 response at Week 24, changes from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) score at Week 16, and change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at Week 52.

TARGET evaluated 546 patients with RA who had an inadequate clinical response or were intolerant to one or more TNF-α antagonists. Patients received Kevzara 200 mg, Kevzara 150 mg, or placebo every 2 weeks with concomitant conventional DMARDs (cDMARDs). The primary endpoints were the proportion of patients who achieved an ACR20 response at Week 24 and the changes from baseline HAQ-DI score at Week 12.

Clinical response
The percentages of Kevzara + DMARDs-treated patients achieving ACR20, ACR50, and ACR70 responses in MOBILITY and TARGET are shown Table 3. In both studies, patients treated with either 200 mg or 150 mg of Kevzara + DMARDs every two weeks had higher ACR20, ACR50, and ACR70 response rates versus placebo-treated patients at Week 24. These responses persisted through 3 years of therapy in an open-label extension study.

In MOBILITY, a greater proportion of patients treated with Kevzara 200 mg or 150 mg every two weeks plus MTX achieved remission, defined as Disease Activity Score 28-C-Reactive Protein (DAS28-CRP) < 2.6 compared with placebo + MTX at Week 52. Results at 24 weeks in TARGET were similar to the results at 52 weeks in MOBILITY (see Table 3).

Table 3: Clinical Response at Weeks 12, 24, and 52 in Placebo-Controlled Studies, MOBILITY and TARGET

	Percentage of Patients					
	MOBILITY MTX Inadequate Responders			**TARGET TNF Inhibitor Inadequate Responders**		
	Placebo + MTX N = 398	**Kevzara 150 mg + MTX N = 400**	**Kevzara 200 mg + MTX N = 399**	**Placebo + cDMARDs[*] N = 181**	**Kevzara 150 mg + cDMARDs[*] N = 181**	**Kevzara 200 mg + cDMARDs[*] N = 184**
Week 12						
DAS28-CRP remission (< 2.6)	4.8%	18.0%[†††]	23.1%[†††]	3.9%	17.1%[†††]	17.9%[†††]
ACR20	34.7%	54.0%[†††]	64.9%[†††]	37.6%	54.1%[†]	62.5%[†††]
ACR50	12.3%	26.5%[†††]	36.3%[†††]	13.3%	30.4%[†††]	33.2%[†††]
ACR70	4.0%	11.0%[††]	17.5%[†††]	2.2%	13.8%[†††]	14.7%[†††]
Week 24						
DAS28-CRP remission (< 2.6)	10.1%	27.8%[†††]	34.1%[†††]	7.2%	24.9%[†††]	28.8%[†††]
ACR20[‡]	33.4%	58.0%[†††]	66.4%[†††]	33.7%	55.8%[†††]	60.9%[†††]
ACR50	16.6%	37.0%[†††]	45.6%[†††]	18.2%	37.0%[†††]	40.8%[†††]
ACR70	7.3%	19.8%[†††]	24.8%[†††]	7.2%	19.9%[††]	16.3%[†]
Week 52						
DAS28-CRP remission (< 2.6)	8.5%	31.0%[†††]	34.1%[†††]	NA[§]	NA[§]	NA[§]
ACR20	31.7%	53.5%[†††]	58.6%[†††]			
ACR50	18.1%	40.0%[†††]	42.9%[†††]			
ACR70	9.0%	24.8%	26.8%			
Major clinical response[¶]	3.0%	12.8%[†††]	14.8%[†††]			

[*] cDMARDs in TARGET included MTX, sulfasalazine, leflunomide and hydroxychloroquine

[†] p-value <0.01 for difference from placebo

[††] p-value <0.001 for difference from placebo

[†††] p-value <0.0001 for difference from placebo

[‡] Primary endpoint

[§] NA=Not Applicable as TARGET was a 24-week study

[¶] Major clinical response = ACR70 for at least 24 consecutive weeks during the 52-week period

In both MOBILITY and TARGET, higher ACR20 response rates were observed within 2 weeks compared to placebo and were maintained for the duration of the studies (see Figures 1 and 2).

Figure 1: Percent of ACR20 Response by Visit for MOBILITY

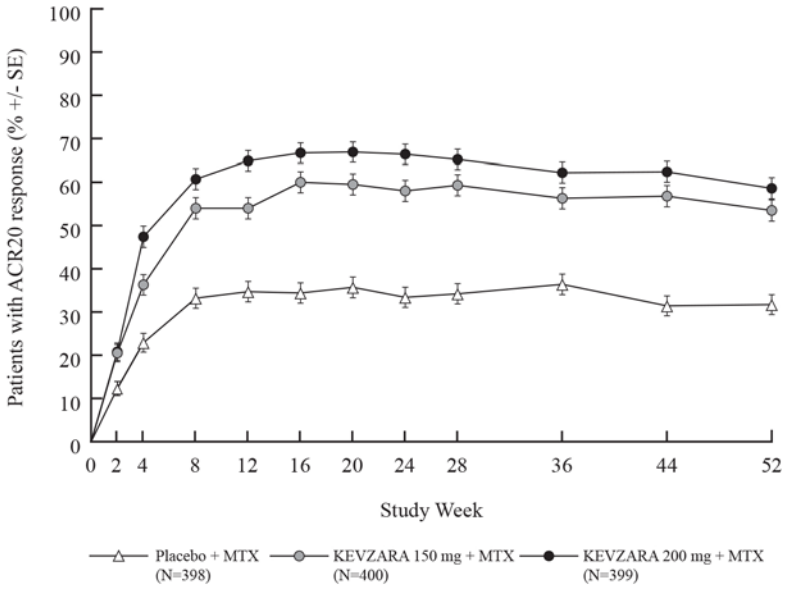
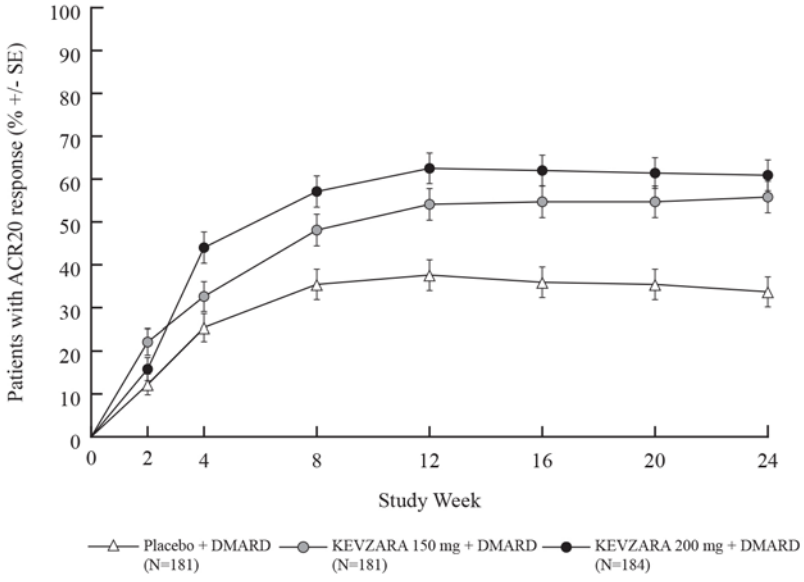


Figure 2: Percent of ACR20 Response by Visit for TARGET



The results of the components of the ACR response criteria at Week 24 for MOBILITY and TARGET are shown in Table 4. Results at 52 weeks in MOBILITY were similar to the results at 24 weeks for TARGET.

Table 4: Mean reductions from baseline to Week 24 in components of ACR score

	MOBILITY			TARGET		
Component (range)	**Placebo + MTX (N = 398)**	**KEVZARA 150 mg q2w* + MTX (N = 400)**	**KEVZARA 200 mg q2w* + MTX (N = 399)**	**Placebo + cDMARDs (N = 181)**	**KEVZARA 150 mg q2w* + cDMARDs (N = 181)**	**KEVZARA 200 mg q2w* + cDMARDs (N = 184)**
Tender Joints (0-68)	-14.38	-19.25†††	-19.00†††	-17.18	-17.30†	-20.58†††
Swollen Joints (0-66)	-8.70	-11.84†††	-12.43†††	-12.12	-13.04††	-14.03†††
Pain VAS† (0-100 mm)	-19.43	-30.75†††	-34.35†††	-27.65	-36.28††	-39.60†††
Physician global VAS‡ (0-100 mm)	-32.04	-40.69†††	-42.65†††	-39.44	-45.09†††	-48.08†††
Patient global VAS‡ (0-100 mm)	-19.55	-30.41†††	-35.07†††	-28.06	-33.88††	-37.36†††
HAQ-DI (0-3)	-0.43	-0.62†††	-0.64†††	-0.52	-0.60†	-0.69††
CRP	-0.14	-13.63†††	-18.04†††	-5.21	-13.11†††	-29.06†††

* q2w = every 2 weeks
‡ Visual analogue scale
†p-value <0.01 for difference from placebo
††p-value <0.001 for difference from placebo
†††p-value <0.0001 for difference from placebo

Radiographic response
In MOBILITY, structural joint damage was assessed radiographically and expressed as change in van der Heijde-modified Total Sharp Score (mTSS) and its components, the erosion score, and joint space narrowing score at Week 52. Radiographs of hands and feet were obtained at baseline, 24 weeks, and 52 weeks and scored independently by at least two well-trained readers who were blinded to treatment group and visit number.

Both doses of Kevzara + MTX were superior to placebo + MTX in the change from baseline in mTSS at 24 and 52 weeks (see Table 5). Less progression of both erosion and joint space narrowing scores at 24 and 52 weeks was reported in the sarilumab treatment groups compared to the placebo group.

Treatment with Kevzara + MTX was associated with significantly less radiographic progression of structural damage as compared with placebo. At Week 52, 55.6% of patients receiving Kevzara 200 mg and 47.8% of patients receiving Kevzara 150 mg had no progression of structural damage (as defined by a change in the TSS of zero or less) compared with 38.7% of patients receiving placebo.

Treatment with Kevzara 200 mg and 150 mg + MTX inhibited the progression of structural damage by 91% and 68%, respectively, compared to placebo + MTX at Week 52.

The efficacy of sarilumab with concomitant DMARDs on inhibition of radiographic progression that was assessed as part of the primary endpoints at Week 52 in MOBILITY was sustained up to three years from the start of treatment.

Table 5: Mean Radiographic Change from Baseline at Week 24 and Week 52 in MOBILITY

	MOBILITY MTX Inadequate Responders		
	Placebo + MTX (N = 398)	**Kevzara 150 mg q2w* + MTX (N = 400)**	**Kevzara 200 mg q2w* + MTX (N = 399)**
Mean change at Week 24			
Modified Total Sharp Score (mTSS)	1.22	0.54†	0.13††
Erosion score (0-280)	0.68	0.26†	0.02††
Joint space narrowing score	0.54	0.28	0.12†
Mean change at Week 52			
Modified Total Sharp Score (mTSS) ‡	2.78	0.90††	0.25††
Erosion score (0-280)	1.46	0.42††	0.05††
Joint space narrowing score	1.32	0.47†	0.20††

* q2w=every two weeks

† p-value <0.001

†† p-value <0.0001

‡ Primary end point

Physical function response

In MOBILITY and TARGET, physical function and disability were assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI). Patients receiving Kevzara 200 mg or 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline in physical function compared to placebo at Week 16 and Week 12 in MOBILITY and TARGET, respectively.

MOBILITY demonstrated significant improvement in physical function, as measured by the HAQ-DI at Week 16 compared to placebo (-0.58, -0.54, and -0.30 for Kevzara 200 mg + MTX, Kevzara 150 mg + MTX, and placebo + MTX, every two weeks, respectively). TARGET demonstrated significant improvement in HAQ-DI scores at Week 12 compared to placebo (-0.49, -0.50, and -0.29 for Kevzara 200 mg + DMARDs, Kevzara 150 mg + DMARDs, and placebo + DMARDs, every two weeks, respectively).

In MOBILITY, the improvement in physical functioning as measured by HAQ-DI was maintained up to Week 52 (-0.75, -0.71, and -0.46 for Kevzara 200 mg + MTX, Kevzara 150 mg + MTX, and placebo + MTX treatment groups, respectively).

Patients treated with Kevzara + MTX (47.6% in the 200 mg treatment group and 47.0% in the 150 mg treatment group) achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥0.3 units) at Week 52 compared to 26.1% in the placebo + MTX treatment group.

Patient reported outcomes

General health status was assessed by the Short Form health survey (SF-36). In MOBILITY and TARGET, patients receiving Kevzara 200 mg + DMARDs every two weeks or Kevzara 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline compared to placebo + DMARDs in physical component summary (PCS) and no worsening on the mental component summary (MCS) at Week 24. Patients receiving Kevzara 200 mg + DMARDs reported greater improvement relative to placebo in the domains of *Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, and Mental Health.*

Fatigue was assessed by the FACIT-Fatigue scale. In MOBILITY and TARGET, patients receiving sarilumab 200 mg + DMARDs every two weeks or sarilumab 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline compared to placebo + DMARDs.

Active Comparator-controlled Study
MONARCH was a 24 –week randomised double-blind, double-dummy study that compared Kevzara 200 mg monotherapy with adalimumab 40 mg monotherapy administered subcutaneously every two weeks in 369 patients with moderately to severely active RA who were inappropriate for treatment with MTX including those who were intolerant of or inadequate responders to MTX.

Kevzara 200 mg was superior to adalimumab 40 mg in reducing disease activity and improving physical function, with more patients achieving clinical remission over 24 weeks (see Table 6).

Table 6: Efficacy results for MONARCH

	Adalimumab 40 mg q2w* (N=185)	**Kevzara 200 mg q2w (N=184)**
DAS28-ESR (primary endpoint) p-value versus adalimumab	-2.20 (0.106)	-3.28 (0.105) < 0.0001
DAS28-ESR remission (< 2.6), n (%) p-value versus adalimumab	13 (7.0%)	49 (26.6%) < 0.0001
ACR20 response, n (%) p-value versus adalimumab	108 (58.4%)	132 (71.7%) 0.0074
ACR50 response, n (%) p-value versus adalimumab	55 (29.7%)	84 (45.7%) 0.0017
ACR70 response, n (%) p-value versus adalimumab	22 (11.9%)	43 (23.4%) 0.0036
HAQ-DI p-value versus adalimumab	-0.43(0.045)	-0.61(0.045) 0.0037

*Includes patients who increased the frequency of dosing of adalimumab 40 mg to every week because of an inadequate response

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Kevzara (sarilumab) in one or more subsets of the paediatric population in chronic idiopathic arthritis (including rheumatoid arthritis, spondylarthritis, psoriatic arthritis and juvenile idiopathic arthritis) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of sarilumab were characterised in 2186 patients with RA treated with sarilumab which included 751 patients treated with 150 mg and 891 patients treated with 200 mg subcutaneous doses every two weeks for up to 52 weeks.

Absorption
The absolute bioavailability for sarilumab after SC injection was estimated to be 80% by population PK analysis. The median t_{max} after a single subcutaneous dose was observed in 2 to 4 days. After multiple dosing of 150 to 200 mg every two weeks, steady state was reached in 12 to 16 weeks with a 2- to 3-fold accumulation compared to single dose exposure.

For the 150 mg every two weeks dose regimen, the estimated mean (± standard deviation, SD) steady-state area under curve (AUC), C_{min}, and C_{max} of sarilumab were 210 ± 115 mg.day/L, 6.95 ± 7.60 mg/L, and 20.4 ± 8.27 mg/L, respectively.

For the 200 mg every two weeks dose regimen, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 396 ± 194 mg.day/L, 16.7 ± 13.5 mg/L, and 35.4 ± 13.9 mg/L, respectively.

In a usability study sarilumab exposure after 200 mg Q2W was slightly higher (C_{max} + 24-34%, $AUC_{(0-2w)}$ +7-21%) after use of a pre-filled pen compared to the pre-filled syringe.

Distribution
In patients with RA, the apparent volume of distribution at steady state was 8.3 L.

Biotransformation
The metabolic pathway of sarilumab has not been characterised. As a monoclonal antibody sarilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination
Sarilumab is eliminated by parallel linear and non-linear pathways. At higher concentrations, the elimination is predominantly through the linear, non-saturable proteolytic pathway, while at lower concentrations, non-linear saturable target-mediated elimination predominates. These parallel elimination pathways result in an initial half-life of 8 to 10 days, and at steady-state an effective half-life of 21 days is estimated.

After the last steady state dose of 150 mg and 200 mg sarilumab, the median times to non-detectable concentration are 30 and 49 days, respectively.
Monoclonal antibodies are not eliminated via renal or hepatic pathways.

Linearity/non-linearity
A more than dose-proportional increase in pharmacokinetic exposure was observed in patients with RA. At steady state, exposure over the dosing interval measured by AUC increased approximately 2-fold with a 1.33-fold increase in dose from 150 to 200 mg every two weeks.

Interactions with CYP450 substrates
Simvastatin is a CYP3A4 and OATP1B1 substrate. In 17 patients with RA, one week following a single 200-mg subcutaneous administration of sarilumab, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively (see section 4.5).

Special populations
Age, gender, ethnicity and body weight
Population pharmacokinetic analyses in adult patients with RA (ranging in age from18 to 88 years with 14% over 65 years) showed that age, gender and race did not meaningfully influence the pharmacokinetics of sarilumab.
Body weight influenced the pharmacokinetics of sarilumab. In patients with higher body weight (>100 Kg) both 150 mg and 200 mg doses demonstrated efficacy; however, patients weighing >100 Kg had greater therapeutic benefit with the 200 mg dose.

Renal impairment
No formal study of the effect of renal impairment on the pharmacokinetics of sarilumab was conducted. Mild to moderate renal impairment did not affect the pharmacokinetics of sarilumab. No dosage adjustment is required in patients with mild to moderate renal impairment. Patients with severe renal impairment were not studied.

Hepatic impairment
No formal study of the effect of hepatic impairment on the pharmacokinetics of sarilumab was conducted (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeated-dose toxicity studies, carcinogenic risk assessment and reproductive and developmental toxicity studies.

No long-term animal studies have been performed to establish the carcinogenicity potential of sarilumab. The weight of evidence for IL-6Rα inhibition mainly indicates anti-tumour effects mediated by multiple mechanisms predominantly involving STAT-3 inhibition. *In vitro* and *in vivo* studies with sarilumab using human tumour cell lines showed inhibition of STAT-3 activation and inhibition of tumour growth in human tumour xenograft animal models.

Fertility studies conducted in male and female mice using a murine surrogate antibody against mouse IL-6Rα showed no impairment of fertility.

In an enhanced pre-/postnatal developmental toxicity study, pregnant Cynomolgus monkeys were administered sarilumab once-weekly intravenously from early gestation to natural birth (approximately 21 weeks) Maternal exposure up to approximately 83 times the human exposure based on AUC after subcutaneous doses of 200 mg every 2 weeks, did not cause any maternal or embryo-fetal effects. Sarilumab had no effect on maintenance of pregnancy or on the neonates evaluated up to 1 month after birth in body weight measurements, in parameters of functional or morphological development including skeletal evaluations, in immunophenotyping of peripheral blood lymphocytes, and in microscopic evaluations. Sarilumab was detected in the serum of neonates up to 1 month. The excretion of sarilumab in Cynomolgus monkey's milk has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Arginine
Polysorbate 20
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC). Do not freeze.

Store pre-filled syringe/pre-filled pen in the original carton in order to protect from light.

6.5 Nature and contents of container

All presentations contain a 1.14 ml solution in a syringe (type 1 glass) equipped with a stainless steel staked needle and an elastomer plunger stopper.

Pre-filled syringe 150 mg:
The single-use pre-filled syringe has a styrene-butadiene elastomer needle cap and is equipped with a white polystyrene plunger rod and a light-orange polypropylene finger flange.

Pre-filled syringe 200 mg:
The single-use pre-filled syringe has a styrene-butadiene elastomer needle cap and is equipped with a white polystyrene plunger rod and a dark-orange polypropylene finger flange.

Pre-filled pen 150 mg:
The syringe components are pre-assembled into a single-use pre-filled pen with a yellow needle cover and light-orange cap.

Pre-filled pen 200 mg:
The syringe components are pre-assembled into a single-use pre-filled pen with a yellow needle cover and dark-orange cap.

Pack sizes:
- 1 pre-filled syringe
- 2 pre-filled syringes
- Multipack containing 6 (3 packs of 2) pre-filled syringes
- 1 pre-filled pen
- 2 pre-filled pens
- Multipack containing 6 (3 packs of 2) pre-filled pens

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The pre-filled syringe/pre-filled pen should be inspected before use. The solution should not be used if it is cloudy, discoloured, or contains particles, or if any part of the device appears to be damaged.

After removing the pre-filled syringe/pre-filled pen from the refrigerator, it should be allowed to reach room temperature (<25°C) before injecting Kevzara.
Comprehensive instructions for the administration of Kevzara in a pre-filled syringe/pre-filled pen are given in the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. After use, place the pre-filled syringe/ pre-filled pen into a puncture-resistant container and discard as required by local regulations. Do not recycle the container. Keep the container out of sight and reach of children.

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
75008 Paris
France

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1196/001
EU/1/17/1196/002
EU/1/17/1196/003
EU/1/17/1196/004

EU/1/17/1196/005
EU/1/17/1196/006
EU/1/17/1196/007
EU/1/17/1196/008
EU/1/17/1196/009
EU/1/17/1196/010
EU/1/17/1196/011
EU/1/17/1196/012

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 June 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu