Sarilumab

Targets (6) Enzymes (4) Biointeractions (5)

IDENTIFICATION

Name

Sarilumab

Accession Number

DB11767

Type

Biotech

Groups

Approved, Investigational

Biologic Classification

Protein Based Therapies
Monoclonal antibody (mAb)

Description

Sarilumab is a fully human anti-IL-6R monoclonal IgG1 antibody that binds to both membrane bound and soluble interleukin 6 (IL-6) receptor forms, thus blocking the cis- and trans-inflammatory signalling cascades of IL-6 [1]. Sarilumab was developped by Sanofi and Regeneron Pharmaceuticals, Inc; it was US FDA-approved in May 2017 and followed by EU approval in June 2017 for the treatment of moderate to severe Rheumatoid Arthritis (RA) in combination with methotrexate [4]. RA is a chronic inflammatory disease characterized by polyarthritis and its treatment has been challenged by the different response in every patient [3]. Subcutaneous administration of Sarilumab has been shown to decrease acute-phase reactant levels and improve in clinical RA symptoms [2].

Protein structure

Protein chemical formula

$C_{6388}H_{9918}N_{1718}O_{1998}S_{44}$

Protein average weight

150000.0 Da (143900 Da in absence of N-glycosylation in heavy chains (Asn296))

Sequences

```
> Heavy chain
EVQLVESGGGLVQPGRSLRLSCAASRFTFDDYAMHWVRQAPGKGLEWVSGISWNSGRIGY
ADSVKGRFTISRDNAENSLFLQMNGLRAEDTALYYCAKGRDSFDIWGQGTMVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK
```

```
>Light chain
DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYGASSLESGVPS
RFSGSGSGTDFTLTISSLQPEDFASYYCQQANSFPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Download FASTA Format

Synonyms

REGN88

SAR153191

Prescription Products

Search

NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END		
Kevzara	Solution	150 mg	Subcutaneous	Sanofi Aventis	2017-03-29	Not applicable		

	solution	mg/1.14mL					
Kevzara	Solution	150 mg	Subcutaneous	Sanofi Aventis	Not applicable	Not applicable	
Kevzara	Solution	200 mg	Subcutaneous	Sanofi Aventis	2017-02-08	Not applicable	
Kevzara	Injection, solution	150 mg/1.14mL	Subcutaneous	Sanofi Aventis	2017-05-22	Not applicable	
Kevzara	Injection, solution	200 mg/1.14mL	Subcutaneous	Sanofi Aventis	2017-05-22	Not applicable	

Showing 1 to 8 of 8 entries

Categories

Amino Acids, Peptides, and Proteins

Antibodies

Antibodies, Monoclonal

Biologics for Rheumatoid Arthritis Treatment

Blood Proteins

Cytochrome P-450 CYP3A Inhibitors

Cytochrome P-450 CYP3A4 Inhibitors

Cytochrome P-450 CYP3A4 Inhibitors (weak)

Cytochrome P-450 Enzyme Inhibitors

Disease-modifying Antirheumatic Agents

Globulins

Immunoglobulins

Immunoproteins

Immunosuppressive Agents

Interleukin-6 Receptor Antagonist

Proteins

Serum Globulins

UNII

PHARMACOLOGY

Indication

Indicated for modere to severe reactive RA in adult patients who are irresponsive, respond inadequately or present intolerance to disease-modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) antagonists. It is indicated to be used in combination with methotrexate (MTX) or as a monotherapy when there is intolerance to MTX or MTX administration is inappropriate.

Associated Conditions

Moderate, active Rheumatoid arthritis

Severe, active Rheumatoid arthritis

Pharmacodynamics

Single-dose subcutaneous administration of Sarilumab produced a rapid reduction of CRP levels, leading to normal levels after two weeks of treatment. Peak reduction in the absolute neutrophile count was observed after 3 to 4 days of treatment followed by a recovery to baseline levels. It is observed a decrease in fibrinogen and serum amyloid A as well as an increase in hemoglobin and serum albumin.

Mechanism of action

Sarilumab is a human recombinant IgG1 antibody that binds to both forms of interleukin 6 receptors (IL-6R), thus inhibiting the IL-6-mediated signaling. IL-6 is known to be a pleiotropic cytokine that activates immune cells (T and B cells), as well as hepatocytes for the release of acute phase proteins like CRP, serum amyloid A and fibrinogen which are biomarkers of RA activity. IL-6 is also found in synovial fluid and plays a major role in the pathological inflammation and joint destruction features of RA. Thus, it is used for the treatment of RA due to its ability to inhibit intra-articular and systemic IL-6 signaling [5, 6].

(A)	Interleukin-6 receptor subunit alpha
	antagonist antibody
	Human

U	Low affinity immunoglobulin gamma Fc region receptor II-a	
	unknown	
	Human	
U	Low affinity immunoglobulin gamma Fc region receptor II-b	
	unknown	
	Human	
U	Low affinity immunoglobulin gamma Fc region receptor III-A	
	unknown	
	Human	
U	Low affinity immunoglobulin gamma Fc region receptor III-B	
	unknown	
	Human	

Absorption

Sarilumab is shown to be well absorbed in RA patients after single SC administration with a maximum of serum concentration presented after 2 to 4 days. For the 150 mg every two weeks dose regimen, the AUC, Cmin and Cmax of sarilumab were 202 ± 120 mg.day/L, 6.35 ± 7.54 mg/L, and 20.0 ± 9.20 mg/L, respectively. For the 200 mg every two weeks dose regimen, the AUC, Cmin and Cmax of sarilumab were 395 ± 207 mg.day/L, 16.5 ± 14.1 mg/L, and 35.6 ± 15.2 mg/L, respectively [6].

Volume of distribution

In patients with RA, the apparent volume of distribution at steady state was 7.3 L [6].

Protein binding

Sarilumab is a covalent heterotetramer composed by two disulfide linked heavy chains covelently linked to a kappa light chain. The heavy chain has a IgG1 constant region with a single N-linked glycosylation site in the Fc portion of the molecule. [6] The complimentarity-determining regions (CDRs) within variable domains of both light and heavy chains combine to form the binding site for IL-6R. As Sarilumab is an IgG1 molecule, it presents Fc-effector function and it is prompt to bind to FcγRI, FcγRIIa, FCγRIIb, FcγRIIIa and FcγRIIIB. However, it does not induce Antibody-Dependant Cell-mediated Cytotoxicity (ADCC) or Complement-Dependant Cytotoxicity (CDC) [5].

Metabolism

Route of elimination

At high concentrations, Sarilumab is thought to be eliminated predominantly through a non-saturated proteolytic pathway, while at lower concentrations, the elimination will be done by saturable target-mediated elimination [1].

Half life

The half life will depend on the administered concentration. At 200 mg every 2 weeks, half-life is up to 10 days in patients with RA at steady state. At 150 mg every 2 weeks, half-life is up to 8 days in patients with RA at steady state. After the last steady state dose of 150 mg and 200 mg, the time to reach nondetectable concentration is 28 and 43 days, respectively [5].

Clearance

Sarilumab is not eliminated via renal or hepatic pathways. RA patients have shown a trend toward higher clearance in presence of anti-sarilumab antibodies [FDA file].

Toxicity

Repeat dose exposure has been shown to produce a partially reversible decrease in neutophil count and a reversible decrease in fibrinogen [5].

Affected organisms

Humans and other mammals

Pathways

Not Available

Pharmacogenomic Effects/ADRs

Not Available

INTERACTIONS

Drug Interactions

Search

DRUG	INTERACTION	DRUG GROUP

	decreased when used in combination with Sarilumab.	Investigational
Abiraterone	The therapeutic efficacy of Abiraterone can be decreased when used in combination with Sarilumab.	Approved
Aceclofenac	Sarilumab may increase the immunosuppressive activities of Aceclofenac.	Approved, Investigational
Acemetacin	Sarilumab may increase the immunosuppressive activities of Acemetacin.	Approved, Experimental, Investigational
Acenocoumarol	The therapeutic efficacy of Acenocoumarol can be decreased when used in combination with Sarilumab.	Approved, Investigational
Acetaminophen	The therapeutic efficacy of Acetaminophen can be decreased when used in combination with Sarilumab.	Approved
Acetylsalicylic acid	Sarilumab may increase the immunosuppressive activities of Acetylsalicylic acid.	Approved, Vet Approved
Adalimumab	Sarilumab may increase the immunosuppressive activities of Adalimumab.	Approved
Adapalene	Sarilumab may increase the immunosuppressive activities of Adapalene.	Approved

Showing 1 to 10 of 746 entries

‹ ›

Food Interactions

Not Available

REFERENCES

General References

1. Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, Huang X, Yancopoulos GD, Stahl N, Genovese MC: Sarilumab, a fully human monoclonal antibody against IL-6Ralpha in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis. 2014 Sep;73(9):1626-34. doi: 10.1136/annrheumdis-2013-204405. Epub 2013 Dec 2. [PubMed:24297381]
2. Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, Rohane P, van Hoogstraten H, Garg A, Fan C, van Adelsberg J, Weinstein SP, Graham NM, Stahl N, Yancopoulos GD, Huizinga TW, van der Heijde D: Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: Results of a Phase III Study. Arthritis Rheumatol. 2015 Jun;67(6):1424-37. doi: 10.1002/art.39093. [PubMed:25733246]

External Links

PubChem Substance

347911238

Wikipedia

Sarilumab

AHFS Codes

92:36.00 — Disease-modifying Antirheumatic Agents

FDA label

Download (1.31 MB)

MSDS

Download (90.8 KB)

CLINICAL TRIALS

Clinical Trials

Search

PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
1	Completed	Basic Science	Rheumatoid Arthritis	1
1	Completed	Health Services Research	Rheumatoid Arthritis	1
1	Completed	Treatment	Rheumatoid Arthritis	6
2	Completed	Treatment	Ankylosing Spondylitis (AS)	1
2	Recruiting	Treatment	Juvenile Idiopathic Arthritis (JIA)	1
2	Suspended	Treatment	Juvenile Idiopathic Arthritis (JIA)	1
2	Terminated	Treatment	Ankylosing Spondylitis (AS)	1
2	Terminated	Treatment	Rheumatoid Arthritis	1
2, 3	Completed	Treatment	Rheumatoid Arthritis	1

Showing 1 to 10 of 16 entries

PHARMACOECONOMICS

Manufacturers

Not Available

Packagers

Not Available

Dosage forms

Search

FORM	ROUTE	STRENGTH
Injection, solution	Subcutaneous	150 mg/1.14mL
Injection, solution	Subcutaneous	200 mg/1.14mL
Solution	Subcutaneous	150 mg
Solution	Subcutaneous	200 mg

Showing 1 to 4 of 4 entries

Prices

Not Available

Patents

Not Available

PROPERTIES

State

Solid

isoelectric point	6.6 - 7.2	Jin, et al. Electrophoresis. Sep;23(19):3385-91. (2002).

TAXONOMY

Description

Not Available

Kingdom

Organic Compounds

Super Class

Organic Acids

Class

Carboxylic Acids and Derivatives

Sub Class

Amino Acids, Peptides, and Analogues

Direct Parent

Peptides

Alternative Parents

Not Available

Substituents

Not Available

Molecular Framework

Not Available

External Descriptors

Not Available

1. Interleukin-6 receptor subunit alpha

Kind

Protein

Organism

Human

Pharmacological action

Yes

Actions

Antagonist Antibody

General Function

Protein homodimerization activity

Specific Function

Part of the receptor for interleukin 6. Binds to IL6 with low affinity, but does not transduce a signal. Signal activation necessitate an association with IL6ST. Activation may lead to the regulati...

Gene Name

IL6R

Uniprot ID

P08887

Uniprot Name

Interleukin-6 receptor subunit alpha

Molecular Weight

51547.015 Da

References

1. Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, Huang X, Yancopoulos GD, Stahl N, Genovese MC: Sarilumab, a fully human monoclonal antibody against IL-6Ralpha in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis. 2014 Sep;73(9):1626-34. doi: 10.1136/annrheumdis-2013-204405. Epub 2013 Dec 2. [PubMed:24297381]

Cardiel M, Combe B, Cutolo M, van Eijk-Hustings Y, Emery P, Finckh A, Gabay C, Gomez-Reino J, Gossec L, Gottenberg JE, Hazes JMW, Huizinga T, Jani M, Karateev D, Kouloumas M, Kvien T, Li Z, Mariette X, McInnes I, Mysler E, Nash P, Pavelka K, Poor G, Richez C, van Riel P, Rubbert-Roth A, Saag K, da Silva J, Stamm T, Takeuchi T, Westhovens R, de Wit M, van der Heijde D: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Jun;76(6):960-977. doi: 10.1136/annrheumdis-2016-210715. Epub 2017 Mar 6. [PubMed:28264816]

4. Kampan NC, Xiang SD, McNally OM, Stephens AN, Quinn MA, Plebanski M: Immunotherapeutic Interleukin-6 or Interleukin-6 receptor blockade in cancer: challenges and opportunities. Curr Med Chem. 2017 Jul 12. doi: 10.2174/0929867324666170712160621. [PubMed:28707587]
5. Lin P: Targeting interleukin-6 for noninfectious uveitis. Clin Ophthalmol. 2015 Sep 11;9:1697-702. doi: 10.2147/OPTH.S68595. eCollection 2015. [PubMed:26392750]

2. High affinity immunoglobulin gamma Fc receptor I

Kind

Protein

Organism

Human

Pharmacological action

Unknown

Actions

Unknown

General Function

Receptor signaling protein activity

Specific Function

High affinity receptor for the Fc region of immunoglobulins gamma. Functions in both innate and adaptive immune responses.

Gene Name

FCGR1A

Uniprot ID

P12314

Uniprot Name

References

1. ema.europa [Link]

3. Low affinity immunoglobulin gamma Fc region receptor II-a

Kind

Protein

Organism

Human

Pharmacological action

Unknown

Actions

Unknown

General Function

Not Available

Specific Function

Binds to the Fc region of immunoglobulins gamma. Low affinity receptor. By binding to IgG it initiates cellular responses against pathogens and soluble antigens. Promotes phagocytosis of opsonized ...

Gene Name

FCGR2A

Uniprot ID

P12318

Uniprot Name

Low affinity immunoglobulin gamma Fc region receptor II-a

Molecular Weight

35000.42 Da

References

4. Low affinity immunoglobulin gamma Fc region receptor II-b

Kind

Protein

Organism

Human

Pharmacological action

Unknown

Actions

Unknown

General Function

Not Available

Specific Function

Receptor for the Fc region of complexed or aggregated immunoglobulins gamma. Low affinity receptor. Involved in a variety of effector and regulatory functions such as phagocytosis of immune complex...

Gene Name

FCGR2B

Uniprot ID

P31994

Uniprot Name

Low affinity immunoglobulin gamma Fc region receptor II-b

Molecular Weight

34043.355 Da

References

1. ema.europa [Link]

5. Low affinity immunoglobulin gamma Fc region receptor III-A

Human

Pharmacological action

Unknown

Actions

Unknown

General Function

Not Available

Specific Function

Receptor for the Fc region of IgG. Binds complexed or aggregated IgG and also monomeric IgG. Mediates antibody-dependent cellular cytotoxicity (ADCC) and other antibody-dependent responses, such as...

Gene Name

FCGR3A

Uniprot ID

P08637

Uniprot Name

Low affinity immunoglobulin gamma Fc region receptor III-A

Molecular Weight

29088.895 Da

References

1. ema.europa [Link]

6. Low affinity immunoglobulin gamma Fc region receptor III-B

Kind

Protein

Organism

Human

Unknown

General Function

Not Available

Specific Function

Receptor for the Fc region of immunoglobulins gamma. Low affinity receptor. Binds complexed or aggregated IgG and also monomeric IgG. Contrary to III-A, is not capable to mediate antibody-dependent...

Gene Name

FCGR3B

Uniprot ID

O75015

Uniprot Name

Low affinity immunoglobulin gamma Fc region receptor III-B

Molecular Weight

26215.64 Da

References

1. ema.europa [Link]

ENZYMES

1. Alanine aminotransferase 1

Kind

Protein

Organism

Human

Inducer

General Function

Pyridoxal phosphate binding

Specific Function

Catalyzes the reversible transamination between alanine and 2-oxoglutarate to form pyruvate and glutamate. Participates in cellular nitrogen metabolism and also in liver gluconeogenesis starting wi...

Gene Name

GPT

Uniprot ID

P24298

Uniprot Name

Alanine aminotransferase 1

Molecular Weight

54636.415 Da

References

1. Kevzara product monograph [Link]

2. Alanine aminotransferase 2

Kind

Protein

Organism

Human

Pharmacological action

No

Actions

Inducer

General Function

and glutamate.

Gene Name

GPT2

Uniprot ID

Q8TD30

Uniprot Name

Alanine aminotransferase 2

Molecular Weight

57903.11 Da

References

1. Kevzara product monograph [Link]

3. Aspartate aminotransferase

Kind

Protein

Organism

Human

Pharmacological action

No

Actions

Inducer

General Function

Pyridoxal phosphate binding

Specific Function

Not Available

Gene Name

GIG18

Aspartate aminotransferase

Molecular Weight

46319.2 Da

References

1. Kevzara product monograph [Link]

4. Cytochrome P450 3A4

Kind

Protein

Organism

Human

Pharmacological action

No

Actions

Inhibitor

General Function

Vitamin d3 25-hydroxylase activity

Specific Function

Cytochromes P450 are a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. It performs a variety of oxidation react...

Gene Name

CYP3A4

Uniprot ID

P08684

Uniprot Name

Cytochrome P450 3A4

1. ema.europa [Link]

Drug created on October 20, 2016 14:46 / Updated on August 03, 2018 14:30

This project is supported by the **Canadian Institutes of Health Research** (award #111062), **Alberta Innovates - Health Solutions**, and by **The Metabolomics Innovation Centre (TMIC)**, a nationally-funded research and core facility that supports a wide range of cutting-edge metabolomic studies. TMIC is funded by **Genome Alberta**, **Genome British Columbia**, and **Genome Canada**, a not-for-profit organization that is leading Canada's national genomics strategy with funding from the federal government. Maintenance, support, and commercial licensing is provided by **OMx Personal Health Analytics, Inc.** Designed by **Educe Design & Innovation Inc.**