Benralizumab

Targets (2) | Biointeractions (1)

IDENTIFICATION

Name

Benralizumab

Accession Number

DB12023 (DB06024)

Type

Biotech

Groups

Approved, Investigational

Biologic Classification

Protein Based Therapies
Monoclonal antibody (mAb)

Description

Benralizumab is a humanized recombinant monoclonal antibody of the isotype IgG1k immunoglobulin that specifically binds to the alpha chain of the interleukin 5 receptor (IL-5R) expressed on eosinophils and basophils.[2] It inhibits the binding of IL-5 as well as the hetero-oligomerization of the alpha and beta subunits of the IL-5R, thus blocking, signal transduction. Besides, it is an afucosylated IgG which gives it high affinity for the FcγRIIIα receptor in natural killer cells, macrophages and neutrophils.[1] Benralizumab, FDA approved on November 14, 2017, was developed by MedImmune, the AstraZeneca's global biologic research and development arm. [6]

Protein structure

Protein chemical formula

$C_{6492}H_{10060}N_{1724}O_{2028}S_{42}$

Protein average weight

146054.0 Da

Sequences

```
>Heavy chain
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYVIHWVRQRPGQGLAWMGYINPYNDGTKY
NERFKGKVTITSDRSTSTVYMELSSLRSEDTAVYLCGREGIRYYGLLGDYWGQGTLVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
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>Light chain
DIQMTQSPSSLSASVGDRVTITCGTSEDIINYLNWYQQKPGKAPKLLIYHTSRLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQGYTLPYTFGQGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

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Synonyms

Not Available

External IDs

BIW-8405 / MEDI-563

Prescription Products

Search

NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END

Fasenra	Solution	30 mg	Subcutaneous	Astra Zeneca	2018-03-28	Not applicable	

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Categories

Respiratory Agents, Miscellaneous

UNII

71492GE1FX

CAS number

1044511-01-4

PHARMACOLOGY

Indication

Benralizumab is indicated as a maintenance treatment of patients 12 years or older with severe asthma and an eosinophilic phenotype.[7] The pathology of severe asthma with eosinophilic phenotype is also denotated as TH2-high phenotype. The patients with this phenotype are characterized by the expression of IL-5 and IL-13, airway hyperresponsiveness, responsiveness to inhaled corticosteroids, high serum IgE and eosinophilia in blood and airway. In the TH2-high phenotype, IL-5 presents a central role as it is responsible for eosinophil differentiation, survival, activation and migration to the lungs.[3]

Associated Conditions

Severe Eosinophilic Asthma

Pharmacodynamics

Eosinophils are the key target of inflammatory respiratory diseases and they undergo apoptosis in absence of IL-5. Therefore, benralizumab action on the IL-5 receptor in basophils and eosinophils produces the apoptosis and its significant reduction in the blood.[2] On the other hand, Benralizumab binding to natural killer cells FcγRIIIα receptor produces a direct antibody-dependent cell-mediated cytotoxicity. All these effects produce a reduction in eosinophil count in airway mucosa, submucosa, sputum, blood and bone marrow.[4]

signaling and the proliferation of IL-5-dependent cell lines. On the other hand, Benralizumab is an afucosylated antibody in the CH2 region which gives it a high affinity for the FcγRIIIa on natural killer cells, macrophages and neutrophils. This binding triggers a magnified apoptosis response in eosinophils via antibody-dependent cell-mediated cytotoxicity.[1, 3]

A	Interleukin-5 receptor subunit alpha
	antibody
	Human
A	Low affinity immunoglobulin gamma Fc region receptor III-A
	binding
	Human

Absorption

Subcutaneous administration of Benralizumab presented a dose-proportional pharmacokinetic profile. The administration of 20-200 mg presented an absorption half-life of 3.6 days with a bioavailability of 58%.[Label] It is also reported for Benralizumab a Cmax of 82 mcg/ml and AUC of 775 mcg day/ml.[1]

Volume of distribution

Pharmacokinetic reports of Benralizumab showed a volume of distribution in a range of 52-93ml/kg. For a 70kg individual, the central volume of distribution of Benralizumab is 3.2 L while the peripheral volume of distribution is reported to be 2.5 L.[5]

Protein binding

There is no reports indicating that Benralizumab binds to plasma proteins.

Metabolism

As any monoclonal IgG antibody, Beralizumab is degraded by proteases widely spread in the body. [Label]

Route of elimination

Benraluzimab presents a linear pharmacokinetic without target-receptor mediated clearance.[Label] The presence of a dose-proportional pharmacokinetics suggests a rapid depletion of the target and an elimination mainly mediated through the reticuloendothelial system.[5]

Clearance

For a subject weighting 70kg, the typical systemic clearance is 0.29L/day.[Label]

Toxicity

There are not reports of long-term studies regarding tumorgenesis or carcinogenesis. Fertility studies performed in aminal trials showed no adverse histopathological findings.[Label]

Affected organisms

Humans and other mammals

Pathways

Not Available

Pharmacogenomic Effects/ADRs

Not Available

INTERACTIONS

Drug Interactions

Not Available

Food Interactions

Not Available

REFERENCES

General References

1. Ghazi A, Trikha A, Calhoun WJ: Benralizumab--a humanized mAb to IL-5Ralpha with enhanced antibody-dependent cell-mediated cytotoxicity--a novel approach for the treatment of asthma. Expert Opin Biol Ther. 2012 Jan;12(1):113-8. doi: 10.1517/14712598.2012.642359. Epub 2011 Dec 5. [PubMed:22136436]
2. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, Busse WW, Wenzel S, Wu Y, Datta V, Kolbeck R, Molfino NA: Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol. 2013 Nov;132(5):1086-1096.e5. doi: 10.1016/j.jaci.2013.05.020. Epub 2013 Jul 16. [PubMed:23866823]
3. Bagnasco D, Ferrando M, Varricchi G, Puggioni F, Passalacqua G, Canonica GW: Anti-Interleukin 5 (IL-5) and IL-5Ra Biological Drugs: Efficacy, Safety, and Future Perspectives in Severe Eosinophilic Asthma. Front Med

10.1002/psp4.12160. Epub 2017 Jan 21. [PubMed:28109128]
6. Newswire [Link]
7. Astra Zeneca news [Link]

External Links

PubChem Substance

347911271

Wikipedia

Benralizumab

AHFS Codes

48:92.00 — Respiratory Agents, Miscellaneous

FDA label

Download (858 KB)

CLINICAL TRIALS

Clinical Trials

Search

PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
1	Completed	Not Available	Asthma Bronchial	1
1	Completed	Treatment	Asthma Bronchial	1
1	Completed	Treatment	Asthma Bronchial / Chronic Obstructive Pulmonary Disease (COPD)	1
1, 2	Recruiting	Treatment	Eosinophilic Gastritis or Gastroenteritis	1
2	Active Not Recruiting	Treatment	Hypereosinophilic Syndromes	1
2	Completed	Treatment	Asthma Bronchial	3
2	Completed	Treatment	Chronic Obstructive Pulmonary Disease (COPD) / Pulmonary Disease, Chronic Obstructive	1
2	Completed	Treatment	Eosinophilic Chronic Rhinosinusitis	1

			Skin Diseases, Eczematous / Skin Diseases, Genetic / Skin Inflammation	
2	Recruiting	Treatment	Asthma Bronchial	1

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PHARMACOECONOMICS

Manufacturers

Not Available

Packagers

Not Available

Dosage forms

Search

FORM	ROUTE	STRENGTH
Injection, solution	Subcutaneous	30 mg/mL
Solution	Subcutaneous	30 mg

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Prices

Not Available

Patents

Not Available

PROPERTIES

State

Solid

point (°C)	(whole IgG1)	10.1371/journal.pone.0143520. (2015).
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

1. Interleukin-5 receptor subunit alpha

Kind

Protein

Organism

Human

Pharmacological action

Yes

Actions

Antibody

General Function

Interleukin-5 receptor activity

Specific Function

This is the receptor for interleukin-5. The alpha chain binds to IL5.

Gene Name

IL5RA

Uniprot ID

Q01344

Uniprot Name

Interleukin-5 receptor subunit alpha

Molecular Weight

47684.225 Da

References

1. Ghazi A, Trikha A, Calhoun WJ: Benralizumab--a humanized mAb to IL-5Ralpha with enhanced antibody-dependent cell-mediated cytotoxicity--a novel approach for the treatment of asthma. Expert Opin Biol Ther. 2012 Jan;12(1):113-8. doi: 10.1517/14712598.2012.642359. Epub 2011 Dec 5. [PubMed:22136436]
2. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, Busse WW, Wenzel S, Wu Y, Datta V, Kolbeck R, Molfino NA: Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol. 2013 Nov;132(5):1086-1096.e5. doi: 10.1016/j.jaci.2013.05.020. Epub 2013 Jul 16. [PubMed:23866823]

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

Kind

Protein

Organism

Human

Pharmacological action

Yes

Actions

Binding

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. Ghazi A, Trikha A, Calhoun WJ: Benralizumab--a humanized mAb to IL-5Ralpha with enhanced antibody-dependent cell-mediated cytotoxicity--a novel approach for the treatment of asthma. Expert Opin Biol Ther. 2012 Jan;12(1):113-8. doi: 10.1517/14712598.2012.642359. Epub 2011 Dec 5. [PubMed:22136436]

Benralizumab in Healthy Volunteers and Patients With Asthma. CPT Pharmacometrics Syst Pharmacol. 2017 Apr;6(4):249-257. doi: 10.1002/psp4.12160. Epub 2017 Jan 21. [PubMed:28109128]

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