Ravulizumab

Targets (1) Biointeractions (1)

IDENTIFICATION

Name	Ravulizumab
Accession Number	DB11580
Type	Biotech
Groups	Approved, Investigational
Biologic Classification	Protein Based Therapies Monoclonal antibody (mAb)

Description

Ravulizumab is considered a long-acting complement 5 (C5) inhibitor that has been undergoing clinical trials for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) as of 4 February, 2016. A drug similar to ravulizumab (ALXN1210), called eculizumab, is currently approved for the treatment of PNH in 46 countries under the brand name Soliris®. Ravulizumab is considered by Alexion Pharmaceuticals Inc. to be a "next-generation" eculizumab molecule. Ravulizumab was subsequently approved by the US FDA in December of 2018 for a variety of beneficial characteristics that make it an advanced, next-generation agent in comparison to eculizumab [3]. In particular, ravulizumab is currently the first and only long-acting C5 complement inhibitor that can be administered every eight weeks for the treatment of adult patients with PNH whereas eculizumab is a bi-weekly treatment [3]. Moreover, virtually all of the phase 3 trial results for ravulizumab have demonstrated the equivalent efficacy and safety established by eculizumab and that patients transition safely and effectively from using eculizumab to ravulizumab [3]. Subsequently, whereas PNH patients may have needed to previously plan their lives rather strictly around the bi-weekly infusion administrations of eculizumab, with ravulizumab such patients can find a more relaxed dosing schedule of only six or seven infusions over an entire year [3].

Just as the US FDA permitted a timely and expedited approval of ravulizumab ahead of the Prescription Drug User Fee Act (PDUFA) date of February 18, 2019 following the use of a rare disease priority review voucher by Ultomiris (ravulizumab) developer Alexion for many of the aforementioned beneficial treatment reasons, regulatory authorities in the European Union (EU) and Japan have currently accepted and are reviewing applications for the approval of Ultomiris (ravulizumab) as a treatment for adults with PNH as well [3].

Protein chemical formula	Not Available
Protein average weight	Not Available

Sequences

```
>Light Chain
DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
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>Heavy Chain
QVQLVQSGAEVKKPGASVKVSCKASGHIFSNYWIQWVRQAPGQGLEWMGEILPGSGHTEY
TENEKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYEEGSSPNWYFDVWGQGTLVTV
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VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
GNVFSCSVLHEALHSHYTQKSLSLSLGK
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References:

1. METHOD FOR SIMULTANEOUS QUANTIFICATION OF ALXN1210 AND ECULIZUMAB IN HUMAN SERUM OR URINE: International Publication Number WO 2018/183449 A1 [File]

Download FASTA Format

Synonyms

Ravulizumab

ravulizumab-cwvz

External IDs

ALXN-1210 / ALXN1210

Prescription Products

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NAME	DOSAGE	STRENGTH	ROUTE	LABELLER	MARKETING START	MARKETING END		
Ultomiris	Solution, concentrate	300 mg/30mL	Intravenous	Alexion Pharmaceuticals Inc.	2018-12-21	Not applicable		

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Categories

Antibodies, Monoclonal
Antibodies, Monoclonal, Humanized
Complement Inactivating Agents
Complement Inactivator Proteins
Immunoglobulins
Serum Globulins

UNII

C3VX249T6L

CAS number

1803171-55-2

PHARMACOLOGY

Indication

Ravulizumab is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) [Label].

Associated Conditions

Paroxysmal Nocturnal Hemoglobinuria PNH

Pharmacodynamics

Immediate and complete inhibition of serum-free complement protein C5 (concentration of less than 0.5 mcg/mL) was observed by the end of the first ravulizumab infusion and sustained throughout the entire 26-week treatment period in all patients, both complement-inhibitor naïve and previously treated with eculizumab [Label].

The extent and duration of the pharmacodynamic response in patients with PNH were exposure dependent for ravulizumab [Label]. Free C5 levels of <0.5 mcg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition [Label].

Complete terminal complement inhibition following initiation of ravulizumab treatment led to normalization of serum LDH by week 4 in complement-inhibitor naïve patients and maintained LDH normalization in patients previously treated with eculizumab [Label].

Mechanism of

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, debilitating and life-

action	threatening ultra-rare blood disorder characterized by hemolysis (destruction of red blood cells) that is mediated by the uncontrolled activation of the complement system, a component of the body's immune system [1].

particular complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b9 [Label]. Ravulizumab inhibits terminal complement-mediated intravascular hemolysis in patients with PNH [Label].

TARGET	ACTIONS	ORGANISM
(U) Complement C5	inhibitor	Humans

Absorption	It has been demonstrated that mean ravulizumab Cmax and AUC∞ increase in a dose-proportional manner and that a single 400 mg intravenous dose of ravulizumab administered to subjects reach or exceed the threshold level of 100 µg/mL [2].
Volume of distribution	The mean (SD) volume of distribution at steady state was 5.34 (0.92) L [Label].
Protein binding	Readily accessible data regarding the protein binding of ravulizumab is not available.
Metabolism	Monoclonal antibody agents like ravulizumab are not expected to generate toxic metabolites as they generally undergo proteolysis to their constituent amino acids [F94].
Route of elimination	Monoclonal antibody agents like ravulizumab are generally not eliminated via hepatic, renal, or biliary routes [F94].
Half life	The mean (SD) terminal elimination half-life of ravulizumab in patients with PNH was recorded as 49.7 (8.9) days [Label].
Clearance	The mean (SD) clearance of ravulizumab in patients with PNH was recorded as being 0.08 (0.022) L/day respectively [Label].
Toxicity	Although PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages, increased maternal mortality, and adverse fetal outcomes like fetal death and premature delivery, there are no available data on ravulizumab use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes [Label]. Although there are currently no human reproductive studies, human immunoglobulins like ravulizumab are known to cross the human placental barrier, and thus may potentially cause terminal complement inhibition in the fetal circulation [Label]. There are no data on the presence of ravulizumab in human milk, the effect on the breastfed child, or the effect on milk production [Label]. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in a nursing child, breastfeeding should be discontinued during treatment and for 8 months after the final dose [Label]. The safety and efficacy of ravulizumab in pediatric patients and geriatric use have not yet been established [Label]. Genotoxicity studies have not been conducted with ravulizumab [Label]. Effects of ravulizumab upon fertility have not been studied in animals [Label]. Intravenous injections of male and female mice with a murine anti-C5 antibody at up to 0.8-2.2 times the equivalent of the clinical dose of ravulizumab had no adverse effects on mating or fertility [Label].
Affected organisms	Humans and other mammals

Pathways Not Available

Drugs

INTERACTIONS

Drug Interactions

ALL DRUGS | APPROVED | VET APPROVED | NUTRACEUTICAL | ILLICIT | WITHDRAWN | INVESTIGATIONAL | EXPERIMENTAL

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DRUG	INTERACTION
Abciximab	The risk or severity of adverse effects can be increased when Abciximab is combined with Ravulizumab.
Abituzumab	The risk or severity of adverse effects can be increased when Ravulizumab is combined with Abituzumab.
Adalimumab	The risk or severity of adverse effects can be increased when Adalimumab is combined with Ravulizumab.
Adecatumumab	The risk or severity of adverse effects can be increased when Adecatumumab is combined with Ravulizumab.
Aducanumab	The risk or severity of adverse effects can be increased when Ravulizumab is combined with Aducanumab.
Afelimomab	The risk or severity of adverse effects can be increased when Afelimomab is combined with Ravulizumab.
Alemtuzumab	The risk or severity of adverse effects can be increased when Alemtuzumab is combined with Ravulizumab.
Alirocumab	The risk or severity of adverse effects can be increased when Alirocumab is combined with Ravulizumab.
Amatuximab	The risk or severity of adverse effects can be increased when Ravulizumab is combined with Amatuximab.
AMG 108	The risk or severity of adverse effects can be increased when AMG 108 is combined with Ravulizumab.

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Food Interactions Not Available

REFERENCES

Synthesis Reference Method for simultaneous quantification of alxn1210 and eculizumab in human serum or urine: WO20 8183449A1, Ryan Pelto, Meng Chen

General References

1. Alexion Receives Early FDA Approval for ULTOMIRIS™ (Ravulizumab-cwvz) in Adults with Paroxysmal Nocturnal Hemoglobinuria (PNH) [Link]
2. First in Human Single-Ascending Dose Study: Safety, Biomarker, Pharmacokinetics and Exposure-Response Relationships of ALXN1210, a Humanized Monoclonal Antibody to C5, with Marked Half-Life Extension and Potential for Significantly Longer Dosing Intervals / Blood 2015 125:4777 [Link]
3. Ravulizumab FDA Approval Press Release [File]

External Links Wikipedia Ravulizumab

FDA label Download (1.29 MB)

CLINICAL TRIALS

Clinical Trials

Show 10 entries Search

PHASE	STATUS	PURPOSE	CONDITIONS	COUNT
	Recruiting			
2	Active Not Recruiting	Treatment	Paroxysmal Nocturnal Haemoglobinuria (PNH) / PNH	1
3	Active Not Recruiting	Treatment	Atypical Hemolytic Uremic Syndrome (aHUS)	1
3	Active Not Recruiting	Treatment	Paroxysmal Nocturnal Haemoglobinuria (PNH)	1
3	Recruiting	Treatment	Adult Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Are Currently Being Treated With Eculizumab / Paroxysmal Nocturnal Haemoglobinuria (PNH)	1
3	Recruiting	Treatment	Atypical Hemolytic Uremic Syndrome (aHUS)	1
3	Recruiting	Treatment	Paroxysmal Nocturnal Haemoglobinuria (PNH)	1

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Drugs

PHARMACOECONOMICS

Manufacturers Not Available

Packagers Not Available

Dosage forms

Show 10 entries Search

FORM	ROUTE	STRENGTH
Solution, concentrate	Intravenous	300 mg/30mL

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Prices Not Available

Patents Not Available

PROPERTIES

State Solid

Experimental Properties Not Available

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

Framework

External Descriptors	Not Available

TARGETS

1. Complement C5

Details

Kind	Protein
Organism	Humans
Pharmacological action	Unknown
Actions	Inhibitor
General Function	Receptor binding
Specific Function	Activation of C5 by a C5 convertase initiates the spontaneous assembly of the late complement components, C5-C9, into the membrane attack complex. C5b has a transient binding site for C6. The C5b-C...
Gene Name	C5
Uniprot ID	P01031
Uniprot Name	Complement C5
Molecular Weight	188303.705 Da

References

1. Ravulizumab FDA Label [File]

Drug created on April 17, 2016 16:44 / Updated on January 03, 2019 18:41

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