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▸ P T. 2009 Aug;34(8):422–427.

Warfarin Pharmacogenomics

Jiayi Li, Shan Wang, Joseph Barone, Brian Malone

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PMCID: PMC2799123 PMID: 20140106

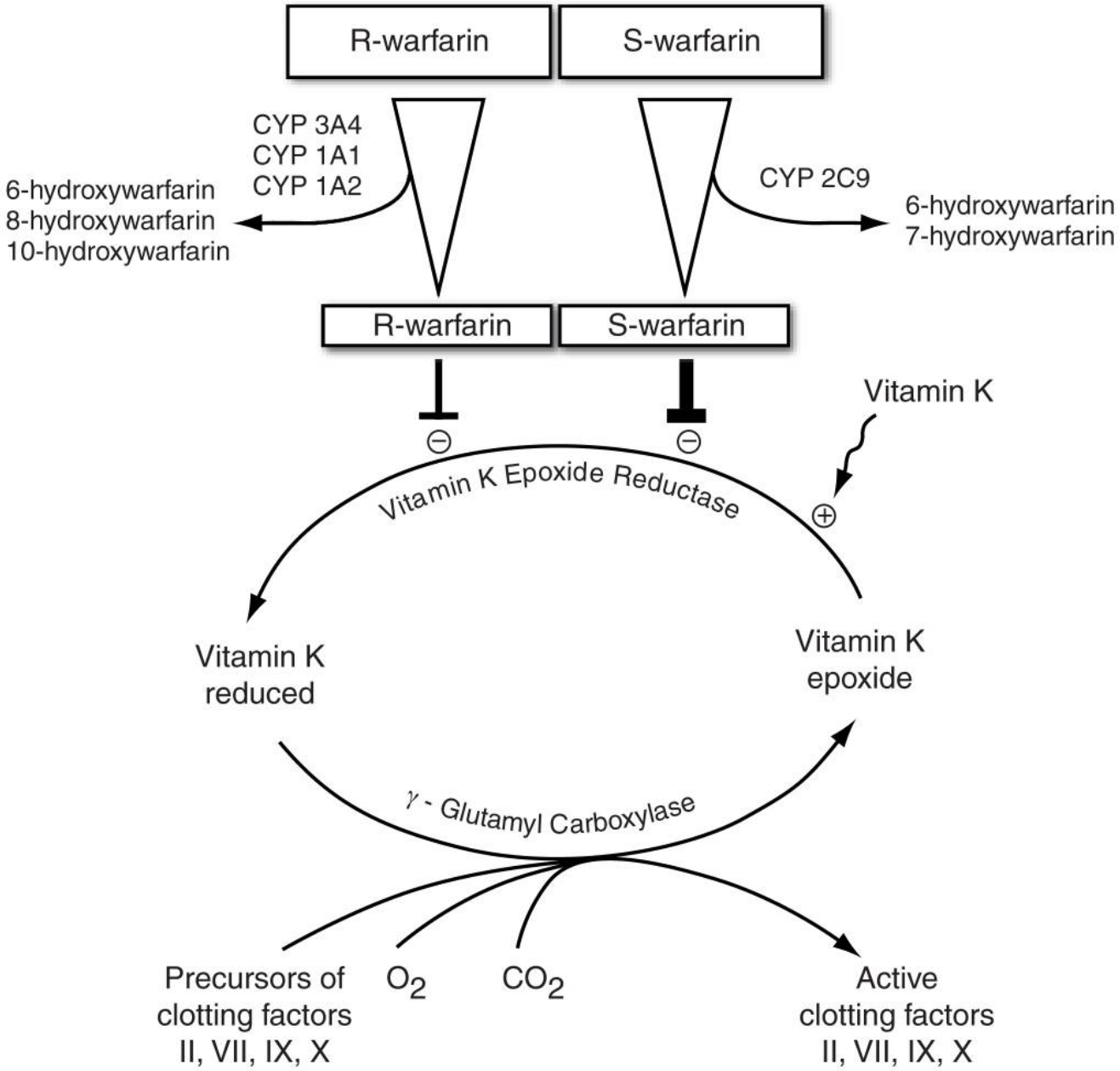
Warfarin is a racemic mixture of S and R enantiomers.
The anticoagulant property of S-warfarin is much greater than that of R-warfarin.

S-warfarin is metabolized mainly by **CYP 2C9**, which converts the drug into inactive metabolites;

this is why the CYP 2C9 gene contributes to the variability in response of warfarin therapy.

CYP 2C9*2 (or 430 C>T) and CYP 2C9*3 (1075A>C) are the two alleles that are considered strong risk factors for overanticoagulation.

Moreover, it has been suggested that CYP2C9 *5, *6, *8, and *11 may also slow S-warfarin metabolism.



VKORC1 is the vitamin K cycle enzyme that controls the regeneration of reduced vitamin K (KH2). It is an essential cofactor in the formation of clotting factors.

Warfarin works by noncompetitively inhibiting VKORC1, thus blocking the clotting cascade.

Many polymorphisms in **VKORC1** that influence warfarin dosing have been identified.

The most commonly studied SNPs of VKORC1 include the 1173 C>T (CC is the wild-type) and 1639 G>A alleles (GG is the wild type).

They are associated with a **lower level of expression of VKORC1** because of their decreased translation of mRNA into proteins.

Because there is already less enzyme to start with, these patients are highly sensitive to warfarin. They require significantly lower doses to achieve the target INR (International Normalized Ratio) and are at a higher **risk of major bleeding** if given standard doses.

The patient's warfarin dose, age, body surface area, and CYP 2C9 genotype contributed significantly to S-warfarin clearance. Only age, body size, and warfarin dose contributed to R-warfarin clearance.

IN CONCLUSION….

Both VKORC1 and CYP 2C9 play an active role in the potential for predicting therapeutic warfarin doses.

The role of genetic testing in warfarin patients is an important yet controversial topic.

Genetic testing can be costly as well.

The new and growing field of pharmacogenetics may one day enable clinicians to tailor a patient's warfarin regimen.

However, because pharmacogenetics is still in its infancy, more clinical trials, especially prospective randomized studies, are needed to gain a full understanding of the true ramifications in terms of the efficacy and cost of such gene-guided drug therapy.

warfarin

Overview
Prescribing Info
Drug Label Annotations
Summary Annotations
Variant Annotations
Literature
Pathways
Related To
Links

PRESCRIBING INFO 12

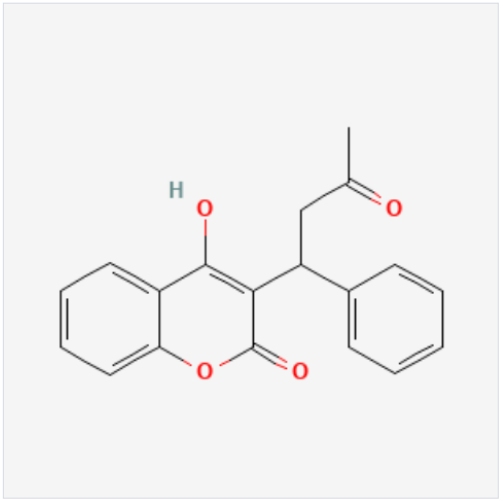
DRUG LABEL ANNOTATIONS 4

CLINICAL ANNOTATIONS 90

PATHWAYS 2

Pediatric

Structure



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Overview
Prescribing Info
Drug Label Annotations
Summary Annotations
Variant Annotations
Literature
Pathways
Related To
Links

Drug Label Annotations

ClinPGx annotates regulatory agency-approved drug labels containing PGx information. Read more about ClinPGx drug label annotations, the drug label sources, PGx Levels and the "tags" found in the table below. FDA, EMA and HCSC labels are annotated when found on the FDA Table of Pharmacogenomic Biomarkers in Drug Labels. Labels from other regulatory agencies were annotated as collaborations and are not routinely updated.

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4 annotations

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	PGX LEVEL	SOURCE	TITLE	GENES	DRUGS
	All	All			
Details	Actionable PGx	FDA	Annotation of FDA Label for warfarin and CYP2C9, VKORC1 Dosing Info Prescribing Info FDA Biomarker	CYP2C9, VKORC1	warfarin
Details	Actionable PGx	FDA	Annotation of FDA Label for warfarin and PROC, PROS1 Other Guidance Prescribing Info FDA Biomarker	PROC, PROS1	warfarin
Details	Actionable PGx	HCSC	Annotation of HCSC Label for warfarin and PROC, PROS1 Other Guidance Prescribing Info	PROC, PROS1	warfarin
Details	Actionable PGx	HCSC	Annotation of HCSC Label for warfarin and CYP2C9, VKORC1 Dosing Info Prescribing Info	CYP2C9, VKORC1	warfarin

Annotation of FDA Label for warfarin and CYP2C9, VKORC1

Actionable PGx | Dosing Info | Prescribing Info | FDA Biomarker

Warfarin (COUMADIN) is an anticoagulant used as a prophylaxis and to treat venous thrombosis, pulmonary embolism, thromboembolic complications from atrial fibrillation and cardiac valve replacement, and to reduce the recurrence of myocardial infarction. Pharmacogenomics-related dosing information for CYP2C9 and VKORC1 variants is provided within the label.

Prescribing Information

Table 1 in the drug label provides ranges of expected maintenance daily doses of warfarin (COUMADIN) based on CYP2C9*2, CYP2C9*3 and "VKORC1–1639G>A (rs9923231)" genotypes.

View Highlighted Label

The VKORC1:G-1639A polymorphism is associated with lower dose requirements for warfarin in Caucasian and Asian patients. Increased bleeding risk and lower initial warfarin dose requirements have been associated with the CYP2C9*2 and CYP2C9*3 alleles. Approximately 30% of the variance in warfarin dose could be attributed to genetic variation in VKORC1, and about 40% of dose variance could be explained taking into consideration both VKORC1 and CYP2C9 genetic polymorphisms. Accounting for genetic variation in both VKORC1 and CYP2C9, age, height, body weight, interacting drugs, and indication for warfarin therapy explained about 55% of the variability in warfarin dose.

Excerpts from the warfarin (COUMADIN) drug label:

> Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants...If the patient's CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants.

> Known or suspected deficiency in protein C mediated anticoagulant response: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration.

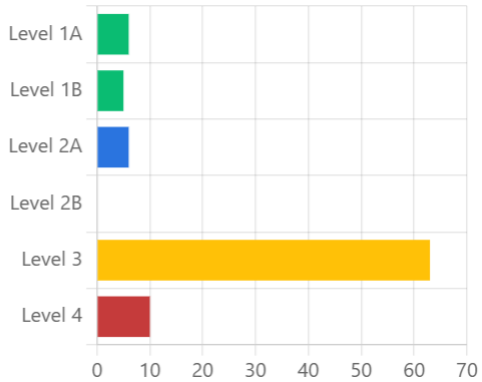
Overview
Prescribing Info
Drug Label Annotations
Summary Annotations
Variant Annotations
Literature
Pathways
Related To
Links

Summary Annotations

Focus on Pediatrics OFF

Summary annotations (formerly "clinical annotations") provide information about variant-drug pairs based primarily on variant annotations and incorporating variant-specific prescribing guidance from clinical guidelines and FDA-approved drug labels, when available. Curators manually review annotations and create genotype-based summaries describing the phenotypic impact of the variant. Each summary annotation is assigned a Level of Evidence, which is generally informed by the summary annotation's score.

Note: Alleles in ClinPGx are mapped to the positive chromosomal strand. Therefore, variants in genes on the "minus" strand (eg. *VKORC1*) are complemented in ClinPGx annotations.



Annotations by level

Read more about Summary Annotations | Read more about Variant Annotations

90 summary annotations

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	LEVEL	VARIANT	GENE	DRUGS	PHENOTYPE CATEGORIES	PHENOTYPE	PEDIATR
Details	Level 1A	CYP2C9*1, CYP2C9*2, CYP2C9*3, CYP2C9*5, CYP2C9*6 see 1 more	CYP2C9	warfarin	Toxicity	over-anticoagulation	☑
Details	Level 1A	CYP2C9*1, CYP2C9*2, CYP2C9*3, CYP2C9*4, CYP2C9*5 see 3 more	CYP2C9	warfarin	Dosage	Cardiovascular Disease	☑
Details	Level 1A	CYP2C9*1, CYP2C9*2, CYP2C9*3, CYP2C9*5, CYP2C9*6	CYP2C9	warfarin	Toxicity	Hemorrhage	☑

90 summary annotations

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	LEVEL	VARIANT	GENE	DRUGS	PHENOTYPE CATEGORIES	PHENOTYPE	PEDIATR
Details	Level 3	rs17880887	VKORC1	warfarin	Dosage		
Details	Level 3	rs11150606	VKORC1	warfarin	Dosage		
Details	Level 3	rs7196161	VKORC1	warfarin	Dosage		
Details	Level 3	rs72547529	VKORC1	warfarin	Dosage, Efficacy		
Details	Level 3	rs7200749	VKORC1	warfarin	Dosage		
Details	Level 3	rs61162043	VKORC1	warfarin	Dosage		
Details	Level 3	rs104894542	VKORC1	warfarin	Dosage		
Details	Level 3	rs104894541	VKORC1	warfarin	Dosage		
Details	Level 3	rs4072879	VKORC1L1	warfarin	Dosage		

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▸ Pharmgenomics Pers Med. 2016 Oct 3;9:97–106. doi: 10.2147/PGPM.S86013

Pharmacogenomics of statins: understanding susceptibility to adverse effects

Joseph P Kitzmiller [1,✉], Eduard B Mikulik [1], Anees M Dauki [2], Chandrama Murkherjee [1], Jasmine A Luzum [3]

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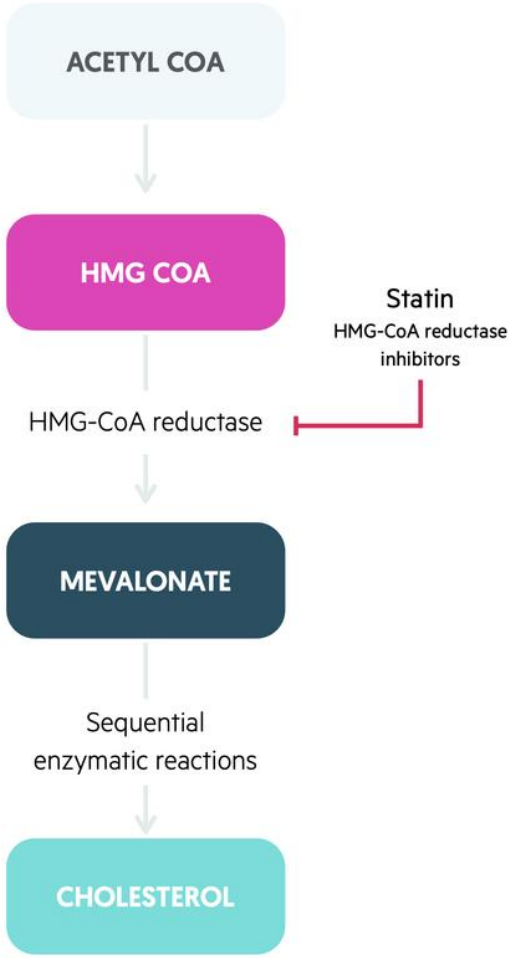
PMCID: PMC5055044 PMID: 27757045

https://pmc.ncbi.nlm.nih.gov/articles/PMC5055044/

Not all patients, however, respond favorably to statins, and some do not achieve their cholesterol-reduction goals



A considerable number of patients experience adverse effects.

Statin myositis and statin-associated muscle symptoms (SAMS) comprise the most commonly reported adverse effect of statins, often leading to poor adherence or discontinuation of statin pharmacotherapy regimens.

Statin myositis is characterized by inflammation of muscle tissue resulting in muscle pain or weakness and is accompanied by increased blood concentration of CK, a protein biomarker of damaged myocytes.

Another reported adverse effect associated with statins pharmacotherapy is **liver toxicity, characterized by elevated blood concentrations of transaminases**

Table 1.

Nongenetic clinical risk factors for statin adverse reactions

Age (advanced age)
Body mass index (low)
Concomitant medications
CYP3A-inhibiting medications
SLCO1B1-inhibiting medications
Antiretrovirals
Amprenavir
Atazanavir
Darunavir
Indinavir
Lopinavir
Nelfinavir
Ritonavir
Saquinavir
Azole antifungals
Clotrimazole
Ketoconazole
Miconazole
Pantoprazole
Cyclosporine
Digoxin
Fibrates
Bezafibrate
Fenofibrate
Gemfibrozil
Macrolide antibiotics
Erythromycin
Clarithromycin
Rifampin
Thyroxine
Tacrolimus
Verapamil
Diseased states
Alcohol consumption (excessive)
Diabetes
Hypothyroidism
Hyperuricemia
Infectious state
Liver disease
Muscle disorders
McArdle's disease
History of muscle pain with other lipid-lowering pharmacotherapy
History of malignant hyperthermia
Renal insufficiency
Trauma
Sex (female)
Physical exercise (intense)
Race (Asian and African American)
Statin dose (higher dose)

Polymorphisms in several key genes that affect statin **pharmacokinetics** (eg, transporters and metabolizing enzymes), statin **efficacy** (eg, drug targets and pathways), and **end-organ toxicity** (eg, myopathy pathways).

PHARMACOKINETICS

The gene encoding the **SLCO1B1**, result in altered transport of statins and their metabolites into the liver. It is within hepatocytes that statins exert their lipid-lowering action, inhibition of the cholesterol-synthesizing enzyme HMGCR.

SLCO1B1 521C (rs4149056) was associated with statistically significant, albeit marginal (<5%), **attenuation of the lipid-lowering effect** of simvastatin, atorvastatin, lovastatin, and pravastatin.

The AUC for simvastatin was approximately double for SLCO1B1 521C carriers compared to wild type

SLCO1B1 521C is the most clinically relevant

PHARMACOKINETICS

Table 2.

Recommended dosing of simvastatin based on SLCO1B1 phenotype

Phenotype	Genotype	Myopathy risk	Dosing recommendations
Normal function, homozygous wild type	TT	Normal	Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines
Intermediate function, heterozygotyes	TC	Intermediate	Prescribe a lower dose or consider an alternative statin (eg, pravastatin or rosuvastatin); consider routine CK surveillance
Low function, homozygous variant or mutant	CC	High	Prescribe a lower dose or consider an alternative statin (eg, pravastatin or rosuvastatin); consider routine CK surveillance

Notes: The minor C allele at rs4149056 is contained within SLCO1B1*5 (rs4149056 alone) as well as the *15 and *17 haplotypes and is associated with lower plasma clearance of simvastatin. The magnitude of this effect is similar for *5, *15, and *17 haplotypes.

Hepato-biliary and renal–urinary transport of statins and their metabolites occurs largely via **ABCB1 transport protein** (synonymous with MDR1).

Three polymorphisms in the ABCB1 gene: 1236T, 2677T, and 3435T (rs1128503, rs2032582, and rs1045642, respectively).

AUC that was nearly 60% greater for simvastatin acid and 55% larger for atorvastatin acid compared to controls → This finding has not been replicated

As the clinical research findings regarding ABCB1 variants have been inconclusive and discordant, routine clinical use of ABCB1 genotyping to predict statin toxicity is not currently recommended

Simvastatin, atorvastatin, and lovastatin are primarily metabolized by **cytochrome P450** (CYP) 3A enzymes.

Most CYP3A metabolism occurs within hepatocytes, but some also occurs in the small intestine.

Significant associations between CYP3A polymorphisms and statin blood concentrations have been reported → marked increase in the risk of simvastatin myotoxicity.

This was verified when drug able to inhibit this enzyme were used in parallel

Table 3.

CYP3A-inhibiting medications

Amiodarone
Anastrozole
Azithromzcin
Cannabinoids
Cimetidine
Clarithromycin
Clotrimazole
Cyclosporine
Danazol
Delavirdine
Dexamethasone
Diethyldithiocarbamate
Diltiazem
Dirithyromycin
Disulfiram
Entacapone
Erythromycin
Erythromycin
Ethinyl estradiol
Fluconazole
Fluoxetine
Fluvoxamine
Gestodene
Grapefruit juice
Indinavir
Isoniazid
Ketoconazole
Metronidazole
Mibefradil
Miconazole
Nefazodone
Nelfinavir
Nevirapine
Norfloxacin
Norfluoxetine
Omeprazole
Oxiconazole
Paroxetine
Propoxyphene
Quinidine
Quinine
Quinupristine
Ranitidine
Ritonavir
Saquinavir
Sertindole
Sertraline
Troglitazone
Troleandomycin
Valproic acid

PHARMACOKINETICS

Table 4.

PHARMACOKINETICS

Select transport and metabolism proteins by statin type

Transport	
ABCB1	Atorvastatin, lovastatin, pravastatin, simvastatin
ABCC2	Atorvastatin, lovastatin, pravastatin, simvastatin
ABCG2	Pravastatin
ABCB11	Pravastatin, rosuvastatin
SLC15A1	Fluvastatin
SLC22A6	Pravastatin
SLC22A8	Pravastatin
SLCO1B1	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin
SLCO2B1	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin
SLCO1B3	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin
SLCO10A1	Atorvastatin, lovastatin, simvastatin

Metabolism	PHARMACOKINETICS
CYP3A4	Atorvastatin, lovastatin, simvastatin
CYP3A5	Atorvastatin, lovastatin, simvastatin
CYP2C8	Atorvastatin, fluvastatin, lovastatin, simvastatin
CYP2C9	Atorvastatin, fluvastatin, lovastatin, simvastatin
CYP2C19	Atorvastatin, fluvastatin, lovastatin, simvastatin
CYP2D6	Atorvastatin, lovastatin, simvastatin
UGT1A1	Atorvastatin, fluvastatin, lovastatin, simvastatin
UGT1A3	Atorvastatin, fluvastatin, lovastatin, simvastatin
UGT2B7	Atorvastatin, lovastatin, simvastatin

*CYP3A4*22* (rs35599367) is a decrease-of-function polymorphism that results in significantly decreased CYP3A4 enzyme level and activity and altered pharmacokinetics and dynamics of simvastatin, atorvastatin, and lovastatin

The role of CYP3A5 in statin metabolism is less prominent than that of CYP3A4, but polymorphism have been reported.

The most frequent and commonly studied CYP3A5 polymorphism is the loss of function CYP3A5*3 (rs776746) allele

PHARMACODINAMICS

HMGCR ((rs17244841, rs3846662, and rs17238540), is polymorphic, and genetic variation can significantly affect statin efficacy.

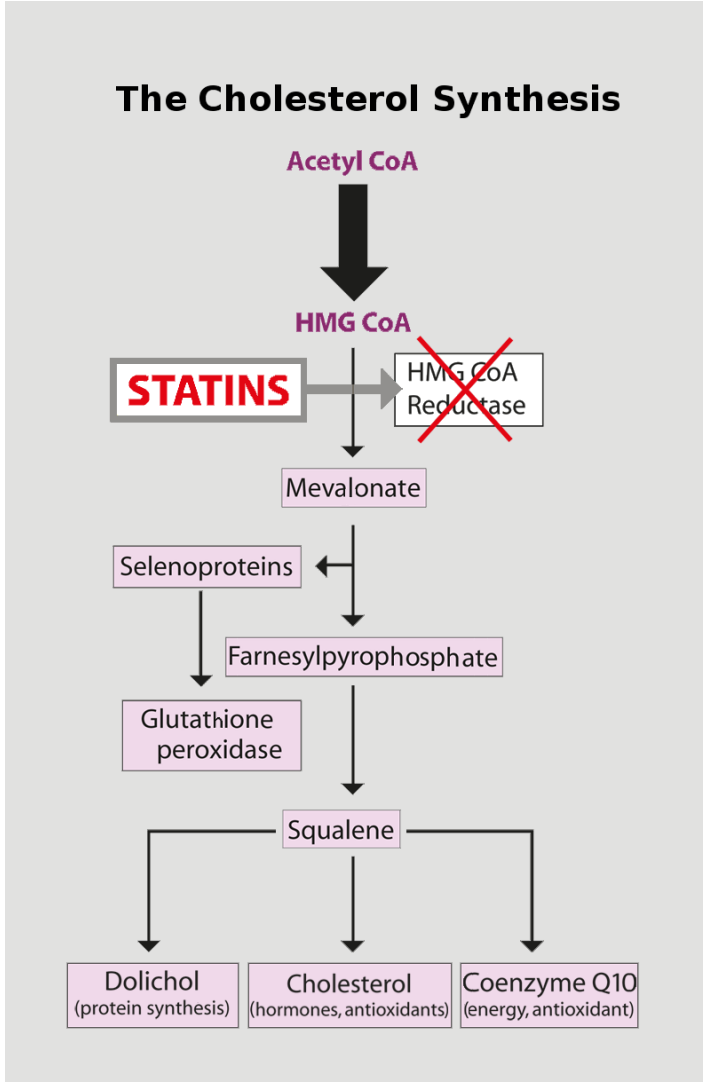
CETP (CETP Taq 1B polymorphism (rs708272)) plays an important role in cholesterol metabolism, bringing cholesterol esters into the liver and transferring triglycerides from LDL to high-density lipoprotein → Polymorphisms in CETP have been associated with cholesterol levels, clinical outcomes (eg, myocardial infarction or stroke), and response to statins

END-ORGAN TOXICITY

***SLCO1B1* 521C** does result in increased systemic statin exposure and increased risk of statin myopathy.

Associations between genetic variation in **COQ2** (rs4693075) (encode for coenzyme Q10) and statin myopathy have been reported. → increase the susceptibility to myophaty.

Although some patient reports have described benefits from COQ2 supplementation in cases of statin myopathy, neither COQ2 supplementation nor COQ2 testing is currently recommended for routine use in patients receiving statin pharmacotherapy.



GATM is the rate-limiting enzyme in the creatine biosynthesis pathway.

Providing an important source of cellular energy, creatine is predominantly synthesized in the liver and kidneys and subsequently transported to skeletal muscle.

GATM is heavily studied for **its potential role in statin-induced myopathy (SIM).**

Research suggests that reduced creatine storage or altered cellular processes involving GATM **may play a part in why some muscles are vulnerable to statin damage**

Certain genetic **variants** (such as the rs9806699 G>A polymorphism) within the GATM gene have been **linked to a reduced risk of developing statin-induced myopathy**.

Some studies hypothesize that **these variants lower GATM expression**, thus **reducing the creatine demand and cellular energy stress associated with statin exposure.**

While initial studies showed promise regarding GATM's protective effect, subsequent studies and meta-analyses have found inconsistent results, concluding that its clinical significance as a predictor for myopathy is still debated and requires further research

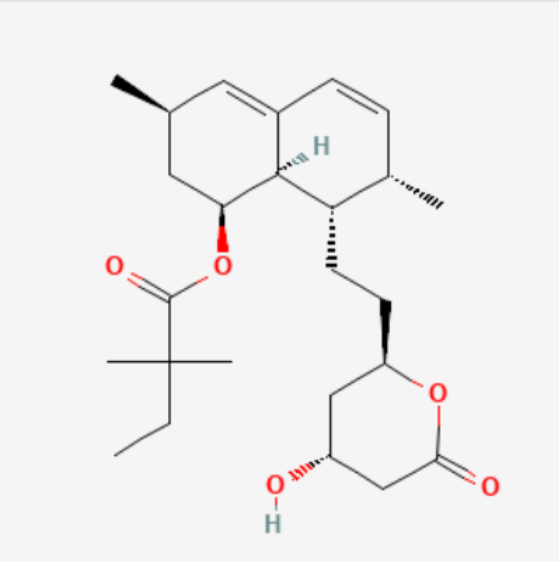
simvastatin

- Overview
- Prescribing Info
- Drug Label Annotations
- Summary Annotations
- Variant Annotations
- Literature
- Pathways
- Related To
- Links

PRESCRIBING INFO	DRUG LABEL ANNOTATIONS	CLINICAL ANNOTATIONS	PATHWAYS
8	5	55	1

Pediatric

Structure



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Drug Label Annotations

ClinPGx annotates regulatory agency-approved drug labels containing PGx information. Read more about ClinPGx drug label annotations, the drug label sources, PGx Levels and the "tags" found in the table below. FDA, EMA and HCSC labels are annotated when found on the FDA Table of Pharmacogenomic Biomarkers in Drug Labels. Labels from other regulatory agencies were annotated as collaborations and are not routinely updated.

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5 annotations

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	PGX LEVEL	SOURCE	TITLE	GENES	DRUGS
	All	All			
Details	Testing Recommended	Swissmedic	Annotation of Swissmedic Label for simvastatin and SLCO1B1 Prescribing Info	SLCO1B1	simvastatin
Details	Testing Recommended	Swissmedic	Annotation of Swissmedic Label for ezetimibe / simvastatin and SLCO1B1 Dosing Info Prescribing Info	SLCO1B1	ezetimibe / simvastatin
Details	Actionable PGx	Swissmedic	Annotation of Swissmedic Label for fenofibrate, simvastatin and SLCO1B1	SLCO1B1	fenofibrate, simvastatin
Details	Criteria Not Met	FDA	Annotation of FDA Label for simvastatin and SLCO1B1 Pediatric	SLCO1B1	simvastatin
Details	Criteria Not Met	HCSC	Annotation of HCSC Label for simvastatin and SLCO1B1 Pediatric	SLCO1B1	simvastatin

Afatinib

• belongs to a new class of antitumor drugs, **tumor growth inhibitors**: Afatinib is an irreversible, potent, and selective inhibitor of the **ErbB family**.

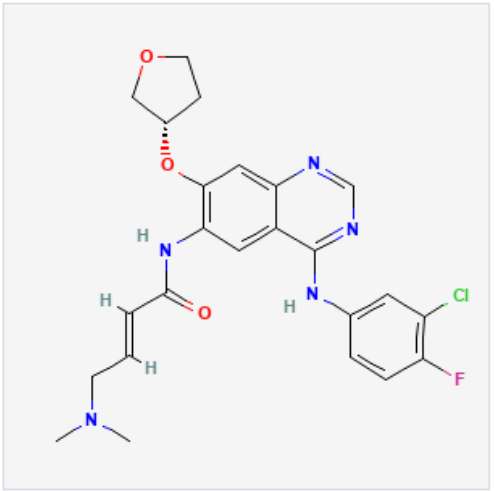
- Afatinib binds covalently and irreversibly blocks the signal from all homo- and heterodimers formed by the members of the ErbB family EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4

• acts against tumors selectively, as it recognizes some proteins that are found on the membrane of tumor cells or inside the cell. The binding to these proteins blocks/slows down the cell-division mechanisms

• since these proteins are also found in small quantities on healthy cells, the result is that the action is prevalent on tumor cells, but ADRs can occur.

Overview
Prescribing Info
Drug Label Annotations
Clinical Annotations
Variant Annotations
Literature
Pathways
Related To
Links

Structure



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source: PubChem

Type : Drug

PharmGKB ID : PA165981154

Description

Afatinib is a selective, irreversible tyrosine kinase inhibitor that acts against epidermal growth factor receptor, EGFR also known as an EGFR-TKI. Afatinib is a second generation EGFR-TKI designed to have more potent inhibition and also overcome activating mutations in EGFR that lead to drug resistance in first generation EGFR-TKIs such as gefitinib and erlotinib. Afatinib is an orally bioavailable aniline-quinazoline. It is also an inhibitor of ERBB2 (HER2), and ERBB4 (HER4).

Side effects of diarrhea and skin toxicities were higher in afatinib than first generation EGFR-TKIs due to greater inhibition of the wild type EGFR in non-cancer cells. Third generation EGFR-TKIs are in development that are specifically targeted against mutant EGFR (T790M) that are expected to have fewer toxicities (reviewed in [Article:25611025]).

Indication

First-line treatment of advanced Non-small cell lung cancer NSCLC with activating mutations in EGFR.

Afatinib

(Gilotrif) as monotherapy is indicated for the treatment of adult patients with:

- locally advanced or metastatic non-small cell lung cancer (NSCLC) with an **EGFR activating mutation**;

- With locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy

Drug Label Annotations

Overview
Prescribing Info
Drug Label Annotations
Clinical Annotations
Variant Annotations
Literature
Pathways
Related To
Links

PharmGKB annotates drug labels containing pharmacogenetic information from multiple drug regulatory agencies. Labels from the FDA, EMA and HCSC are updated as labels are added to the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels." Labels from other regulatory agencies were annotated as collaborations and are not routinely updated. Read more about drug label sources, PharmGKB label annotations, PGx Levels and the "tags" found in the table below. Sort and filter the table using the column headers and selection boxes. Download the entire table using the button below.

We welcome any information regarding drug labels containing PGx information approved regulatory agencies around the world - please contact feedback.

3 annotations

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	PGX LEVEL	SOURCE	TITLE	GENES	DRUGS
	All	All			
Details	Testing Required	EMA	Annotation of EMA Label for afatinib and EGFR Cancer Genome Indication	EGFR	afatinib
Details	Testing Required	FDA	Annotation of FDA Label for afatinib and EGFR FDA Biomarker Cancer Genome Indication	EGFR	afatinib
Details	Testing Required	HCSC	Annotation of HCSC Label for afatinib and EGFR Cancer Genome Indication	EGFR	afatinib

Annotation of FDA Label for afatinib and EGFR

Testing Required | Indication | FDA Biomarker | Cancer Genome

PharmGKB ID : PA166114903

Summary

Afatinib (GILOTRIF) is indicated for patients with metastatic non-small cell lung cancer (NSCLC) who have tumors with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations, as detected by an FDA-approved test.

Annotation

The FDA-approved drug label for afatinib (GILOTRIF) states that it is intended for patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test, and that the safety and efficacy of the drug in patients who have other EGFR mutations have not been established.

Excerpts from the GILOTRIF drug label:

> GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

> Patient Selection: Select patients for the first-line treatment of metastatic NSCLC with GILOTRIF based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor specimens...Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

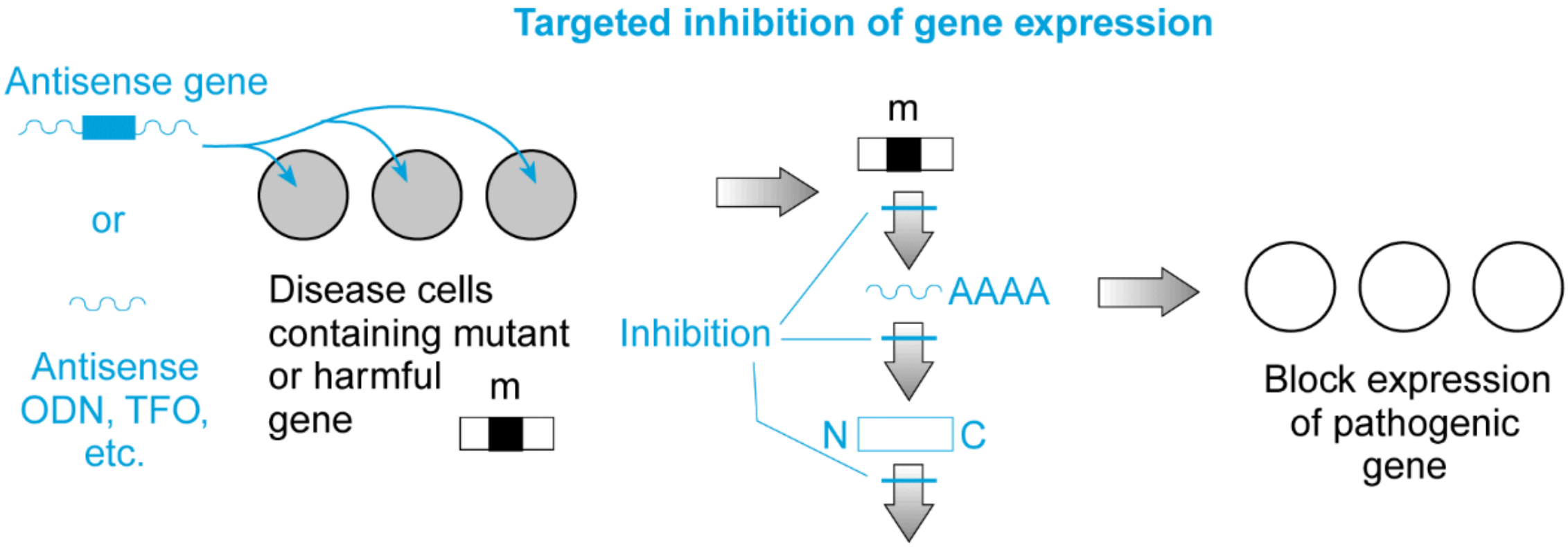
> Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations.

> Tumor samples from 264 patients...were tested retrospectively by the companion diagnostic *therascreen(R)* EGFR RGQ PCR Kit, which is FDA-approved for selection of patients GILOTRIF treatment.

For the complete drug label text with sections containing pharmacogenetic information highlighted, see the afatinib drug label.

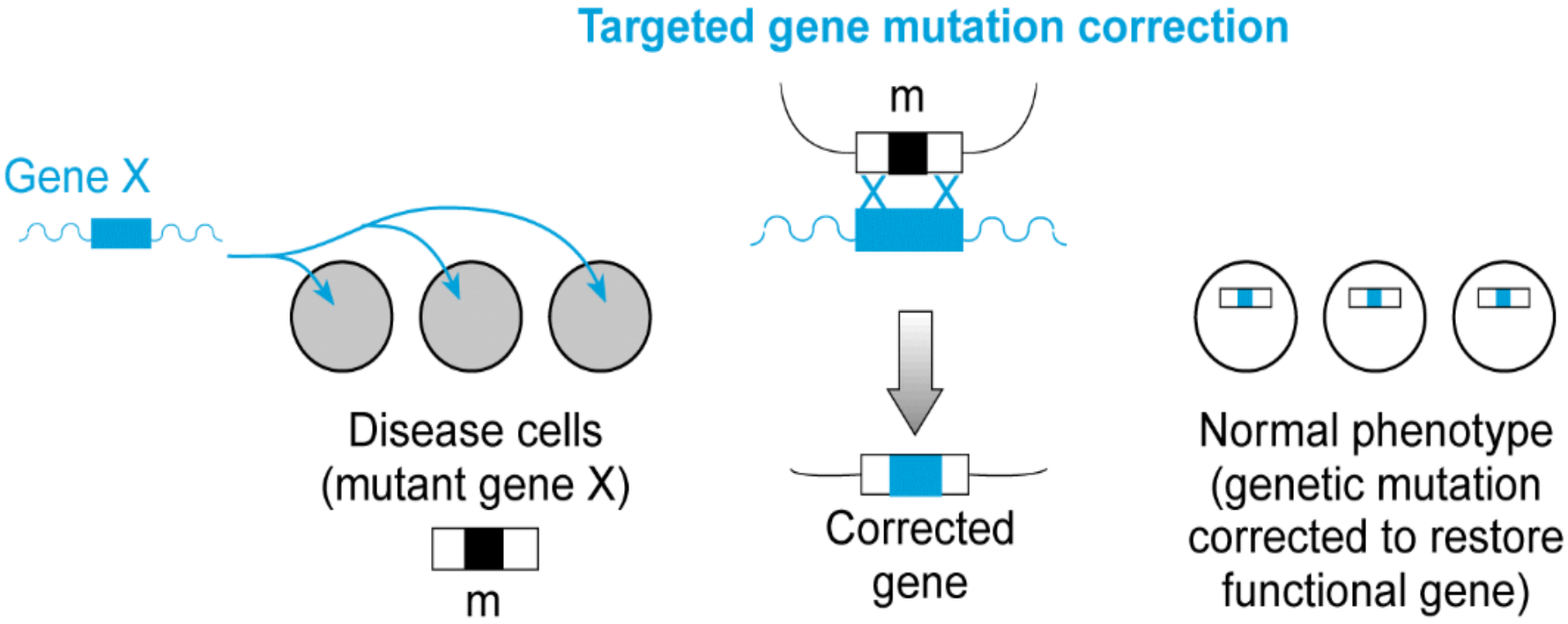
Non conventional gene therapy

To inhibit the genes involved in the pathogenesis



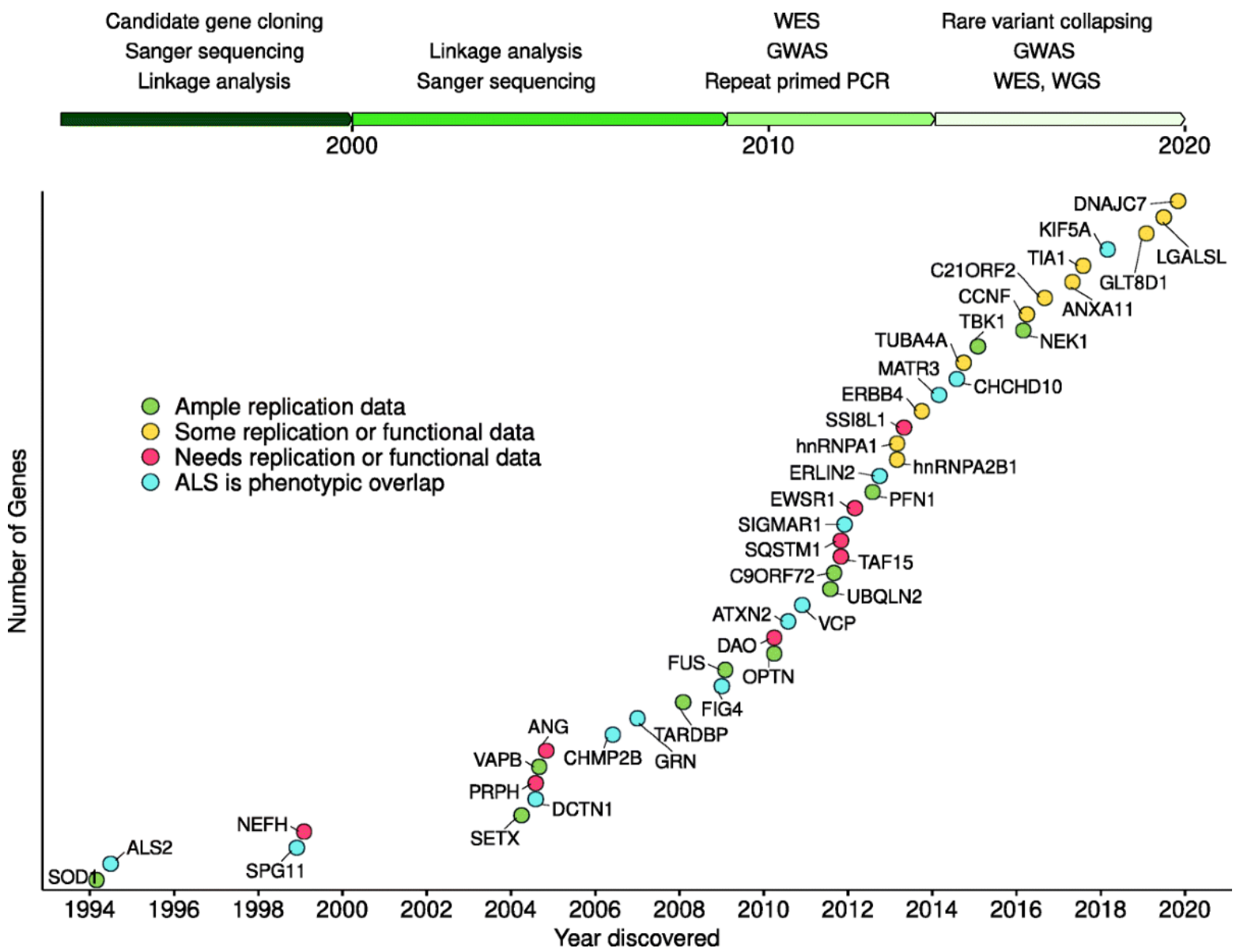
Non conventional gene therapy

To correct the gene defect and to rescue the normal gene expression



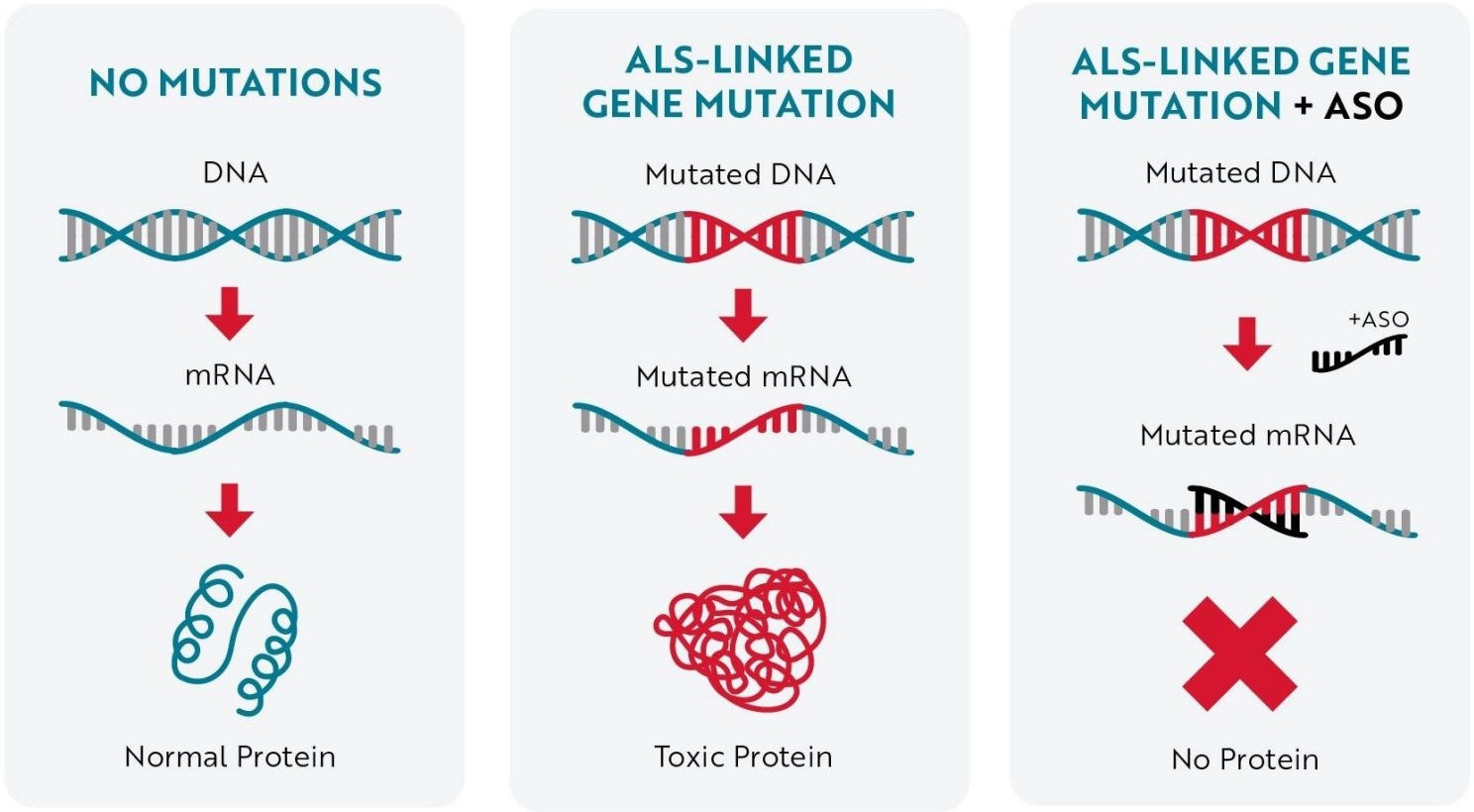
Amyotrophic lateral sclerosis ALS

Testing required



Tofersen (Qalsody, Biogen): approved by FDA to counteract SOD1-ALS

Antisense oligonucleotide that targets SOD1 mRNA, reducing SOD1 protein synthesis



Qalsody

Tofersen

Medicine | Human

Share | RSS

Authorised

This medicine is authorised for use in the European Union

Qalsody received a marketing authorisation under exceptional circumstances valid throughout the EU on 29 May 2024.

Page contents

Overview

Product information

Product details

Authorisation details

Assessment history

News on Qalsody

More information on Qalsody

Application under evaluation — CHMP opinion — **European Commission decision**

Overview

Qalsody is a medicine for treating adults with a type of amyotrophic lateral sclerosis (ALS) caused by a mutation (defect) in the gene responsible for producing an enzyme called superoxide dismutase 1 (SOD1). ALS is a progressive disease of the nervous system where nerve cells in the brain and spinal cord that control voluntary movement gradually deteriorate, causing loss of muscle function and paralysis.

ALS is rare, and Qalsody was designated an 'orphan medicine' (a medicine used in rare diseases) on 29 August 2016. ALS caused by a mutation in the *SOD1* gene represents about 2% of patients with ALS.

Qalsody contains the active substance tofersen.

Route: intrathecally using a lumbar puncture.

What are the benefits?

In a main study involving patients with ALS associated with a mutation in the *SOD1* gene, **72 patients received Qalsody and 36 received placebo** for 28 weeks. The main measure of efficacy was the rate at which a patient's disease symptoms worsened during the study.

This was assessed using a standard rating scale known as 'ALS functional rating scale revised' (ALSFRS-R), which measures aspects of a patient's physical functioning, such as difficulty talking, breathing, eating and performing other normal daily activities. The total score ranges from 0 (no function) to 48 (normal function).

After 28 weeks, the ALSFRS-R score decreased by 4.5 points in patients who received Qalsody compared with 5.8 in patients who received placebo; however, **this difference was not statistically significant**, meaning that it could be due to chance.

Other measurements, in particular **long-term data**, indicated that Qalsody may slow down the course of the disease. In addition, results showed **reductions in the levels of the SOD1 protein in patients who received Qalsody** compared with those who received placebo, confirming the way the medicine is expected to work. There were also **reductions in the levels of a protein called neurofilament light chain (NfL,** an indicator of nerve damage), suggesting reduced nerve damage

What are the risks?

For the full list of side effects and restrictions with Qalsody, see the package leaflet.

The most common side effects with Qalsody (which may affect more than 1 in 10 people) include pain in the back, arms, legs, muscles or joints, tiredness, increased levels of protein and/or white blood cells in the cerebrospinal fluid, and fever.

The most common serious side effects with Qalsody include myelitis (inflammation of the spinal cord), increased pressure around the brain, papilloedema (swelling of the nerve that connects the eyes with the brain), radiculitis (irritation and injury of nerve roots) and aseptic meningitis (inflammation of the lining around the brain and spinal cord).

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

AGENZIA ITALIANA DEL FARMACO

DETERMINA 31 luglio 2024

Classificazione, ai sensi dell'articolo 12, comma 5, della legge 8 novembre 2012, n. 189, del medicinale per uso umano, a base di tofersen, «Qalsody». (Determina n. 412/2024). (24A04222) (GU Serie Generale n.191 del 16-08-2024)

Articoli
1

Allegati
Allegato
Allegato

IL PRESIDENTE

Visti gli articoli 8 e 9 del decreto legislativo 30 luglio 1999, n. 300;

Visto l'art. 48 del decreto-legge 30 settembre 2003, n. 269, convertito dalla legge 24 novembre 2003, n. 326, che istituisce l'Agenzia italiana del farmaco;

Vista la legge 24 dicembre 1993, n. 537 e successive modificazioni con particolare riferimento all'art. 8, comma 10, lettera c);

Visto il decreto del Ministro della salute di concerto con i Ministri della funzione pubblica e dell'economia e finanze del 20 settembre 2004, n. 245 recante norme sull'organizzazione e il funzionamento dell'Agenzia italiana del farmaco, a norma del comma 13

Approved by AIFA on July 31st 2024

Lo studio ATLAS (Tofersen) per la SLA-SOD1 continua il reclutamento in Italia

Pubblicato il *16 marzo 2023*

Biogen sta conducendo uno studio clinico di fase 3, noto come **ATLAS**, volto a valutare l'efficacia e la sicurezza di un farmaco sperimentale per gli adulti che non hanno segni o sintomi clinici di Sclerosi Laterale Amiotrofica (SLA) – cioè elementi che indichino con certezza l'insorgenza della malattia – ma che sono tuttavia portatori di una variante patologica del gene della **superossido dismutasi 1 (SOD1)**.

Farmaco sperimentale
Tofersen (BIIB067) è un oligonucleotide antisenso (ASO), studiato per ridurre i livelli di proteina SOD1 nelle persone affette da SLA alle quali è associata una variante del gene SOD1.
Infatti, circa il 2% delle persone affette da SLA presenta una mutazione nel gene SOD1. Le mutazioni nel gene SOD1 possono portare alla produzione di proteina SOD1 anomala, che è probabile sia tossica per le cellule, e potrebbe portare alla morte delle cellule nervose osservata nelle persone affette da SLA. Lo studio ATLAS sta valutando se un farmaco sperimentale (tofersen) può ritardare l'insorgenza dei segni o sintomi della SLA e/o rallentare il declino delle funzioni una volta comparsi i segni o sintomi clinici (al momento della comparsa della SLA o dopo la comparsa della SLA rispetto a quando il paziente ha iniziato a prendere tofersen).

NCT04856982 Active, not recruiting

A Study of BIIB067 (Tofersen) Initiated in Clinically Presymptomatic Adults With a Confirmed **Superoxide Dismutase 1** Mutation

Conditions

Amyotrophic Lateral Sclerosis Associated With a **SOD1 Gene Mutation**

Locations

Scottsdale, Arizona, United States
La Jolla, California, United States
San Francisco, California, United States
Fort Lauderdale, Florida, United States

Show all 29 locations

Approved for marketing

Expanded Access Program for Tofersen in Participants With Superoxide Dismutase 1-Amyotropic Lateral Sclerosis

ClinicalTrials.gov ID NCT04972487

Sponsor Biogen

Information provided by Biogen (Responsible Party)

Last Update Posted 2024-06-10

NCT02623699 Completed WITH RESULTS

An Efficacy, Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Study of BIIB067 (Tofersen) in Adults With Inherited Amyotrophic Lateral Sclerosis (ALS)

Conditions

Amyotrophic Lateral Sclerosis

Locations

Phoenix, Arizona, United States

La Jolla, California, United States

San Francisco, California, United States

Jacksonville, Florida, United States

Show all 40 locations

Completed

Long-Term Evaluation of BIIB067 (Tofersen)

ClinicalTrials.gov ID NCT03070119

Sponsor Biogen

Information provided by Biogen (Responsible Party)

Last Update Posted 2024-08-19

NCT04931862 Terminated

Study of WVE-004 in Patients With C9orf72-associated **Amyotrophic Lateral Sclerosis** (**ALS**) or Frontotemporal Dementia (FTD)

Conditions

ALS FTD

Locations

North Ryde, New South Wales, Australia

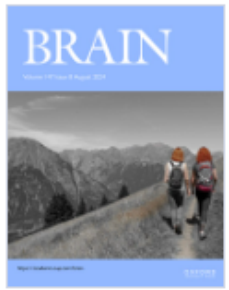
Brisbane, Queensland, Australia

Nedlands, Western Australia, Australia

Leuven, Belgium

Show all 17 locations

2023_ This is a Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of intrathecal (IT) WVE-004 in adult patients with C9orf72-associated ALS or FTD. To participate in the study, patients must have a documented mutation (GGGGCC [G4C2] repeat expansion) in the first intronic region of the C9orf72 gene and be diagnosed with ALS or FTD.



Volume 147, Issue 8
August 2024

Article Contents

Funding
Competing interests
References

< Previous Next >

JOURNAL ARTICLE

Failure of *C9orf72* sense repeat-targeting antisense oligonucleotides: lessons learned and the path forward FREE

Alexander J Cammack , Rubika Balendra , Adrian M Isaacs

Brain, Volume 147, Issue 8, August 2024, Pages 2607–2609,
https://doi.org/10.1093/brain/awae168
Published: 29 May 2024 **Article history**

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Issue Section: Opinion

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Mol Ther Nucleic Acids. 2023 Jan 16:31:353-366. doi: 10.1016/j.omtn.2023.01.006.
eCollection 2023 Mar 14.

Sustained therapeutic benefits by transient reduction of TDP-43 using ENA-modified antisense oligonucleotides in ALS/FTD mice

Toshihide Takeuchi [1 2], Kazuhiro Maeta [2], Xin Ding [3 2], Yukako Oe [2], Akiko Takeda [3 2], Mana Inoue [3], Seiichi Nagano [2 4], Tsuyoshi Fujihara [5], Seiji Matsuda [5], Shinsuke Ishigaki [6], Kentaro Sahashi [6], Eiko N Minakawa [7], Hideki Mochizuki [4], Masahiro Neya [5], Gen Sobue [6], Yoshitaka Nagai [1 3 2 4]

Affiliations + expand

PMID: 36817728 PMCID: PMC9925842 DOI: 10.1016/j.omtn.2023.01.006

Abstract

The abnormal aggregation of TDP-43 into cytoplasmic inclusions in affected neurons is a pathological hallmark of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Although how TDP-43 forms cytoplasmic aggregates and causes neurodegeneration in patients with ALS/FTD remains unclear, reducing cellular TDP-43 levels is likely to prevent aggregation and to rescue neurons from TDP-43 toxicity. To address this issue, here we developed gapmer-type antisense oligonucleotides (ASOs) against human TDP-43 using 2'-*O*,4'-*C*-ethylene nucleic acids (ENAs), which are modified nucleic acids with high stability, and tested the therapeutic potential of lowering TDP-43 levels using ENA-modified ASOs. We demonstrated that intracerebroventricular administration of ENA-modified ASOs into a mouse model of ALS/FTD expressing human TDP-43 results in the efficient reduction of TDP-43 levels in the brain and spinal cord. Surprisingly, a single injection of ENA-modified ASOs into TDP-43 mice led to long-lasting improvement of behavioral abnormalities and the suppression of cytoplasmic TDP-43 aggregation, even after TDP-43 levels had returned to the initial levels. Our results demonstrate that transient reduction of TDP-43 using ENA-modified ASOs leads to sustained therapeutic benefits *in vivo*, indicating the possibility of a disease-modifying therapy by lowering TDP-43 levels for the treatment of the TDP-43 proteinopathies, including ALS/FTD.

Keywords: ENA; MT: Oligonucleotides: Therapies and Applications; TDP-43; aggregation; amyotrophic lateral sclerosis; antisense oligonucleotides; frontotemporal dementia; therapy.

NCT06665165 Recruiting

AMX0114 in Adult Participants With **Amyotrophic Lateral Sclerosis**

Conditions

ALS

Locations

London, Ontario, Canada

“AMX0114 targets calpain-2, a calcium-activated protease, which has been found to be an important contributor to axonal degeneration and studied over decades of research as a potential target for the treatment of ALS and other neurodegenerative diseases. In preclinical studies, AMX0114 showed improved neuronal survival and reductions in extracellular NfL levels across multiple disease models. We are excited to progress AMX0114 into the clinic for people with ALS as we work to advance a potential therapy for this relentlessly progressive, fatal disease,” said Camille L. Bedrosian, MD, Chief Medical Officer at Amylyx.

Recruiting

A Study Evaluating the Safety and Tolerability of QRL-201 in ALS

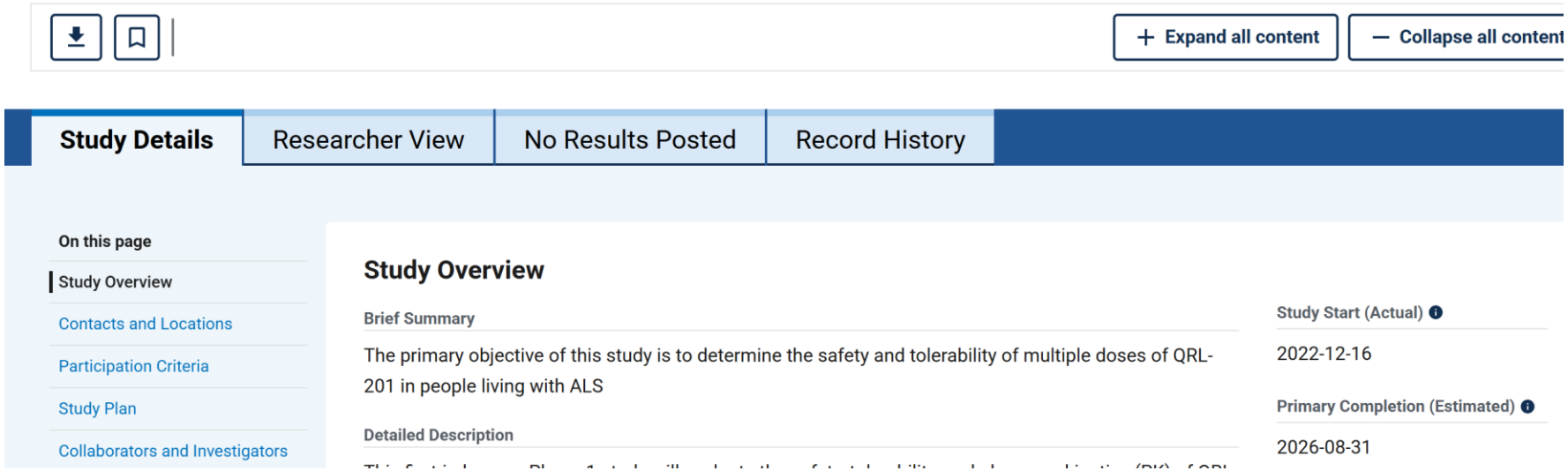
ClinicalTrials.gov ID NCT05633459

Sponsor QurAlis Corporation

Information provided by QurAlis Corporation (Responsible Party)

Last Update Posted 2025-04-08

QRL-201 is an antisense oligonucleotide, or a small DNA molecule, that's designed to restore STMN2 levels by correcting such abnormal mRNA processing. Raising STMN2 production levels with QRL-201 reversed nerve damage in lab-grown nerve cells and animal models.



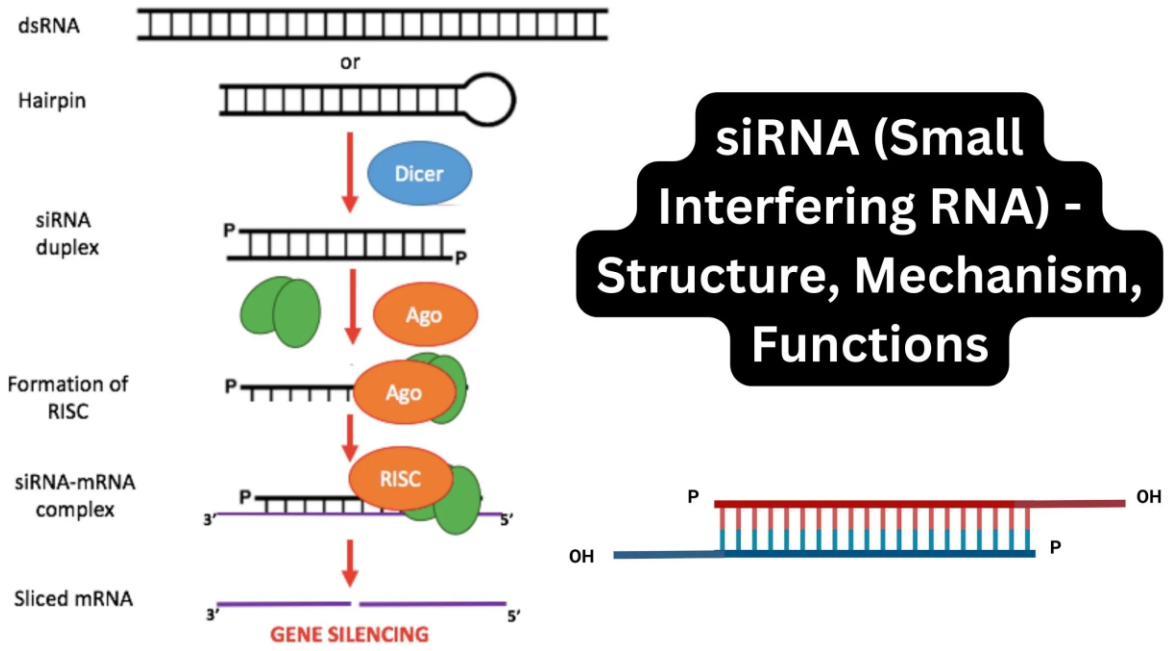
Stathmin-2 is a neuronally enriched protein that plays a crucial role in axonal outgrowth during development and regeneration.

Small RNA Interference (siRNA)

- It is a mechanism by which small fragments of **double-stranded RNA** trigger the sequence-specific degradation of an mRNA
- By the action of the endonuclease DICER, segments of 20-23 bases called small interference RNA (siRNA) are formed
- Then by the action of the multiprotein complex RISC (RNA-induced silencing complex) the two strands of the siRNA are separated and the single strands bind to the complementary sequences of the mRNA
- The formation of the complex can:

Activate the degradation of the mRNA, if the bond is not very stable

Block the function of the mRNA if the bond is very stable



BEVASIRANIB:

- The first siRNA developed for age-related maculopathy is bevasiranib (Acuity Pharmaceuticals).
- Used for the treatment of exudative age-related maculopathy, responsible for 60% of cases of age-related blindness
- Vascular endothelial growth factor (VEGF) plays a primary role in the development of maculopathy
- Administered intravitreally, **bevasiranib inhibits NEW VEGF production**, without interfering with existing VEGF.

Ophthalmol Eye Dis. 2010; 2: 75–83.
Published online 2010 Dec 19. doi: 10.4137/OED.S4878
PMCID: PMC3661434
PMID: 23861616

Bevasiranib for the Treatment of Wet, Age-Related Macular Degeneration

Adinoyi O. Garba[1] and Shaker A. Mousa[1,2]

– L'utilizzo dei siRNA in terapia è limitato perché
  - le cellule di mammifero non hanno il patrimonio enzimatico necessario (RNA polimerasi RNA dipendente)
  - RNA non attraversa facilmente le membrane
  - RNA è altamente instabile

L'alternativa è l'uso dei short RNA interference (shRNA)

Critical points of the use of siRNA in therapy:

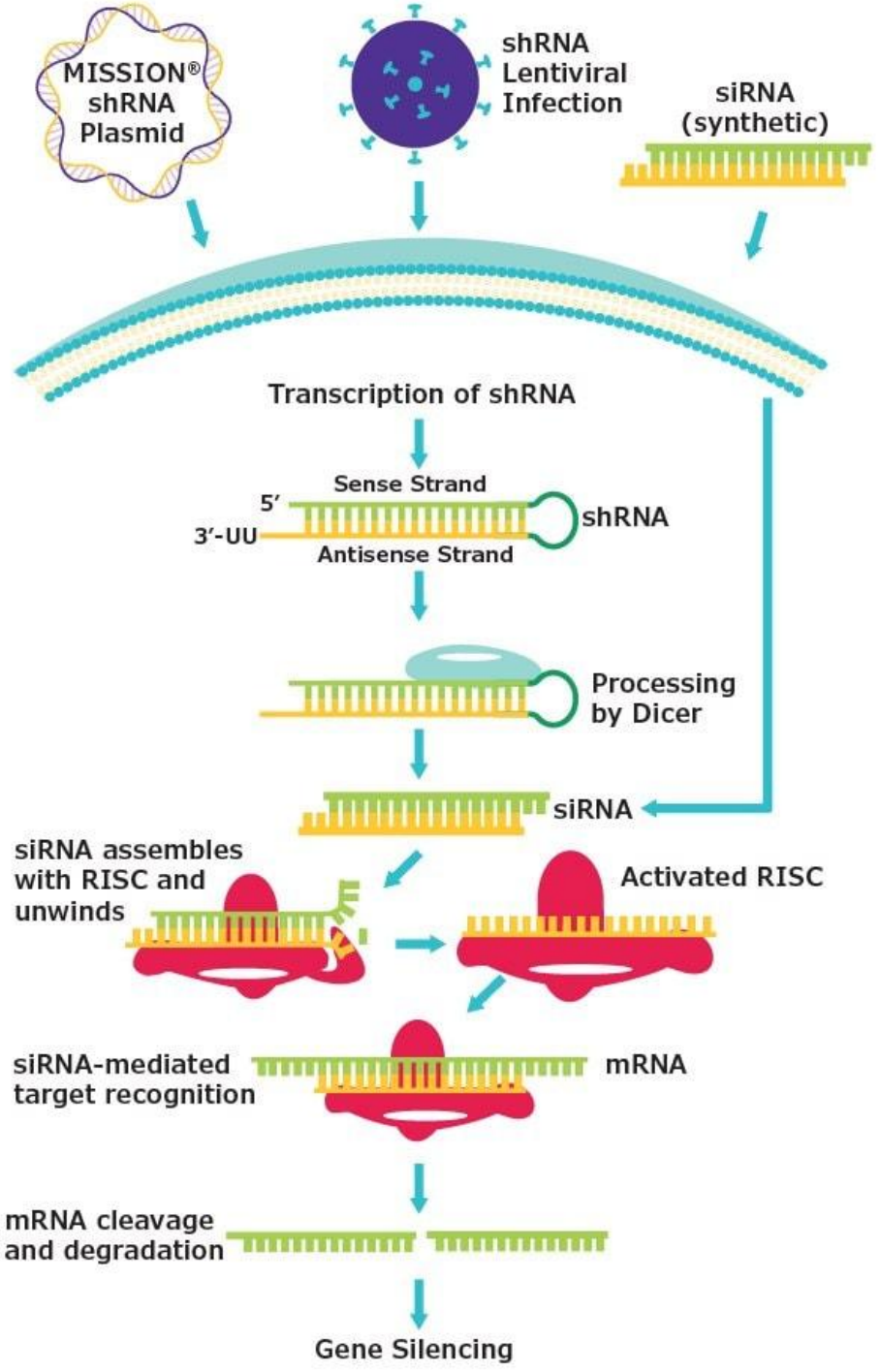
- Mammal cells do not have specific enzymes (RNA polymerase RNA-dependent)
- RNA does not easily cross the membrane
- RNA is unstable

Transfection of an exogenous siRNA can be problematic, since gene silencing is **only transient**, especially in rapidly growing cells.

One way to overcome this problem is to introduce a vector (such as a plasmid) into the target cell that expresses the desired siRNA molecule. This is possible by designing vectors that can produce **small hairpin RNA** (shRNA) molecules containing a dsRNA, which have the advantage of being transcribed just like any other RNA. These vectors are in fact able to transcribe shRNAs through specific eukaryotic promoters for RNA polymerase III (such as the promoter of the human H1 gene, which encodes a catalytic RNA, or the promoter of the U6 snoRNA), which usually induce the transcription of small nuclear RNAs (or snRNA) involved in splicing. The resulting shRNAs are processed into siRNAs by the RNase Dicer, although the actual involvement of Dicer in this step is not yet confirmed by the entire scientific community.

shRNA

- Short Hairpin RNA (RNA a forcina, shRNA), single-stranded that folds back on itself and in this hairpin conformation activates DICER forming fragments of 20-23 bases similar to those produced by siRNA



FDA Approved siRNA Drugs

- **Patisiran:** Approved for hATTR.
- **Givosiran:** Approved for AHP.
- **Lumasiran:** Approved for AHP.
- **Inclisiran:** Approved for reducing LDL cholesterol in subjects with HeFH or ASCVD.
- **Vutrisiran:** Approved for PH1 in adults and pediatric patients.
- **Nedosiran:** Approved for PH1.

Fitusiran: A GalNAc-siRNA conjugate targeting SERPINC1 mRNA for hemophilia A and B

Other siRNA drugs: Tafamidis, Inotersen.

Small Interfering RNA (siRNA) Therapy

Inderbir S. Padda; Arun U. Mahtani; Preeti Patel; Mayur Parmar.

Author Information and Affiliations

Last Update: March 20, 2024.

Continuing Education Activity

Go to:

This activity focuses on small interfering RNA (siRNA) therapy, exemplified by FDA-approved agents such as patisiran, givosiran, lumasiran, inclisiran, nedosiran, and vutrisiran. These therapies are pivotal in managing rare metabolic ailments, including hereditary transthyretin amyloidosis (hATTR), acute hepatic porphyria (AHP), primary hyperoxaluria type 1 (PH1), and lowering low-density lipoprotein cholesterol (LDL-C) in subjects with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD). The activity will discuss the mechanism of action of siRNA, its adverse event profile, and other key factors essential for interprofessional team members involved in patient care. Furthermore, participants will gain insights into administration techniques, contraindications, clinical toxicology, and monitoring strategies necessary to safely and effectively utilize siRNA therapies in clinical practice.

Understanding the intricate pharmacology of siRNA is crucial for healthcare professionals to deliver precise therapeutic interventions in various clinical scenarios. This activity equips participants with comprehensive knowledge encompassing the mechanism of action, potential adverse reactions, and contraindications, empowering them to integrate advanced therapeutic strategies into patient care. This comprehension ensures that professionals possess the requisite expertise to provide optimal and innovative patient care within the dynamic realm of medical science, thereby enhancing patient outcomes and contributing to the advancement of medical practice.

Objectives:

EMA Approved siRNA Drugs

Several small interfering RNA (siRNA) drugs have been authorized by the European Medicines Agency (EMA). These include patisiran (Onpattro), givosiran, lumasiran (Oxlumo), inclisiran (Leqvio), and vutrisiran (Amvuttra).

Here's a more detailed look at some of the approved siRNA drugs:

- **Patisiran (Onpattro):** Approved for the treatment of polyneuropathy caused by hereditary transthyretin-mediated (hATTR) amyloidosis.
- **Givosiran:** Approved for the treatment of acute intermittent porphyria.
- **Lumasiran (Oxlumo):** Approved for the treatment of congenital alpha-1 antitrypsin deficiency.
- **Inclisiran (Leqvio):** Approved for the treatment of primary hypercholesterolemia (both heterozygous familial and non-familial) or mixed dyslipidemia.
- **Vutrisiran (Amvuttra):** Approved for the treatment of polyneuropathy caused by hereditary transthyretin-mediated (hATTR) amyloidosis.

patisiran

Overview
Prescribing Info
Drug Label Annotations
Summary Annotations
Variant Annotations
Literature
Pathways
Related To
Links

PRESCRIBING INFO	DRUG LABEL ANNOTATIONS	CLINICAL ANNOTATIONS	PATHWAYS
0	3	0	0

Type : Drug

ID : PA166182884

Classifications

Drug
Nervous System

Drug
Other Nervous System Drugs

Molecular Properties

Not Available

patisiran

- Overview
- Prescribing Info
- Drug Label Annotations
- Summary Annotations
- Variant Annotations
- Literature
- Pathways
- Related To
- Links

Drug Label Annotations

ClinPGx annotates regulatory agency-approved drug labels containing PGx information. Read more about ClinPGx drug label annotations, the drug label sources, PGx Levels and the "tags" found in the table below. FDA, EMA and HCSC labels are annotated when found on the FDA Table of Pharmacogenomic Biomarkers in Drug Labels. Labels from other regulatory agencies were annotated as collaborations and are not routinely updated.

Sort and filter the table using the column headers and selection boxes. Download the entire table using the button at the top right of the table.

3 annotations

Legend Download

	PGX LEVEL	SOURCE	TITLE	GENES	DRUGS
	All	All			
Details	Testing Required	EMA	Annotation of EMA Label for patisiran and TTR Indication	TTR	patisiran
Details	Testing Required	FDA	Annotation of FDA Label for patisiran and TTR FDA Biomarker Indication	TTR	patisiran
Details	Testing Required	HCSC	Annotation of HCSC Label for patisiran and TTR Indication	TTR	patisiran

Annotation of EMA Label for patisiran and TTR

Testing Required | Indication

Patisiran (Onpattro) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Transthyretin is encoded by the *TTR* gene. Patisiran causes degradation of mutant and wild-type *TTR* mRNA through RNA interference, resulting in a reduction of serum TTR protein and TTR protein deposits in tissues.

Excerpts from the patisiran (Onpattro) EPAR:

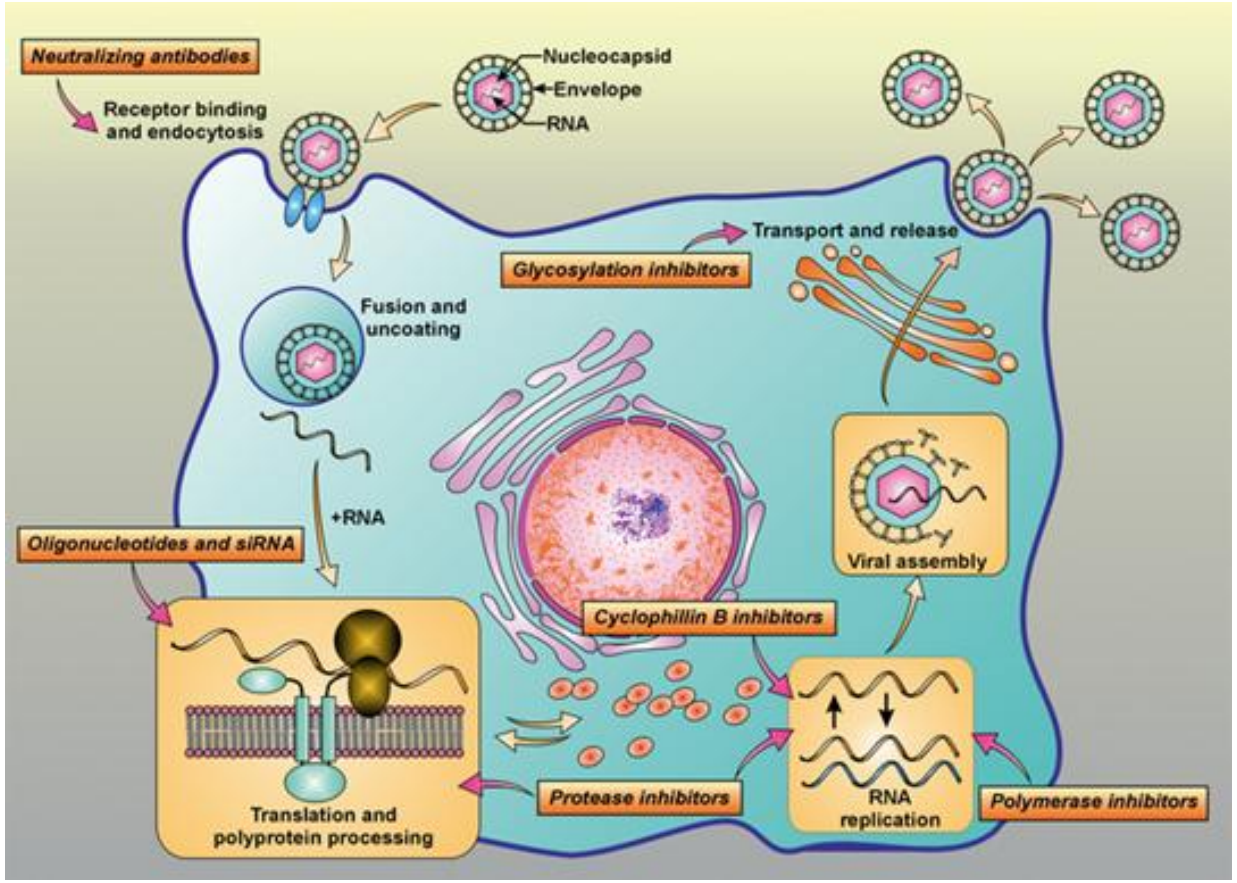
> Onpattro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

> Onpattro contains patisiran, a double-stranded small interfering ribonucleic acid (siRNA) thatspecifically targets a genetically conserved sequence in the 3' untranslated region of all variant and wild-type TTR mRNA. Patisiran is formulated as lipid nanoparticles to deliver the siRNA to hepatocytes, the primary source of TTR protein in the circulation. Through a natural process called RNA interference (RNAi), patisiran causes the catalytic degradation of TTR mRNA in the liver, resulting in a reduction of serum TTR protein.

For the complete EPAR text with sections containing pharmacogenetic information highlighted, see the patisiran EPAR PDF.

Sofosbuvir (Sovaldi®)

- ANT to inhibit HCV RNA polymerase



As a prodrug nucleotide analog, Sofosbuvir is metabolized into its active form as the antiviral agent 2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-triphosphate (also known as GS-461203), which acts as a defective substrate for NS5B (non-structural protein 5B)

- Sofosburiv is a prodrug used to treat hepatitis C.
- Its main metabolite, 2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-monophosphate, inhibits the RNA polymerase that the hepatitis C virus uses to replicate its RNA.
- It is marketed in Italy as Sovaldi;
- since March 2013 it has been available for prescription by centers authorized by the Italian Medicines Agency, for patients with chronic hepatitis C in the advanced stages of the disease or with liver cirrhosis.
- **It must always be used together with another drug, never alone: the duration of therapy varies from 12 to 24 weeks.**

Sofosbuvir eliminates the hepatitis C virus because it acts directly against the virus, blocking its replication process.

Given in combination with other drugs including:

- Pegylated interferon alfa (2a and 2b): stimulates the immune system's response against the virus
- Ribavirin: indirectly interferes with viral replication
- daclatasvir and/or simeprevir: direct-acting antivirals

The dose of sofosbuvir should not be reduced. If treatment with other medicinal products used in combination with Sofosbuvir is permanently discontinued, the administration of Sofosbuvir should also be discontinued.

secondo farmaco, dopo simeprevir, approvato dall'FDA nelle ultime due settimane per trattare l'infezione cronica da HCV.

L'epatite C è una malattia virale che causa infiammazione del fegato che può portare a funzionalità epatica ridotta o insufficienza epatica. La maggior parte dei malati di HCV non ha sintomi della malattia fino a che i danni al fegato sono divenuti evidenti, il che può richiedere diversi anni. Alcune persone con infezione cronica da HCV sviluppano cicatrici e scarsa funzionalità del fegato (cirrosi) nel corso di molti anni, che possono portare a complicazioni come emorragie, ittero (occhi o pelle giallastri), accumulo di liquido nell'addome, infezioni o cancro al fegato. Secondo i Centers for Disease Control and Prevention, circa 3,2 milioni di americani sono infettati con l'HCV.

Sofosburiv è un analogo nucleotidico a somministrazione orale monogiornaliera, che blocca una proteina specifica necessaria al virus dell'epatite C per replicarsi. Deve essere utilizzato come componente di un regime di trattamento di combinazione antivirale per infezione da HCV cronica. Ci sono diversi tipi di infezione da HCV. A seconda del tipo di infezione da HCV del paziente, il regime di trattamento potrebbe includere sofosburiv e ribavirina o sofosburiv, ribavirina e peginterferone alfa. Anche ribavirina e peginterferone alfa sono due farmaci utilizzati per trattare l'infezione da HCV.

L'efficacia di sofosburiv è stata valutata in sei studi clinici, che hanno coinvolto 1.947 partecipanti che non avevano precedentemente ricevuto un trattamento per la malattia (pazienti naive) o non avevano risposto al trattamento precedente (con esperienza di trattamento), compresi i partecipanti co-infettati con HCV e HIV. I trial sono stati progettati per misurare se il virus dell'epatite C non fosse rilevato nel sangue almeno 12 settimane dopo la fine del trattamento (risposta virologica sostenuta), suggerendo che l'infezione da HCV di un partecipante fosse stata curata.

6 clinical trials to evaluate the efficacy of sofosbuvir (1947 patients)

L'efficacia di sofosbuviv è stata valutata in sei studi clinici, che hanno coinvolto 1.947 partecipanti che non avevano precedentemente ricevuto un trattamento per la malattia (pazienti naive) o non avevano risposto al trattamento precedente (con esperienza di trattamento), compresi i partecipanti co-infettati con HCV e HIV. I trial sono stati progettati per misurare se il virus dell'epatite C non fosse rilevato nel sangue almeno 12 settimane dopo la fine del trattamento (risposta virologica sostenuta), suggerendo che l'infezione da HCV di un partecipante fosse stata curata.

I risultati di tutti gli studi clinici hanno mostrato che un regime terapeutico contenente sofosbuviv è efficace nel trattamento di diversi tipi di virus dell'epatite C. Inoltre, sofosbuviv si è dimostrato efficace nei partecipanti che non potevano tollerare o accettare un regime di trattamento a base di interferone e nei partecipanti con cancro al fegato in attesa di trapianto di fegato, andando incontro alle esigenze mediche insoddisfatte di queste popolazioni.

Gli effetti collaterali più comuni riportati nei partecipanti allo studio clinico trattati con sofosbuviv e ribavirina sono stati affaticamento e mal di testa. In partecipanti trattati con sofosbuviv, ribavirina e peginterferone alfa, gli effetti indesiderati più comunemente riportati sono stati affaticamento, cefalea, nausea, insonnia e anemia.

Leggi sul sito dell'FDA

No important ADRs (1947 patients)

Pubblicato il: 12 dicembre 2013

Ribavirin (Rebetol®) is the active substance specifically indicated for influenza viruses with severe manifestations. **It is a guanosine analogue, but has a modified nitrogenous base**. This induces errors in the replication and transcription of the viral genome, producing mutations that inactivate mRNA and proteins. It acts by inhibiting nucleoside synthesis, mRNA capping and other processes important for the replication of many DNA and RNA viruses. Like many nucleoside analogue antiviral drugs, it must be triphosphorylated by enzymes (cellular and/or viral) to become pharmacologically active.

Declatasvir (Daklinza) is an **inhibitor of nonstructural protein 5A (NS5A),** a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir inhibits both viral RNA replication and virion assembly

Simeprevir (Olysio) is a specific **inhibitor of the HCV NS3/4A serine protease**, which is essential for viral replication. In a biochemical assay, simeprevir was found to inhibit the proteolytic activity of recombinant HCV genotype 1a and 1b NS3/4A proteases, with median Ki values of 0.5 nM and 1.4 nM, respectively.

Conjugation of PEG (bis-monomethoxy polyethylene glycol) to **interferon alfa-2a forms** a pegylated interferon alfa-2a (Pegasys). Pegasys has the antiviral and antiproliferative activities characteristic of interferon alfa-2a in vitro.

- The efficacy of sofosbuvir has been confirmed in patients with genotypes 1 - 4, including those awaiting liver transplantation due to liver cancer and with HCV/HIV-1 co-infection.
- Clinical data to support the use of sofosbuvir in patients with genotypes 5 and 6 are limited.
- In January **2014**, EMA (European Medicines Agency) granted the marketing authorization in the Community for sofosbuvir. The therapeutic indications include adult patients with chronic hepatitis C with genotypes 1, 2, 3, 4, 5, 6

- who have never undergone any antiviral treatment (Naïve Patients);

- who have already undergone one or more antiviral treatments with alpha interferon (pegylated or non-pegylated) alone or in combination with ribavirin, who have had a relapse of the disease (Relapser), who have responded partially (Partial Responder) or who have not responded at all (Null Responder).

- The therapy, with peg-interferon and ribavirin, or with ribavirin alone and/or other antivirals, differs depending on the viral genotype and the clinical condition.

AGENZIA ITALIANA DEL FARMACO

DETERMINA 24 marzo 2017

Ridefinizione dei criteri di trattamento per la terapia dell'Epatite C cronica. (Determina n. 500/2017). (17A02374)

(GU n.75 del 30-3-2017)

Determina:

Art. 1

Approvazione criteri di trattamento
per la terapia dell'epatite C cronica

1. Sono approvati i seguenti criteri di trattamento per la terapia dell'epatite C cronica:

criterio 1: pazienti con cirrosi in classe di Child A o B e/o con HCC con risposta completa a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico nei quali la malattia epatica sia determinante per la prognosi;

criterio 2: epatite ricorrente HCV-RNA positiva del fegato trapiantato in paziente stabile clinicamente e con livelli ottimali di immunosoppressione;

criterio 3: epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B, insufficienza renale);

criterio 4: epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak);

criterio 5: in lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilita' di una attesa in lista di almeno due mesi;

criterio 6: epatite cronica dopo trapianto di organo solido (non fegato) o di midollo in paziente stabile clinicamente e con livelli ottimali di immunosoppressione;

criterio 7: epatite cronica con fibrosi METAVIR F2 (o corrispondente Ishak) e/o comorbilita' a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesita' (body mass index ≥30 kg/m2), emoglobinopatie e coagulopatie congenite];

criterio 8: epatite cronica con fibrosi METAVIR F0-F1 (o corrispondente Ishak) e/o comorbilita' a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesita' (body mass index ≥30 kg/m2), emoglobinopatie e coagulopatie congenite];

criterio 9: operatori sanitari infetti;

criterio 10: epatite cronica o cirrosi epatica in paziente con insufficienza renale cronica in trattamento emodialitico;

criterio 11: epatite cronica nel paziente in lista d'attesa per trapianto di organo solido (non fegato) o di midollo.

Art. 2

Art. 2

Implementazione dei criteri

1. I criteri di trattamento per la terapia dell'epatite C cronica di cui al precedente art. 1, sono implementati nell'ambito dei registri dei farmaci sottoposti a monitoraggio, che tracceranno la gestione della terapia dei singoli pazienti da parte dei centri prescrittori individuati dalle regioni.

2. All'interno dei registri dei farmaci sottoposti a monitoraggio e' garantita un'apposita funzionalita' in modo da poter inserire i pazienti da ritrattare con un'associazione di almeno due farmaci antivirali ad azione diretta di seconda generazione (Direct Acting Agents-DAAs) in seguito al fallimento di regimi di trattamento senza interferone.

Art. 3

Disposizioni finali

1. La presente determinazione ha effetto dal giorno successivo alla sua pubblicazione nella Gazzetta Ufficiale della Repubblica italiana.

Roma, 24 marzo 2017

Il direttore generale: Melazzini

In Italy all patients are eligible for treatment, according to Determina n. 500/2017 di AIFA published in Gazzetta Ufficiale il 30/3/2017.

4.2 Posology and method of administration

Sovaldi treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Posology

The recommended dose of Sovaldi in adults is one 400 mg tablet, taken orally, once daily with food (see section 5.2).

The recommended dose of Sovaldi in paediatric patients aged 3 years and above is based on weight (as detailed in Table 2). Sovaldi should be taken with food (see section 5.2).

sofosbuvir

Overview
Prescribing Info
Drug Label Annotations
Summary Annotations
Variant Annotations
Literature
Pathways
Related To
Links

PRESCRIBING INFO 1

DRUG LABEL ANNOTATIONS 5

CLINICAL ANNOTATIONS 6

PATHWAYS 1

Structure

large version

3D version

source: PubChem

Type : Drug

ID : PA166122593

Classifications

Search

sofosbuvir

Overview
Prescribing Info
Drug Label Annotations
Summary Annotations
Variant Annotations
Literature
Pathways
Related To
Links

Genotype/Phenotype-based Prescribing Info

Drug Label Annotations: 1

Prescribing information explains how to adjust treatment of certain medications based on a person's genetic information, and includes information from clinical guideline annotations, drug label annotations and the FDA Table of Pharmacogenetic Associations.

Drug Label Annotations with Genotype-Based Prescribing Information

These are PharmGKB Drug Label Annotations with a "Prescribing" section. Information is added to this section if an annotation is tagged with "Dosing Info" or "Alternative Drug", or if any other guidance is given on the label for patients with a particular genotype or metabolizer phenotype. Examples of such guidance are (1) if a dosing change or alternate drug is "recommended", "suggested" or "should be considered", (2) if a drug "should be used with caution", or (3) if clinicians should "monitor" these patients for adverse events/reactions.

Annotation of Swissmedic Label for sofosbuvir

Consideration should be given to possibly extending the duration of therapy beyond 12 weeks up to 24 weeks, in particular for subgroups with one or more of the previously identified negative predictive factors associated in the past with lower response rates to interferon-containing therapies (e.g. advanced fibrosis/cirrhosis, high initial viral load, black skin, IL28B-Non-CC genotype, earlier non-response to peginterferon alfa and ribavirin).

Continue reading Annotation of Swissmedic Label for sofosbuvir

Overview
Prescribing Info
Drug Label Annotations
Summary Annotations
Variant Annotations
Literature
Pathways
Related To
Links

Drug Label Annotations

ClinPGx annotates regulatory agency-approved drug labels containing PGx information. Read more about ClinPGx drug label annotations, the drug label sources, PGx Levels and the "tags" found in the table below. FDA, EMA and HCSC labels are annotated when found on the FDA Table of Pharmacogenomic Biomarkers in Drug Labels. Labels from other regulatory agencies were annotated as collaborations and are not routinely updated.

Sort and filter the table using the column headers and selection boxes. Download the entire table using the button at the top right of the table.

5 annotations

Legend Download

	PGX LEVEL	SOURCE	TITLE	GENES	DRUGS
	All	All			
Details	Actionable PGx	Swissmedic	Annotation of Swissmedic Label for sofosbuvir and IFNL3, IFNL4 Prescribing Info	IFNL3, IFNL4	sofosbuvir
Details	Criteria Not Met	FDA	Annotation of FDA Label for sofosbuvir and IFNL3 FDA Biomarker	IFNL3	sofosbuvir
Details	Criteria Not Met	FDA	Annotation of FDA Label for sofosbuvir / velpatasvir and IFNL3 FDA Biomarker	IFNL3	sofosbuvir / velpatasvir
Details	Criteria Not Met	FDA	Annotation of FDA Label for ledipasvir / sofosbuvir and IFNL3 FDA Biomarker	IFNL3	ledipasvir / sofosbuvir
Details	Criteria Not Met	FDA	Annotation of FDA Label for sofosbuvir / velpatasvir / voxilaprevir and IFNL3	IFNL3	sofosbuvir / velpatasvir /

Annotation of Swissmedic Label for sofosbuvir and IFNL3, IFNL4

Actionable PGx | Prescribing Info

The Swiss drug label for sofosbuvir (Sovaldi) states that "consideration should be given to possibly extending the duration of therapy beyond 12 weeks up to 24 weeks, in particular for subgroups with one or more of the previously identified negative predictive factors associated in the past with lower response rates to interferon-containing therapies (e.g. advanced fibrosis/cirrhosis, high initial viral load, black skin, IL28B-Non-CC genotype, earlier non-response to peginterferon alfa and ribavirin)."

Please note that this drug label annotation was created from a collaboration between ClinPGx and Pharmaceutical Care Research Group in University of Basel in 2019. The label has not been subsequently reviewed or updated.

Prescribing Information

Consideration should be given to possibly extending the duration of therapy beyond 12 weeks up to 24 weeks, in particular for subgroups with one or more of the previously identified negative predictive factors associated in the past with lower response rates to interferon-containing therapies (e.g. advanced fibrosis/cirrhosis, high initial viral load, black skin, IL28B-Non-CC genotype, earlier non-response to peginterferon alfa and ribavirin).

IFNL3

Overview
Prescribing Info
Drug Label Annotations
Summary Annotations
Variant Annotations
Named Variants
Literature
Pathways
Related To
Links

PRESCRIBING INFO 1

CLINICAL ANNOTATIONS 28

PATHWAYS 1

Pediatric

Overview VIP

Type III interferons (IFN-λs) are produced in response to viral infection and can elicit an antiviral state as well as modulate innate and adaptive immune responses. Genetic variants around the IFNL3/4 gene locus are associated with spontaneous clearance of HCV, and therapeutic responses to pegylated interferon alpha and ribavirin (PEG-IFN/RBV) therapy.

Location

Strand	Minus
Cytogenetic	chr19 : q13.13 - q13.2
GRCh37	chr19 : 39734193 - 39735717
GRCh38	chr19 : 39243455 - 39245250