Drug Profile of Ivacaftor and Lumacaftor

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Abstract- *Ivacaftor and lumacaftor are vocally available in the form of correctors of the cystic fibrosis transmembrane conductance regulator (CFTR) that are used to care for patients with cystic fibrosis with specific mutations of the CFTR. Ivacaftor alone or in combination with lumacaftor has been associated with transient serum enzyme elevations during treatment.*

Keywords- Ivacaftor and Lumacaftor, cystic fibrosis transmembrane conductance regulator.

Drug Profile of Ivacaftor

Molecular structure

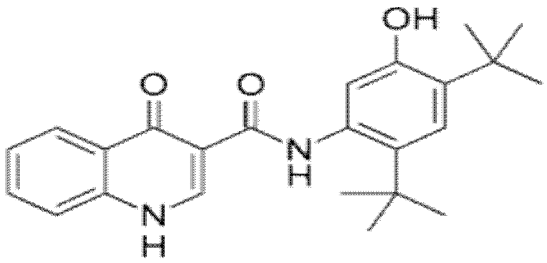

Fig. Structure of Ivacaftor

IUPAC Name	N-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide.
CAS Number	873054-44-5
Drug Bank	DB08820
Molecular formula	$C_{24}H_{28}N_2O_3$
Molecular weight	392.4907 gm/mol
Category	For the treatment of Cystic Fibrosis
Description	Ivacaftor is a drug used to treat cystic fibrosis in people with certain mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.
Solubility	**S**oluble in methyl ethyl ketone and Water
pK_a value	9.40
Mechanism of action	

Cystic fibrosis is caused by any one of several defects in a protein, cystic fibrosis transmembrane conductance regulator, which regulates fluid flow within cells and affects the components of sweat, digestive fluids and mucus. The defect, which is caused by a mutation in the individual's DNA, can be in any of several locations along the protein, each of which interferes with a different function of the protein.

Pharmacokinetic data

Absorption

The pharmacokinetics of Ivacaftor is similar between healthy adult volunteers and patients with CF. When given a single oral dose of 150 mg to healthy subjects, the parameters were as follows: Tmax = 4 hours; Cmax = 768 ng/mL; AUC = 10600 ng*hr/mL; Time to steady state, 12 hour dosing = 3-5 days Following repeated doses for Ivacaftor, accumulation occurs.

Volume of distribution

The mean apparent volume of distribution (Vz/F) of Ivacaftor after a single dose of 275 mg of Ivacaftor in the fed state was similar for healthy subjects and patients with CF. After oral administration of 150 mg every 12 hours for 7 days to healthy volunteers in a fed state, the mean (±SD) for apparent volume of distribution was 353 (122) L.

Protein binding

Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. Ivacaftor does not bind to human red blood cells.

Metabolism

Ivacaftor is extensively metabolized in humans. In vitro and clinical studies indicate that Ivacaftor is primarily metabolized by CYP3A. M1 and M6 are the two major metabolites of Ivacaftor in humans. M1 has approximately one-sixth the potency of Ivacaftor and is considered pharmacologically active. M6 has less than one-fiftieth the

potency of Ivacaftor and is not considered pharmacologically active.

Route of elimination

Following oral administration, the majority of Ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. The major metabolites M1 and M6 accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of Ivacaftor as unchanged parent.

Half-life

$t_{1/2}$ = 12 hours following a single dose.

Adversely effects

- ✓ Abdominal Pain
- ✓ Diarrhoea
- ✓ Dizziness
- ✓ Nasal Congestion
- ✓ Oropharyngeal Pain

Uses

- ✓ For the treatment of cystic fibrosis
- ✓ Improves the transport of chloride through the ion channel by binding to the channels directly to induce a non-conventional mode of gating which in turn increases the probability that the channel is open.
- ✓ It is used to treat people with cystic fibrosis who have the F508del mutation in CFTR.

Storage

Should be kept in a tightly closed container. Store at room temperature. Keep out of reach of children.

Dosage

It consists of 125 mg/l tab

Marketed formulation

Orkambi – Ivacaftor + Lumacaftor.

Drug Profile of Lumacaftor

Molecular structure

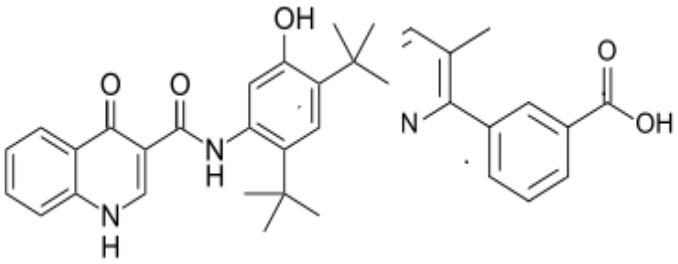

Fig. Structure of Lumacaftor

IUPAC Name 3-{6-[1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl) cyclopropaneamido]-3-methylpyridin-2-yl}benzoic acid.

CAS Number 936727-05-8

Drug Bank DB09280

Molecular formula $C_{24}H_{18}F_2N_2O_5$

Molecular weight 452.41 gm/mol

Category To improve breathing and reduce the risk of lung Infections

Description Lumacaftor is an experimental drug for the treatment of cystic fibrosis developed . The drug is designed to be effective in patients that have the F508del mutation in the cystic fibrosis transmembrane conductance regulator, the defective protein that causes the disease. F508del, meaning that the amino acid phenylalanine in position 508 is missing, is found in about 60% of cystic fibrosis patients in Europe and in about 90% of persons with some mutation in the CFTR gene.

Solubility Soluble in water and buffers at p^H 1-8 sparingly soluble in butanol, freely soluble in formic acid.

pK_a value 2.51

Mechanism of action

The CFTR protein is a chloride channel and is found on the surface of epithelial cells in many tissues and organs. Cystic fibrosis involves an F508del mutation which results in a lower amount of properly processed chloride channels and also less which are successfully trafficked to cellular surfaces. Furthermore, the mutated CFTR that are able to reach cell surfaces will not function optimally. Lumacaftor helps stabilize F508del-CFTR, allowing more processing and trafficking to occur which increases the amount of mature protein that will reach cell surfaces.

Pharmaco kinetic data

Absorption

Lumacaftor taken with fat-containing foods is absorbed 3 times higher when compared to the drug taken in a fasting state. When repeated doses of Lumacaftor combined with Ivacaftor are administered, increases in dose of Lumacaftor are generally correlated to increases in exposure over a range of 200 mg every.

Volume of distribution

Following oral administration of 200 mg of Lumacaftor every 24 hours to cystic fibrosis patients in a fed state for 28 days, the mean (± SD) for apparent volumes of distribution was 86.0 (69.8) L.

Protein binding

Lumacaftor is extensively protein bound in the plasma (99%) and binds primarily to albumin.

Metabolism

Lumacaftor is mostly excreted unchanged in the feces and is not extensively metabolized. When metabolism does occur, oxidation.

Route of elimination

Lumacaftor is primarily excreted unchanged in the feces (51%). A minimal amount of the parent compound and its metabolites.

Half-life

$t_{1/2}$ = Approximately 26 hours in patients who have cystic fibrosis.

Adversely effects

- ✓ Dyspnea
- ✓ Respiration Abnormal
- ✓ Diarrhea
- ✓ Nasopharyngitis
- ✓ Nausea

Uses

- ✓ To improve breathing
- ✓ Reduce lung infections
- ✓ To improve weight gain
- ✓ For the treatment of cystic fibrosis

Storage

Should be kept in a tightly closed container. It protects from moisture. Keep out of reach of children.

Dosage

It consists of 200 mg/1 tab.

Marketed formulation

Orkambi - Ivacaftor + Lumacaftor.

CONCLUSION

Cystic Fibrosis (CF) is a life-shortening inherited disease caused by the loss or dysfunction of the CF transmembrane conductance regulator (CFTR) channel activity resulting from mutations in the CFTR gene. Over the past 20-30 years, significant progress has been made in understanding the CF pathogenesis and development of effective CF therapies, which has dramatically increased the life expectancy of people with CF. The approval of CFTR modulators. With the technological advancements in drug discovery and personalized medicine, we have reasons to believe that the future is bright for effective and personalized CF therapies.

References

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