

# A European regulatory perspective on Cystic Fibrosis: current treatments, trends in drug development, and translational challenges for CFTR modulators

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**Table a.** List of medicinal products which received positive orphan designation for cystic fibrosis between 2001 and 2016

Active substance	Date of decision	Authorised medicine name	Product type
sodium nitrite and ethylenediaminetetraacetic acid (EDTA, edetic acid)	2016	-	Antibacterial
(6aR,10aR)-3-(1',1'-dimethylheptyl)-delta-8-tetrahydrocannabinol-9-carboxylic acid (JBT-101)	2016	-	Anti-inflammatory
Fixed-dose combination of fosfomicin disodium and tobramycin	2015	-	Antibiotic
Recombinant human acid ceramidase	2015	-	Anti-inflammatory
2-(7-ethoxy-4-(3-fluorophenyl)-1-oxophthalazin-2(1H)-yl)-N-methyl-N-(2-methylbenzo[d]oxazol-6-yl)acetamide	2015	-	CFTR modulator
Nitric oxide	2015	-	Antibacterial
Amikacin sulfate	2014	-	Antibiotic
4-[[[(1S,4S)-5-[[4-[4-(oxazol-2-yl)phenoxy]phenyl]methyl]-2,5-diazabicyclo[2.2.1]hept-2-yl]methyl]benzoic acid	2014	-	Anti-inflammatory
Nitric oxide	2014	-	Antibacterial
Lumacaftor / ivacaftor	2014	Orkambi	CFTR modulator
1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide	2014	-	CFTR modulator
Plasmid DNA encoding the human cystic fibrosis transmembrane conductance regulator gene complexed with a non-viral, cationic lipid based gene transfer agent	2014	-	Gene therapy
11-(4-Dimethylamino-3-hydroxy-6-methyl-tetrahydropyran-2-yloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-aza-	2014	-	Anti-inflammatory

Active substance	Date of decision	Authorised medicine name	Product type
cyclopentadecane-13,15-dione			
Cysteamine	2014	-	Mucolytic agent
Nitric oxide	2014	-	Antibacterial
Antisense oligonucleotide targeting the F508delta mutation of CFTR	2013	-	CFTR modulator
Pegylated recombinant anti-Pseudomonas aeruginosa antibody	2013	-	Antibacterial
4,6,4-trimethylangelicin	2013	-	CFTR modulator + anti-inflammatory
Recombinant human CXCL8 mutant	2013	-	Anti-inflammatory
Alpha-1 proteinase inhibitor	2012	-	Anti-inflammatory
Cysteamine	2011	-	Mucolytic agent
Sinapultide, dipalmitoylphosphatidylcholine palmitoyl-oleoyl phosphatidylglycerol, sodium salt and palmitic acid	2011	-	Mucolytic agent
Multilamellar microvesicle comprising phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol and cholesterol	2011	-	Mucolytic agent
Nafamostat mesilate	2010	-	Ion-transport modulator
3-(6-(1-(2,2-Difluorobenzo [d] [1,3] dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid (Lumacaftor)	2010		CFTR modulator
Hypothiocyanite / lactoferrin	2009	-	Antibacterial
Ciprofloxacin	2009	-	Antibiotic
Tobramycin	2009	Vantobra®	Antibiotic
Avian polyclonal IgY antibody against Pseudomonas aeruginosa	2008	-	Antibacterial
Levofloxacin hemihydrate	2008	Quinsair®	Antibiotic
N-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide	2008	Kalydeco®	CFTR modulator
Alpha1-proteinase inhibitor	2007	-	Anti-inflammatory
Alginate oligosaccharide (G-block) fragment	2007	-	Mucolytic agent
Ciprofloxacin	2007	-	Antibiotic
Amikacin sulfate	2006	-	Antibiotic
Heparin sodium	2006	-	Mucolytic agent
Tobramycin	2006	-	Antibiotic
Glutathione	2006	-	Anti-inflammatory
Denufosol tetrasodium	2005	-	Mucolytic agent
Heparin sodium	2005	-	Mucolytic agent
Mannitolum	2005	Bronchitol®	Mucolytic agent
3-[5-(2-Fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid	2005	-	CFTR modulator
Recombinant human bile-salt-stimulated lipase	2005	-	Lipases
Alpha-1 antitrypsin (inhalation use)	2004	-	Anti-inflammatory
Dexamethasone sodium phosphate encapsulated in human erythrocytes	2004	-	Anti-inflammatory

Active substance	Date of decision	Authorised medicine name	Product type
Aztreonam lysinate	2004	Cayston®	Antibiotic
Temocillin sodium	2004	-	Antibiotic
Engineered protein inhibitor of human neutrophil elastase	2003	-	Anti-inflammatory
Recombinant dog gastric lipase	2003	-	Lipases
Amiloride hydrochloride dihydrate	2003	-	Ion-transport modulator
Tobramycin	2003	Tobi Podhaler®	Antibiotic
Duramycin	2002	-	Ion-transport modulator
Carbamic acid (common)/[[4-[[3-[[4-[1-(4-hydroxyphenyl)-1-methyl-ethyl]phenoxy]methyl]phenyl]methoxy]-phenyl]iminomethyl]-,ethyl ester (amelubant)	2002	-	Anti-inflammatory
Colistimethate sodium	2002	Colobreathe®	Antibiotic
Octavalent Pseudomonas aeruginosa O-polysaccharide-toxin A conjugate	2001	-	Antibacterial
8-Cyclopentyl-1,3-dipropylxanthine	2001	-	CFTR modulator
L-Lysine-N-Acetyl-L-Cysteinate	2001	-	Mucolytic agent