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         |
| (6αR,10αR)-3-[(1',1'-dimethylheptyl)-delta-8-tetrahydrocannabinol-9-carboxylic acid (JBT-101) | 2016             | -                        | Anti-inflammatory      |
| Fixed-dose combination of fosfomycin disodium and tobramycin                     | 2015             | -                        | Antibiotic            |
| Recombinant human acid ceramidase                                                | 2015             | -                        | Anti-inflammatory      |
| 2-(7-ethoxy-4-(3-fluorophenyl)-1-oxopthalazin-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-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]cyclopropane| 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-yl)oxyl-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-oleyl phosphatidylglycerol, sodium salt and palmitic acid | 2011             | -                        | Mucolytic agent                     |
| Multilamellar microvesicle comprising phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidyserine, 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                       |
| Levofoxacin 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                     |
| Mannitol                                                                         | 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           |