MINISTRY OF HEALTH,
CONSUMER AFFAIRS
AND SOCIAL WELFARE

DIRECTORATE GENERAL FOR BASIC NHS
SERVICES PORTFOLIO AND PHARMACY

PHARMACOCLINICAL PROTOCOL FOR THE USE OF LUMACAFTOR/IVACAFTOR 100/125 (ORKAMBI 100/125®) AND TEZACAFTOR 100 MG AND IVACAFTOR 150 MG (SYMKEVI®) + IVACAFTOR 150 MG (KALYDECO ®) IN THE TREATMENT OF CYSTIC FIBROSIS IN THE NATIONAL HEALTH SYSTEM

Approved by the Permanent Pharmacy Commission

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All the experts have made a conflict of interest declaration

TABLE OF CONTENTS

1. INTRODUCTION

Cystic fibrosis (CF) is a chronic, progressive, autosomal recessive genetic disease caused by mutations in the gene coding for the cystic fibrosis transmembrane conductance regulator protein (CFTR). The CFTR acts primarily as a cyclic AMP-dependent chlorine channel. It is located on the apical surface of the epithelial cells in different organs such as the lungs, pancreas, intestine and others, where its dysfunction results in the dehydration of secretions which is responsible for the manner in which the disease manifests itself (chronic obstructive pulmonary disease, exocrine pancreatic insufficiency, etc.). Lung involvement is the leading cause of morbidity and mortality in CF patients (1). Other manifestations such as diabetes or liver disease, both related to cystic fibrosis, are also major causes of morbidity and mortality.

Mutations in the gene encoding the CFTR protein are classified according to the major functional defect they cause (1). Thus, class I mutations result in the virtual absence of the CFTR protein, class II mutations are characterised by an altered cell maturation process for the protein, class III mutations affect the regulation of the chloride channel, class IV mutations affect conduction through the chloride channel, class V mutations affect mRNA stability, and class VI mutations affect the stability of the mature protein on the cell surface. However, a single mutation can result in a protein with several defects. Thus, the class II F508del mutation is characterised not only by the synthesis of an altered CFTR protein that does not reach the apical surface of the epithelial cell, or where only a very small amount reaches the cell surface, but it is also characterised by the fact this protein results in defective channel opening.

Data from the 2016 annual report by the European Cystic Fibrosis Society (2), to which 22 cystic fibrosis units from our country contributed, show that almost 30% of the 1898 patients for whom data were provided were homozygous for the F508del mutation. Approximately 50% were patients heterozygous for F508del. No detailed data are available on the second mutation or on the allelic prevalence of mutations with residual function.

Currently, the treatment of CF patients consists of managing the symptoms and signs resulting from altered CFTR activity, mainly lung disease and exocrine pancreatic insufficiency. These treatments include respiratory physiotherapy, nutritional support, inhaled antibiotics (e.g. in patients with chronic Pseudomonas aeruginosa lung infection), azithromycin, inhaled dornase alfa, inhaled hypertonic saline and pancreatic enzyme replacement therapy (in patients with exocrine pancreatic insufficiency).

The combination of lumacaftor/ivacaftor (LUM/IVA) and tezacaftor and ivacaftor (TEZ/IVA) represents a different therapeutic approach to the above-mentioned symptomatic treatment as the target of both drugs is the abnormal CFTR protein.

2. TREATMENT OBJECTIVE

The goal of treatment with ORKAMBI 100/125 (LUM/IVA) and SYMKEVI (TEZ/IVA)+KALYDECO (IVA) is to slow down the deterioration in lung function in patients and to prevent the occurrence of pulmonary exacerbations due to the accelerated deterioration of the lungs and the impact this has on the survival of CF patients.

3. PATIENT SELECTION CRITERIA

Candidates for initiation of treatment with ORKAMBI 100/125 and SYMKEVI+KALYDECO include those patients who **meet <u>all</u> the following criteria, which must be adequately documented.**

ORKAMBI 100/125 (LUM/IVA):

1) Age between 6 and 11 years and clinically stable.

2) Patients with confirmed diagnosis of Cystic Fibrosis (CF) homozygous for the F508del mutation in the CFTR gene.

SYMKEVI (TEZ/IVA)+KALYDECO (IVA):

1) Age over 11 years and clinically stable.

2) Patients with confirmed diagnosis of Cystic Fibrosis (CF) homozygous for the F508del mutation or heterozygous for the F508del mutation with one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G and 3849+10kbC→T.

LUM/IVA 100/125 and COMPLEXION/IVA + IVA should not be administered in the following cases:

1) Hypersensitivity to the active substance(s) or to any of the excipients contained in the medicinal products.
2) Tezacaftor in combination with ivacaftor in patients with CF heterozygous for the F508del mutation who have a second mutation in the CFTR gene that is not included in the approved indications in the data sheet.

There are uncertainties in the following clinical situations as they were criteria for exclusion from pivotal trials:

TEZ/IVA:

- Patients with ppFEV$_1$ <40 percentage points and >90 percentage points.
- Patients with non-stable disease (upper and lower respiratory infections, presence of pulmonary exacerbation or changes in treatment within 4 weeks prior to initiation of study therapy). Do not initiate treatment until the patient is clinically stable.
- Patients with a history of colonisation by microorganisms associated with a rapid decrease in lung function.
- Patients with an increase equal to or greater than 3 times the upper limit of normal (ULN) in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) or total bilirubin ≥ 2 x ULN .
- Patients with impaired renal function Patients with a QTc interval >450 msec.

LUM/IVA:

- Patients with ppFEV$_1$ <70 percentage points. It should be borne in mind that at the beginning of treatment there is a risk lung function will worsen.

- Patients weighing <15 kg
- Patients with non-stable disease (upper and lower respiratory infections, presence of pulmonary exacerbation or changes in treatment within 4 weeks prior to initiation of study therapy). Do not initiate treatment until the patient is clinically stable.
- Patients with a history of colonisation by microorganisms associated with a rapid decrease in lung function.
- Patients with an increase equal to or greater than 3 times the upper limit of normal (ULN) in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) or total bilirubin ≥ 2 x ULN.

4. GENERAL CONSIDERATIONS FOR TREATMENT

Hepatic function

It is recommended that aminotransferases (ALAT or ASAT) be evaluated in all patients prior to initiation of treatment, every 3 months during the first year of treatment, and annually thereafter. More frequent monitoring should be considered in patients with a history of increased aminotransferases. In cases of significant increases in aminotransferases (e.g. patients with ALAT or ASAT >5 times the upper limit of normal (ULN), or ALAT or ASAT >3 times the ULN with bilirubin >2 times the ULN), administration should be discontinued and patients should be closely monitored by laboratory testing until the abnormal values subside. Once the increased aminotransferases subside, the benefits and risks of resuming treatment should be considered.

Patients after an organ transplant

Neither TEZ/IVA in combination with IVA nor LUMA/IVA have been studied in patients with cystic fibrosis who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended.

Interactions with other medicinal products

CYP3A inducers

Exposure to TEZ and IVA as well as LUM/IVA may be reduced by the concomitant use of CYP3A inducers, potentially resulting in reduced efficacy of TEZ/IVA, IVA and LUMA/IVA. Therefore, co-administration with strong CYP3A inducers is not recommended.

CYP3A inhibitors

The dose of TEZ/IVA and IVA should be adjusted when used concomitantly with strong or moderate CYP3A inhibitors.

Table 1: Dosing recommendations for concomitant use with moderate CYP3A inhibitors				
	Day 1	Day 2	Day 3	Day 4*
Morning dose				
Tablet of tezacaftor 100 mg/ivacaftor 150 mg	√	-	√	-
Tablet of ivacaftor 150 mg	-	√	-	√
Evening dose				
Tablet of ivacaftor 150 mg	-	-	-	-
* Continue alternating each day				

In concomitant administration with potent CYP3A inhibitors (e.g. ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin), the dose should be adjusted to one TEZ/IVA tablet twice weekly, to be taken at 3-4 day intervals. The evening dose of ivacaftor should not be taken.

Co-administration of LUM/IVA with itraconazole did not affect LUM exposure, although it increased IVA exposure by 4.3-fold. Due to the steady-state inducing effect of LUM on CYP3A, the exposure of IVA when co-administered with a CYP3A inhibitor is not expected to exceed the exposure observed when administered without LUM at a dose of 150 mg every 12 hours, the approved dose of IVA in monotherapy.

No dose adjustment is necessary when initiating CYP3A inhibitors in patients taking LUM/IVA. However, when initiating LUM/IVA administration in patients who are taking strong CYP3A inhibitors, the dose should be reduced to one tablet per day (100mg/125mg) during the first week of treatment for patients
who are 6 to 11 years old. After this period, the recommended daily dose should be continued. This recommendation should also be followed in the case of discontinuing the administration of LUM/IVA for more than one week.

There are several established drug-drug interactions and other potentially significant interactions not listed in this protocol, especially with LUM/IVA, it is, therefore, recommended that the data sheets be consulted in case of any doubt regarding possible interactions.

Hepatic impairment

TEZ/IVA is not recommended for use in patients with severe hepatic impairment unless the expected benefits outweigh the risks.

For dose adjustments in patients with hepatic impairment, see Table 2. There is no experience of using TEZ/IVA in patients with severe hepatic impairment (Child-Pugh Class C); therefore, its use is not recommended unless the benefits outweigh the risks. In such cases, TEZ/IVA should be used at a reduced dose.

Table 2: Dosing recommendations for use in patients with hepatic impairment			
	Mild (Child-Pugh Class A)	Moderate (Child-Pugh Class B)	Severe (Child-Pugh Class C)
Morning	No dose adjustment is necessary	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily.	One morning tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily or less frequently. Dosing intervals should be modified according to clinical response and tolerability.
Evening	No dose adjustment is necessary	No evening dose	No evening dose

For patients with moderate hepatic impairment (Child-Pugh Class B), dose reduction of LUM/IVA is recommended. There is no experience of using LUMA/IVA in patients with severe hepatic impairment (Child-Pugh Class C), but exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, after weighing the risks and benefits of treatment, LUM/IVA should be used with caution at a reduced dose. See Table 3 for dose adjustments in patients with hepatic impairment.

Table 3. Recommendations for dose adjustment of LUM/IVA in patients aged 6 to 11 with hepatic impairment

Hepatic impairment	Dose adjustment	Total daily dose
Mild hepatic impairment (Child-Pugh Class A)	No dose adjustment is necessary	400mg LUM+500mg IVA
Moderate hepatic impairment (Child-Pugh Class B)	2 tablets of 100mg/125mg in the morning + 1 tablet of 100mg/125mg in the evening (12 hours later)	300mg LUM+375mg IVA
Severe hepatic impairment (Child-Pugh Class C)	1 tablet of 100mg/125mg in the morning + 1 tablet of 100mg/125mg in the evening (12 hours later) or one reduced daily dose	200mg LUM+250mg IVA or a reduced daily dose

Renal impairment

Caution is recommneded when TEZ/IVA is used in combination with IVA or LUM/IVA in patients with severe renal impairment or end-stage renal disease.

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with LUMA/IVA, TEZ/IVA in combination with IVA, as well as with IVA alone. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to treatment cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended for paediatric patients initiating treatment with these drugs.

5. OUTCOME VARIABLES (BASED ON OBJECTIVES INCLUDED IN THE PAYMENT-BY-RESULTS AGREEMENT)

Measurements will be taken 24, 48, and 72 weeks from the start of treatment.

The response variables to evaluate are:

A.1. The percent predicted forced expiratory volume in 1 second (ppFEV1) does not decline by more than 5% in absolute percentage from the pre-treatment assessment in patients aged 6 years and older.

A.2. Pulmonary exacerbations (PE). Evaluations adjusted to clinical practice, and there may be a variation of +/- 4 weeks from the planned time:

a) *Measurement at 24 weeks*:

a.1) There is a reduction of at least one PE with hospitalisation and/or IV antibiotic treatment in the period 0-24 weeks, compared to the same 24 weeks in the previous year (for example, January-June vs January-June the previous year).

a.2) Patients without PE in the previous period: maintenance of absence of pulmonary exacerbation with hospitalisation and/or IV antibiotic treatment in the period 0-24 weeks, compared to the same 24 weeks the previous year.

b) *Measurement at 48 weeks*: maintenance in the number of PE with hospitalisation and/or IV antibiotic treatment with respect to the previous 24 weeks.

c) *Measurement at 72 weeks*: maintenance in the number of PE with hospitalisation and/or IV antibiotic treatment with respect to the previous 24 weeks.

B) Conditions for the patient to be considered as a responder:

- Patients who meet both criteria (A1 and A2) are responders and continue treatment.
- Patients who do not meet any criteria are non-responders and their treatment should be discontinued
- Patients who at week 24 or 48 or 72 meet PE responder criteria but not ppFEV1 will be considered responders in that measurement cycle. These patients will have to meet both criteria in the next measurement, if applicable

In the next measurement, if they do not comply with the two variables included in the payment-by-results agreement, they will be considered non-responders for the last period in which the measurement was made.

Patients who fail the FEV1 criterion in two of the three evaluations will be considered non-responders.

Explanatory table for considering patients a responder in the case of responding to the variable pulmonary exacerbations and not to ppFEV1.

	24 weeks	**48 weeks**	**72 weeks**	**Responder Yes/no at 72 weeks**
COMPLIES WITH ppFEV1 VARIABLE?	COMPLIES	COMPLIES	NOT COMPLIANT	YES
	COMPLIES	NOT COMPLIANT	NOT COMPLIANT	NO
	NOT COMPLIANT	COMPLIES	COMPLIES	YES
	NOT COMPLIANT	COMPLIES	NOT COMPLIANT	NO
	COMPLIES	NOT COMPLIANT	COMPLIES	YES
	NOT COMPLIANT	NOT COMPLIANT		Non-responder at 48 weeks

Monitoring to assess clinical effectiveness and safety will be conducted every 24 weeks from week 72.

6. EVALUATION AND MONITORING

The doctor responsible for the patient in each of the stages of the process must register the following information in VALTERMED.

General patient details (to be collected in VALTERMED before starting treatment to carry out the evaluation):

- NHS code[1]
- CIP/CITE code[1]:
- NIF/NIE[1]
- Health Card No.[1]
- Medical Record No.:
- Sex[2]:
- Date of birth[2]:

DISEASE CHARACTERISATION AT THE BEGINNING OF TREATMENT

BASELINE DATA (mandatory)

- CF diagnosis date:
- Mutation:
- $ppFEV_1$[3]: Date:
- No. of PE in the 12 months prior to starting treatment:
  No. PE with hospitalisation Date:
  No. PE requiring IV antibiotic treatment at home Date:
  Total days IV antibiotic treatment (optional):
- Anthropometric data prior to therapy. Weight (kg): Height (cm): Date:

Optional baseline data (paragraphs 1 to 6) (value and date):

1. **Pulmonary assessment**

   1.1. Respiratory function data

[1] It is mandatory to fill in at least one of these fields
[2] Required fields
[3] Theoretical spirometry values according to the Global Lung Function Initiative (GLI-2012)

Spirometry **Date:**

FEV1 mL:

Forced vital capacity (FVC) mL

ppFVC

FEV1/FVC

Plethysmography **Date:** Total

lung capacity (TLC) mL ppTLC

Residual volume (RV) mL

ppRV

Diffusion **Date:**

Diffusing capacity of the lungs for carbon monoxide (DLCO)

Diffusing capacity per unit lung volume (KCO)

6-metre walk test (WT6M) **Date:**

Distance in metres

Initial oxygen saturation S(O_2I) %

Final oxygen saturation (SO_2(F) %

SO_2 mean %

Heart rate (HR) Borg

Dyspnoea:

1.2. Imaging tests data

Computed tomography, Bhalla Scoring System[4,5] Date:

- Global score:
  - Air entrapment
  - Atelectasis
  - Mucous plugs
  - Severity of bronchiectasis
  - Gravity peribronchial thickening
  - Bronchiectasis extent
  - Emphysema
  - No. bullae

[4] Albi G, Rayón-Aledo JC, Caballero P, Rosado P, García-Esparza E. [Cystic fibrosis in images: the Bhalla scoring system for computed tomography in paediatric patients]. Radiology. 2012 May-Jun;54(3):260-8.
[5] Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, Naidich DP. Cystic fibrosis: scoring system with thin-section CT. Radiology. 1991Jun;179(3):783-8.

- No. bronchial generations

2. Digestive/hepatic parameters

Abdominal data **Date:**

Signs of esophageal varicose veins Use of ursodeoxycholic acid

Faecal elastase (<200mcg/g->200mcg/g): Hepatomegaly

Splenomegaly

Cirrhosis

Hepatic steatosis

Fibroscan data:

- Median in kilopascals
- IQR/median (as %)

Liver biopsy data **Date**

Steatosis >5% (yes/no)

Steatohepatitis (yes/no)

Fibrosis: 0-1-2-3-4.

3. Bone metabolism tests

Densitometry **Date**

Osteopenia (YES/NO)

- Hip (YES/NO)
- Spine (YES/NO)

Osteoporosis (YES/NO)

- Hip (YES/NO)
- Spine (YES/NO)

4. Analytical data

General analytical data **Date**

C-reactive Protein (CRP)

Erythrocyte sedimentation rate (ESR) Fibrinogen

Aspartate aminotransferase (GOT) Alanine aminotransferase (GPT) Gamma-glutamyl transpeptidase (GGT)

Alkaline phosphatase

Total bilirubin

Conjugated bilirubin

Platelets

Vitamin A

Vitamin E

Vitamin D

Prealbumin Total

cholesterol HDL

cholesterol

Microbiology data (Sputum test) Date

Primary infection by *Pseudomonas aeruginosa (P. aeruginosa):*

P. aruginosa eradication:

Chronic bronchial infection by *P. aruginosa:*

Primary infection by methicillin-resistant *Staphylococcus aureus* (MRSA): MRSA eradication:

Chronic bronchial MRSA infection:

Primary infection by other potentially pathogenic microorganisms (PPM): PPM eradication:

Chronic bronchial PPM infection:

Other infections:

- Fungi (Yes/No)
  - Which:
- NTM Non-tuberculous mycobacteria (NTM) (Yes/No)
  - Which:
- Other:

5. Other complications

Diabetes (Type) Date:

Hydrocarbon intolerance (YES/NO) Date:

Ophthalmological examinations: Lens opacity/cataracts Date:

6. Quality of life questionnaire (adults) - CFQR 14 VALIDATED[6] Date:

[6] Oliveira G et al. Validation of the Spanish version of the revised quality of life questionnaire for cystic fibrosis in adolescents and adults (CFQR 14+ Spain). Arch Bronconeumol 2010; 46(4):165-75. Disponible on:v

PREVIOUS AND CONCOMITANT TREATMENTS

All previous treatments received must be justified.

Administration of Orkambi 100/125 or TEZ/IVA+IVA

- Start date of treatment.
- Dosage and schedule.
- Treatment interruptions: reasons and dates.
- Discontinuations of treatment:

  Patient decision, due to adverse effects, due to lack of efficacy, other

  Date:

MEASUREMENT AT 24 WEEKS FROM START OF TREATMENT (mandatory)

No. PE:

No. PE with hospitalisation Date:

No. PE requiring IV antibiotic treatment at home Date:

Total IV antibiotic treatment days:

ppFEV1. Date:

Anthropometric data. Weight (kg): Height (cm): Date:

Medicinal product-related adverse reactions leading to interruption or discontinuation of treatment[7]:

MEASUREMENT AT 48 WEEKS FROM START OF TREATMENT (mandatory).

No. PE:

No. PE with hospitalisation Date:

No. PE requiring IV antibiotic treatment at home Date:

Total IV antibiotic treatment days:

https://www.archbronconeumol.org/es-validacion-version-espanola-del-cuestionario-articulo-S0300289610000414

[7] Safety or tolerability problems leading to discontinuation of treatment must be reported. These problems should be exclusively and unequivocally correlated with the drug, ruling out any other possibility due to concomitant drugs.

ppFEV1. Date:

Anthropometric data. Weight (kg): Height (cm): Date:

Medicinal product-related adverse reactions leading to interruption or discontinuation of treatment[7]:

MEASUREMENT AT 72 WEEKS FROM THE START OF TREATMENT (mandatory).

No. PE:

No. PE with hospitalisation Date:

No. PE requiring IV antibiotic treatment at home Date:

Total IV antibiotic treatment days:

ppFEV1. Date:

Anthropometric data. Weight (kg): Height (cm): Date:

Medicinal product-related adverse reactions leading to interruption or discontinuation of treatment[7]:

MEASUREMENT AT 96 WEEKS FROM THE START OF TREATMENT AND EVERY 24 WEEKS.

No. PE:

No. PE with hospitalisation Date:

No. PE requiring IV antibiotic treatment at home Date:

Total IV antibiotic treatment days:

ppFEV1. Date:

Anthropometric data. Weight (kg): Height (cm): Date:

Medicinal product-related adverse reactions leading to interruption or discontinuation of treatment[7]:

SAFETY Continuous safety monitoring will be carried out. In addition, all suspected adverse reactions will be reported through the appropriate regional pharmacovigilance centre (www.notificaram.es).

In particular, the following must be recorded:

- Suspected adverse reactions leading to interruption or discontinuation of treatment.

  Adverse reactions: Suspension/abandonment: Date:

Hepatobiliary disorders: YES/NO

Respiratory disorders: chest discomfort, dyspnoea and abnormal breathing. YES/NO

Distal intestinal obstruction syndrome (DIOS). YES/NO

High Blood Pressure: YES/NO

Lens opacity/cataracts YES/NO

Other adverse effects.

Transplant: YES/NO Date:

Exitus: YES/NO Date:

Optional data at 48 weeks (+/- 4 weeks) (value and date):

1. Pulmonary assessment

1.1. Respiratory function data

Spirometry Date:

FEV1 mL:

FVC mL

ppFVC

FEV1/FVC

Plethysmography Date:

TLC mL

ppTLC

Residual volume (RV) mL

ppRV

Diffusion Date:

DLCO

KCO

6-metre walk test (WT6M) Date:

Distance in metres

SO_2I %

SO_2F %

SO_2 mean %

HR

Borg Dyspnoea:

1.2. Imaging tests data

Computed tomography, Bhalla Scoring System[8,9] Date:

- Global score:
  - Air entrapment
  - Atelectasis
  - Mucous plugs
  - Severity of bronchiectasis
  - Gravity peribronchial thickening
  - Bronchiectasis extent
  - Emphysema
  - No. bullae
  - No. bronchial generations

2. Digestive/hepatic parameters

Abdominal data Date:

Signs of esophageal varicose veins Use of ursodeoxycholic acid

Faecal elastase (<200mcg/g->200mcg/g):

Hepatomegaly

Splenomegaly

Cirrhosis

Hepatic steatosis

Fibroscan data:

- Median in kilopascals
- IQR/median (as %)

Liver biopsy data Date

Steatosis >5% (yes/no)

[8] Albi G, Rayón-Aledo JC, Caballero P, Rosado P, García-Esparza E. [Cystic fibrosis in images: the Bhalla scoring system for computed tomography in paediatric patients]. Radiology. 2012 May-Jun;54(3):260-8.
[9] Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, Naidich DP. Cystic fibrosis: scoring system with thin-section CT. Radiology. 1991Jun;179(3):783-8.

Steatohepatitis (yes/no) Fibrosis: 0-1-2-3-4.

3. Bone metabolism tests

Densitometry **Date**

Osteopenia (YES/NO)

- Hip (YES/NO)
- Spine (YES/NO)

Osteoporosis (YES/NO)

- Hip (YES/NO)
- Spine (YES/NO)

4. Analytical data

General analytical data **Date**

CRP
ESR
Fibrinogen
GOT
GPT
GGT
Alkaline phosphatase
Total bilirubin Conjugated
bilirubin Platelets
Vitamin A Vitamin
E Vitamin D
Prealbumin Total
cholesterol HDL
cholesterol

Microbiology data (Sputum test) **Date**

Primary infection by *P. aruginosa: P. aruginosa* eradication:

Chronic bronchial infection by *P. aruginosa:*

Primary infection by MRSA:

MRSA eradication:

Chronic bronchial MRSA infection:

Primary infection by other PPMs:

PPM eradication:

Chronic bronchial PPM infection:

Other infections:

- Fungi (Yes/No)
  - Which:
- NTM Non-tuberculous mycobacteria (NTM) (Yes/No)
  - Which:
- Other:

5. Other complications

Diabetes (Type) Date:

Hydrocarbon intolerance (YES/NO) Date:

Ophthalmological examinations: Lens opacity/cataracts Date:

6. Quality of life questionnaire (adults) - CFQR 14 VALIDATED[10] Date:

[10] Oliveira G et al. Validation of the Spanish version of the revised quality of life questionnaire for cystic fibrosis in adolescents and adults (CFQR 14+ Spain). Arch Bronconeumol 2010; 46(4):165-75. Available on:v https://www.archbronconeumol.org/es-validacion-version-espanola-del-cuestionario-articulo-S0300289610000414

1 APPENDIX

The definition of PE will be based on the definition proposed by the EuroCareCF Working Group, 2011

EuroCareCF WG Definition (Bilton JCF 2011)
A PE is defined as the need for complementary antibiotic treatment, indicated by a recent modification based on at least 2 of the following elements: - Modification in sputum volume or colour - Increased cough - Malaise, fatigue or lethargy - Anorexia or weight loss - Decrease in lung function by 10% - Radiographic modification - Increased dyspnoea

2 BIBLIOGRAPHY

1. Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. Lancet Respir Med. 2013; 1 (2): 158-63.
2. European Cystic Fibrosis Society (ECFS) Patient Registry (ECFSPR) Annual Report 2016. Orenti A, Zolin A, Naehrlich L, van Rens J et al, 2018. Available on: https://www.ecfs.eu/sites/default/files/general-content-images/working-groups/ecfs-patient-registry/ECFSPR_Report2016_06062018.pdf (6 de febrero de 2019).
3. Positioning report on treatment with SUMKEVI.AEMPS https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-tezacaftor-ivacaftor-Symkevi.pdf?x61620
4. Authorised data sheet Orkambi 100 mg/125 mg film-coated tablets. Information available on https://cima.aemps.es/cima/pdfs/ft/1151059005/FT_1151059005.pdf : [Accessed 25/10/2019].
5. Authorised data sheet Symkevi 100 mg/150 mg film-coated tablets. Information available on https://cima.aemps.es/cima/dochtml/ft/1181306001/FT_1181306001.html: [Accessed 25/10/2019].
6. Authorised data sheet Kalydeco 150 mg film-coated tablets. Information available on

https://cima.aemps.es/cima/pdfs/ft/112782001/FT_112782001.pdf[Accessed 25/10/2019].

7. P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations Eur Respir J. 2012;40:1324-43.
8. Bilton D, Canny G, Conway S, Dumcius S, Hjelte L, Proesmans M, et al. Pulmonary exacerbation: towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2011;10 Suppl 2:S79-81.