**SUPPLEMENTARY FILE 5: SUMMARY OF THE EVIDENCE – NON-IPF PF-ILD**

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| ***The summary of the evidence presented in this document was intended to help the experts to score the pathology and nintedanib, authorized in August 2020, for non-IPF PF-ILD.*** |

1. **Drug Description**

*Type of drug / category of intervention*: Nintedanib is a molecule that simultaneously inhibits three types of tyrosine kinase receptors, blocking the proliferation, migration and transformation of fibroblasts that are involved in the process of pulmonary fibrosis.

*Indication*: Nintedanib been marketed in Spain since December 2015 for the treatment of adults with idiopathic pulmonary fibrosis (IPF). Recently, it has received authorization in Spain from the Spanish Agency for Medicines and Health Products (AEMPS) for two new indications:

* On July 22, 2020, it received marketing authorization for the indication of interstitial lung disease associated with systemic sclerosis (SSc-ILD).
* On August 5, 2020, it received authorization for the indication in adult patients with non-IPF PF-ILD. The evidence presented in this document focuses on this new indication.

*Administration*: Oral, capsules of 100 mg or 150 mg.

1. **Disease severity**

* Some patients with interstitial lung disease (ILD) may develop a progressive fibrotic behavior characterized by a progressive deterioration in lung function that is maintained regardless of the initial cause and can lead to a great impact on the patient's life and early mortality. Idiopathic pulmonary fibrosis (IPF) is the prototype of progressive pulmonary fibrosis.
* The estimated time between the appearance of the first symptoms of ILD and the diagnosis of non-IPF PF-ILD is between 2.5 and 3 years.
* The mortality of patients with non-IPF PF-ILD could be like that of patients with IPF, given the similarity between the pathologies. The median survival of people with IPF is between 3 and 5 years. In studies with patients with non-IPF PF-ILD, the median overall survival was between 2.6 and 7 years.
* The main predictors of mortality in patients with non-IPF PF-ILD are the decrease in forced vital capacity (FVC), the presence of honeycombing and the extent of fibrosis in HRCT and acute exacerbations.
* Non-IPF PF-ILD is a limiting disease with a high impact for patients, which presents a course similar to that of IPF with worsening of symptoms, decreased lung function, reduced health-related quality of life (HRQoL), presence of dyspnea, dry cough and impairment in the ability to carry out daily activities.

1. **Unmet needs**

* In clinical practice, the pharmacological treatment of patients with non-IPF PF-ILD is based on off - label treatment of the underlying disease, which aims to treat the original disease and reduce symptoms, although they have been shown to be associated to poor tolerability and serious adverse effects.
* The approval by the AEMPS, on August 5, 2020, of the first specific treatment for non-IPF PF-ILD represents an advance for the therapeutic management of these patients, since it is a drug that specifically addresses the fibrotic mechanisms associated with the disease.

1. **Effectiveness**

* Nintedanb slows the progression of the disease in non-IPF PF-ILD patients, reducing the annual rate of decline in FVC by approximately 57% compared to placebo (after 52 weeks of treatment) in the total study population.
* The drug manages to slow the deterioration of FVC, regardless of the fibrotic pattern that appears on HRCT.
* The drug reduces the risk of suffering a first acute exacerbation or death by up to 32-33% at 52 weeks compared to the control group.
* The estimated maximum effect suggests that the annual rate of decline in FVC can be reduced to nearly the natural loss of FVC that occurs with age (approximately 25-30 mL/year), regardless of differences in the natural history of the illness.

1. **Safety / tolerability**

* The safety profile of nintedanib is related to adverse events mainly of mild or moderate intensity, which are managed, in most cases, with symptomatic treatment and/or interruption or temporary reduction of treatment.
* The adverse events that occurred to a greater extent in patients treated with nintedanib were gastrointestinal.
* Diarrhea occurred in 66.9% of drug-treated patients and 23.9% of placebo-treated patients.

1. **Patient reported outcomes**

* In the clinical trial of nintedanib, patients with non-IPF PF-ILD experienced a small improvement in health-related quality of life, of 0.55 points at week 52.

1. **Type of therapeutic benefit**

* Nintedanib modifies the course of the disease, being associated with symptom relief (dyspnea and cough) and a reduction in the time to death.
* The demonstrated efficacy of nintedanib could translate into an increase in patient survival, given that there is an association between the continued decrease in FVC and increased mortality.

1. **Cost of intervention**

* The annual cost of acquiring nintedanib, considering the usual dose described in the technical sheet and the notified price, is €29,247 per patient with non-IPF PF-ILD treated.
* It should be borne in mind that this drug has a price financed by the Spanish NHS that is lower than the notified price.

1. **Other medical costs**

* No specific evidence is available for this criterion. Experts must score it trying to determine to what extent the improvement in health produced with nintedanib would translate into a lower consumption of health resources compared to the use of placebo.
* It is documented that, in Europe, non-IPF PF-ILD is associated with a cost per patient 1.8 times higher than interstitial lung diseases with no or slow progression of fibrosis.
* In Spain, a patient with IPF with rapid disease progression represents a cost 5 times higher than that associated with a patient with stable disease, and almost 3 times higher than that of a patient with slow disease progression.

1. **Non-medical costs**

* There are no studies regarding the impact of nintedanib on other costs (formal and informal care, loss of work productivity) of patients with non-IPF PF-ILD.
* The score must therefore be based on the experts´ experience and/or intuition, trying to assess to what extent the improvement produced by nintedanib in the patient's health could be reflected in a lower loss of work productivity for the patient or in lower costs in personal care.
* Two studies have estimated the possible effects of starting pharmacological treatment on other costs in patients with IPF. In one of them, the introduction of the drug was associated with a 62% reduction in productivity loss (€13,306 vs. €5,164 per year, per patient).

1. **Quality of evidence**

* The trial on which the data on efficacy, safety/tolerability and results reported by patients with non-IPF PF-ILD treated with nintedanib is based is a trial that follows the guidelines of Good Clinical Practices and which was carried out in accordance with the ethical standards of Directive 2001/20/EC.

1. **Clinical practice guidelines**

* There are no specific clinical practice guidelines for non-IPF PF-ILD.
* Studies that reviewed the recent available clinical evidence concluded that this evidence supports: (i) the use of nintedanib in certain groups of patients with non-IPF PF-ILD; (ii) a combined use of nintedanib and immunosuppressive therapy in patients with non-IPF PF-ILD, and that (iii) nintedanib could be also considered as second-line treatment.
* An opinion article recommends the immediate initiation of treatment with nintedanib, after the detection of two risk factors, which are the extension of fibrosis greater than 20% and the presence of honeycombing.

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