**SUPPLEMENTARY FILE 5: SUMMARY OF THE EVIDENCE – SSc-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 July 2020 for systemic sclerosis-associated interstitial lung disease (SSc-ILD).*** |

1. **Drug Description**

*Type of drug / category of intervention*: Nintedanib is a molecule that inhibits tyrosine kinases involved in the pathogenic pathways of systemic sclerosis and interstitial lung disease: the growth factor receptor derived from platelets, the receptor for fibroblast growth factor and the receptor for vascular endothelial growth factor. Consequently, the proliferation, migration and transformation of fibroblasts are inhibited, thus achieving the remodeling of fibrotic tissue in interstitial lung diseases.

*Indication*: Nintedanib has been marketed in Spain since December 2015 for the treatment of adults with idiopathic pulmonary fibrosis (IPF). Recently (July 22, 2020), it has received marketing authorization in Spain from the Spanish Agency for Medicines and Health Products (AEMPS) in the indication of interstitial lung disease associated with systemic sclerosis (SSc-ILD). The evidence presented in this document focuses on this new indication:

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

1. **Disease severity**

* Interstitial lung disease associated with systemic sclerosis is a serious autoimmune disease characterized at the level of the lung parenchyma by damage to endothelial and epithelial cells, and activation of the coagulation and inflammation cascades, causing pulmonary fibrosis. Between 35% and 52% of patients with systemic sclerosis are diagnosed with interstitial lung disease (43% in Spain).
* ILD is mainly diagnosed between 3 and 5 years from the diagnosis of SSc.
* ILD-ES generally affects young patients and the median overall survival is between 5 and 8 years and up to 11 years from diagnosis.
* In healthy adults, the rate of reduction in lung function, measured by FVC, is around 25-30 mL /year, while in patients with SSc-ILD, this decline is between 80 and 110 mL /year.
* The clinical manifestations of interstitial lung disease associated with systemic sclerosis, such as dyspnea and cough, have been shown to be involved in the reduction of the physical capacities of patients, as well as HRQoL

1. **Unmet needs**

* Until the authorization of nintedanib, in July 2020, there was no specific treatment authorized for SSc-ILD that modified or prevented the progression of interstitial lung disease associated with systemic sclerosis.
* Until then, actual practice was based on the use of off-label drugs, with more limited scientific evidence and tolerability problems, which act mainly on inflammatory and immunological pathways.

1. **Effectiveness**

* Nintedanib reduced the decline in FVC by 44% over 52 weeks compared to placebo. The drug has also been shown to be effective against placebo in the other variables related to lung function.
* In the efficacy variables that measure pulmonary diffusing capacity, skin involvement derived from SSc, and mortality, the drug has not shown efficacy compared to placebo.

1. **Safety / tolerability**

* The safety profile of nintedanib for SSc-ILD is related to adverse events mainly of mild or moderate intensity, which are managed, in most of them, with symptomatic treatment and/or the interruption or temporary reduction of treatment.
* The most common adverse event was diarrhoea, which was reported in 75.7% of treated patients and 31.6% of patients in the placebo group.
* Nasopharyngitis and cough were events observed less frequently in the treatment group than in the placebo group.
* Serious adverse events occurred similarly in both groups and were fatal in 1.7% of those treated with nintedanib and in 1.4% of the placebo group.
* More than 80% of patients remained on treatment with nintedanib at 52 weeks.

1. **Patient reported outcomes**

* The observed variations in patient-reported outcomes on questionnaires measuring respiratory capacity, dyspnea, and indices of disability did not differ significantly between trial groups.
* Nintedanib does not have a curative effect, but instead slows down the decline in FVC. For this reason, patient-reported outcomes tend to remain stable at best, which represents a positive effect, based on the natural trajectory of worsening quality of life in these patients.

1. **Type of therapeutic benefit**

* Nintedanib modifies the clinical course of the disease, being associated with a smaller decrease in the patient's FVC over time.
* The demonstrated efficacy of nintedanib could translate into increased patient survival given that there is an association between continued deterioration of FVC and increased mortality.

1. **Cost of intervention**

* The annual cost of acquisition and administration of nintedanib, considering the dose described in the technical sheet and the notified price, is €29,247 for each patient with SSc-ILD treated.
* This drug also has a financed price, which applies to users of the National Health System and, therefore, to the majority of patients with this pathology. Although the financed price of the drug authorized in the indication is not known, in 2019, a price analysis that included 579 drugs concluded that the average difference between the notified price and the financed price was 82.3%, and the median, 43.1%.

1. **Other medical costs**

* No specific evidence is available for this criterion. The experto 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.
* The evidence indicates that the costs associated with SSc increase substantially with the appearance of SSc-ILD, up to double, from which it could be inferred that better control of the disease would be associated with lower direct healthcare costs.
* The costs of hospitalization and outpatient visits are the most relevant within the total direct healthcare costs of these patients. Follow-up costs can represent up to 90% of the costs for each patient in SSc-ILD. Hospitalizations form the largest part of these costs.
* The costs of patients with severe SSc-ILD are 2 times higher than the costs of patients with mild SSc-ILD, and 46% higher than the costs of patients with moderate SSc-ILD.

1. **Non-medical costs**

* No specific evidence is available for this criterion.
* The score must therefore be based on the experts´ experience and/or intuition, trying to assess to what extent the improvement produced by the drug 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 or social services.
* In Spain, patients with SSc have high indirect and direct non-health costs in relation to total costs, due to early retirement (28%) and informal care (22%).
* In a European study, it was observed that 40.4% of patients with SSc-ILD have to retire early, with an average of 11.9 years of lost working life per patient. 37.7% require informal (family) care of 22.3 hours per week

1. **Quality of evidence**

* The trial on which the data on efficacy, safety/tolerability and results reported by patients with SSc-ILD treated with nintedanib are based is a trial that follows the principles of the Declaration of Helsinki and the recommendations of the Tripartite Harmonized Guide to Good Clinical Practices.

1. **Clinical practice guidelines**

* Currently, there are no specific clinical practice guidelines for SSc-ILD.
* The EULAR and EUSTAR recommendations (2009 and 2016), for patients with SSc, include the recommendation that the use of antineoplastic/ immunomodulating agents could be considered for patients with SSc-ILD, despite their known toxicity. These guidelines were published before the SLS II trial, and it was not possible to incorporate the information related to the efficacy and safety in the use of mycophenolate mofetil for patients with SSc-ILD. The British guideline incorporated mycophenolate mofetil as a second treatment option.
* In the absence of specific guidelines for patients with SSc-ILD, some recent publications recommend the use of nintedanib for the treatment of these patients, depending on the type of diagnosis. Other publications include nintedanib as a complementary treatment option to immunosuppressive therapies, arguing that its use as first-line therapy requires further analysis.

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