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Determining the value of two biologic drugs for chronic inflammatory skin diseases: results of a multi-criteria decision analysis

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Supplementary material 1. MCDA Evidence matrix for quantitative criteria. EVIDEM Core model

1.1 Evidence matrix of quantitative criteria for dupilumab

DRUG DESCRIPTION

Drug type/intervention category: Dupilumab is a recombinant human monoclonal antibody that blocks the alpha subunit of the interleukin 4 receptor (IL-4Rα), which is located mainly on the surface of cells of the immune system. This blockade inhibits the signalling of both IL-4 and IL-13 and triggers the Th2 immune response (T-helper type 2 lymphocyte) related to atopic dermatitis and chronic cutaneous inflammation [1].

Indication: Dupilumab was approved in March 2017 by the United States Food and Drug Administration (FDA) for the treatment of moderate-to-severe atopic dermatitis in adult candidates as a systemic therapy [2]. Possible future indications for dupilumab include asthma, nasal polyposis, and eosinophilic oesophagitis [3]. Dupilumab is predicted to be indicated as a systemic therapy for adult candidates who have not responded adequately or in whom systemic immunosuppressants are discouraged.

Other aspects of interest: The FDA granted the designation of *breakthrough* to dupilumab [2], and the National Institute for Health and Clinical Excellence (NICE) has allowed an early access programme for dupilumab (to date, only eight drugs have received approval for this type of programme, and six of them are oncological drugs) [4].

Dosage and administration: Dupilumab is supplied in 2-ml prefilled syringes containing 300 mg (150 mg/ml) [1]. The recommended dosing regimen for dupilumab in adult patients is an initial dose of 600 mg (two injections of 300 mg), followed by 300 mg every 2 weeks.

Duration of the intervention: Treatment should continue until there is clinically relevant improvement.

Comparators: Placebo.

ECONOMIC BURDEN OF DISEASE

Atopic dermatitis (AD) carries a substantial economic burden, especially at the highest severity levels [5,6]. In Spain, no studies have been published on this topic. The only available evidence is a study conducted in the Badalona area (IDEA study), which will soon be presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), showing an estimated economic burden of AD in this region of 9.3 million euros per year [5]. The average cost is 1,504 euros per year per adult patient with AD, of which 75% is due to direct healthcare costs and the remaining 25% work productivity loss. The authors conclude that the economic impact is three times higher in patients with severe AD than in those with mild AD (average annual costs of 3,397 euros per patient with severe AD, 2,111 euros with moderate AD, and 885 euros with mild AD).

QUANTITATIVE CRITERIA

Domain: Need for intervention

1. <u>Disease severity</u>: How severe is the disease for which the intervention is intended?

AD is a chronic inflammatory skin disease that occurs in flares and is characterised by severe pruritus and marked skin dryness [7,8]. The moderate-to-severe forms of AD can be determined from the significant presence of pruritus (itching), dry skin, and skin lesions derived from erythema, prurigo (papular rash), crusting/suppuration, and lichenification (skin thickening), with periods of exacerbation of the lesions [9,10]. Pruritus is always intense, substantially reducing the patient's quality of life. Some common complications of AD are infectious, whether of bacterial, viral, or fungal aetiology [11]. In exceptional cases, one of the major complications of the disease, atopic erythroderma—or scaling of more than 90% of the body surface—may be associated with infections, tachycardia, lymphadenopathy, hepatomegaly, poikilothermia, and oedema [12].

Comorbidities: AD is commonly associated with other immunoallergic processes [13,14]. It is estimated that between 58% and 83% of adults with AD present at least one other atopic disease, and up to 91%, 65%, 50%,and 46% also suffer from allergic rhinitis, allergic conjunctivitis, asthma, and/or food allergies, respectively [15–19]. Recently, AD has been associated with the development of other skin diseases, autoimmune disorders, eye problems, or metabolic diseases, and in rare cases, inflammatory bowel disease [8,9]. Adults with AD are more likely to develop obesity or hypertension, and they have a higher risk of suffering from cardiovascular disease, coronary artery disease, or myocardial infarction than people without this condition [15,20–22]. Some studies have also associated AD with lymphoma, particularly cutaneous lymphoma, when topical immunosuppressants are used [23,24]. Adolescents and adults with AD are at a greater risk of developing depression and anxiety disorders [25], as well as having an increased risk of attention deficit-hyperactivity disorder [26].

Quality of life: The effect on quality of life is directly related to the severity of the disease [14,25,27,28]. Patients with severe AD have a significant burden of stinging, pain, sleep disturbance, and psychological and emotional involvement [25,29,30]. On average, patients with AD experience 9 flares per year, lasting 15 days, so that in total, they live approximately 136 days per year with an AD flare. Patients with severe AD experience longer lasting flares (17.3 days) with a greater frequency (11.1 a year), resulting in approximately 192 days per year with a flare (compared with 113 days for people with moderate AD) [31].

Comparison with other diseases: According to some studies, moderate-to-severe AD has a greater impact on quality of life than other dermatological diseases, such as psoriasis or chronic urticaria. Patients with severe eczema have a poorer self-perceived quality of life than patients with severe psoriasis, both before (mean Dermatological Life Quality Index (DLQI) of 16.2 versus 13.9) and after receiving treatment (mean DLQI of 9.6 versus 6.7) [32]. Patients with moderate-to-severe AD report a mean score on the specific DLQI (higher score, worse quality of life) of 14.3, versus 10.3 for patients with pruritus, 9.9 for patients with chronic urticaria, and 8.8 for patients with psoriasis [33,34]. For the SF-36 index (lower score, worse quality of life), patients with severe AD have a worse score than those with psoriasis, both in the mental component (38.5 versus 50.9) and the physical component (49.0 versus 51.4) [35].

2. <u>Size of the affected population</u>: What is the size of the population for which the intervention is intended?

Considering that dupilumab will be indicated mainly for adults with severe AD, candidates for systemic therapy, who have not responded adequately or for whom systemic immunosuppressants are not recommended, the following data should be considered:

- Prevalence of AD in adults in Spain: the data are unknown in our country. The clinicians agree to use a range between 1.5% and 3% [36].
- Proportion of adult patients with severe AD in Spain: 6.1%[5].

- Proportion of patients with severe AD who do not respond to systemic immunosuppressive therapies: 53.4% [37].
- Population of Spain over 18 years old: 38,128,226 people [38].
- In Spain, the size of the affected population could amount between 18,600 and 37,300 people (equivalent to a population prevalence of between 4.9 and 9.8 per 10,000 adults):

Pop. > 18 years	Atopic dermatitis		Severe (treated with SI)	Not controlled with SI
	1.50%	3%	6.10%	53.40%
38,128,226	571,923	1,143,847		

Note: SI: systemic immunosuppression

3. <u>Unmet needs</u>: Are there many unmet needs in disease management compared with the other available alternatives (in efficacy/effectiveness; in safety/tolerance; in health-related quality of life; in patient requirements)?

Currently, there is no curative treatment for AD. The treatment objective is to reduce the symptoms, reduce the number of relapses, and control the disease in the long term [39]. When the lesions are extensive or patients have not responded to topical treatment, systemic therapy is used. However, there are unmet needs for safer and more effective systemic therapies to treat moderate-to-severe AD [40]. All systemic therapies have a poor response; these therapies are more effective for itching than lesions and thus are used to control the disease and treat flares. However, relapse is common and more or less rapid after treatment discontinuation.

In Spain, the only treatment approved for severe AD is **cyclosporine.** All other drugs that are used are not approved for AD, although they are used routinely in clinical practice, in compassionate use, due to the need to offer solutions to the most severe patients [41–45]. Given the adverse effects of systemic immunosuppression, the guidelines limit the treatment duration. Thus, treatment options are limited for patients with an inadequate response to topical corticosteroids. In addition, the fear of suffering such side effects, together with the time and economic costs associated with the application of topical treatment, frequently causes a lack of compliance in patients with AD [46]. The long-term use of systemic treatments for AD is limited, either due to adverse effects or lack of effectiveness [47,48]. **Azathioprine (AZA), mycophenolate mofetil (MMF), and methotrexate (MTX)** are second-line drugs in the systemic treatment of severe forms of AD in adults. For all these treatments, the prospects for improvement in clinical indices range from 25%-70%, with a response time ranging from 8 to 12 weeks [49]. Long-term survival studies with AZA, MTX, and enteric-coated MMF in AD have demonstrated high discontinuation rates after 1 year due to adverse events, ineffectiveness, or both [47,50]. **Systemic steroids** have been shown to be effective in the short term, achieving an effective resolution of the clinical symptoms of AD. However, their adverse effects and frequent relapses limit their long-term use [51,43]. **Biologics:** Excluding dupilumab, no other biologic has shown efficacy for AD in controlled trials. Phase II studies are currently underway to explore the efficacy and safety of ustekinumab (anti-IL-12/23), mepolizumab (directed against IL-31, involved in pruritus), lebrikizumab, tralokinumab (directed against IL-13), and secukinumab (which inhibits IL-17 A) [52,53].

Domain: Comparative outcomes of the intervention

4. <u>Comparative effectiveness/efficacy</u>: How do the efficacy/effectiveness results of the intervention compare with the alternatives?

EFFECTIVENESS DATA: Not available. **EFFICACY DATA**: Three pivotal phase III trials:

SOLO 1: International, multicentre, randomised, double-blind, parallel-group, phase III trial in adults with moderate-to-severe AD for more than 3 years and poorly controlled with topical treatment (n = 671). Three groups: 1:1:1 (dupilumab 300 mg every two weeks, dupilumab 300 mg per week, placebo). Duration of 16 weeks [54].

SOLO 2: International, multicentre, randomised, double-blind, parallel-group, phase III trial in adults with moderate-to-severe AD for more than 3 years and poorly controlled with topical treatment (n = 708). Three groups 1:1:1 (dupilumab 300 mg every two weeks, dupilumab 300 mg per week, placebo). Duration of 16 weeks [54].

LIBERTY AD CHRONOS: International, multicentre, randomised, double-blind, parallel-group, phase III trial in adults with moderate-to-severe AD for more than 3 years and poorly controlled with topical treatment (n = 740). Three groups 3:1:3 (dupilumab 300 mg per week + TCS, dupilumab 300 mg every two weeks + TCS, placebo + TCS). (TCS: medium- or low-potency topical corticosteroids, the latter in the case of sensitive areas). Duration of 52 weeks, with intermediate results at 16 weeks [55]. The main efficacy results of dupilumab in AD (table 1), published to date, are as follows

Table 1. Comparative efficacy results od dupilumab in pivotal trials

	NCT022777 (SOLO 1)¥		NCT02277769 (SOLO 2)¥		NCT02260986 (LIBERTY AD CHRONOS)Θ			
	Week 16		Week 16		Week 16		Week 52	
	Placebo (N=224)	Dupilumab 300 mg/q2w (N=223)	Placebo (N=236)	Dupilumab 300 mg/q2w (N=239)	Placebo+TCS (N=315)	Dupilumab 300mg/q2w +TCS (N=319)	Placebo+TCS (N=264)	Dupilumab 300 mg/q2w +TCS (N=270)
IGA=0.1 and reduction in IGA score ≥2 points N (%)	23 (10%)	85 (38%)	20 (8%)	84 (36%)	39 (12%)	41 (39%)	33 (13%)	32 (36%)
EASI-75 N (%)	33 (15%)	115 (51%)	28 (12%)	103 (44%)	73 (23%)	73 (69%)	57 (22%)	58 (65%)
EASI-50 N (%)	55 (25%)	154 (69%)	52 (22%)	152 (65%)	118 (37%)	85 (80%)§	79 (30%)	70 (79%)§
EASI-90 N (%)	17 (8%)	80 (36%)	17 (7%)	70 (30%)	-	-	-	-
EASI score mean variation (%)	-37.6% ±3.3	-72.3% ±2.6	-30.9% ±3.0	-67.1% ±2.5	-43.2% ±2.26	-76.7% ±3.77	-45.8% ±2.70	-78.3% ±4.44§

¥: Unless otherwise specified, p <0.001 in comparisons between each regimen of dupilumab and placebo; Θ: unless otherwise specified, p <0.0001 in comparisons between each regimen of dupilumab and placebo; §: nominally significant p values. LSM: least-squares method; q2w: every two weeks;
TCS: topical corticosteroids; IGA: Investigator's Global Assessment; EASI: Eczema Area and Severity Index; EASI-50, 75, 90: proportion of patients with an improvement of more than 50%, 70%, and 90% in EASI.
Note 1: the results of the dupilumab arm corresponding to the dose approved in the USA are shown in the table.
Note 2: The results for EASI (for AD) and PASI (for psoriasis) are not comparable because they are on different scales.
Source: [54,55]

Additional information: A placebo-controlled phase III clinical trial (LIBERTY AD CAFÉ) was initiated in the first trimester of 2016 in adult patients with severe AD treated with dupilumab and topical corticosteroids who were poorly controlled with cyclosporine.

5. <u>Comparative safety/tolerability</u>: How do the safety/tolerability results of the intervention compare with the alternatives?

The safety/tolerability data for dupilumab were also obtained from the three clinical trials indicated above, and the main data are summarised as follows:

Table 2. Comparative safety/tolerability results of dupilumab in pivotal trials

		(SOLO 1)		(SOLO 2)		(LIBERTY AD CHRONOS)	
		Week 16		Week 16		Week 52	
		Placebo (N=224)	Dupilumab 300 mg/q2w (N=223)	Placebo (N=236)	Dupilumab 300 mg/q2w (N=239)	Placebo+TCS (N=315)	Dupilumab 300 mg/q2w +TCS (N=319)
PATIENTS WITH ADVERSE EFFECTS N (%)							
≥1 adverse effect (AE)		145 (65%)	167 (73%)	168 (72%)	154 (65%)	266 (84%)	97 (88%)
≥1 severe AE		11 (5%)	7 (3%)	13 (6%)	4 (2%)	16 (5%)	4 (4%)
AEs that cause treatment discontinuation		2 (1%)	4 (2%)	5 (2%)	2 (1%)	24 (8%)	2 (2%)
Deaths		0	0	0	1 (<1%)	0	0
Non-infectious AEs*	Injection site reaction‡	13 (6%)	19 (8%)	15 (6%)	32 (14%)	24 (8%)	16 (15%)
	AD Exacerbation‡	67 (30%)	30 (13%)	81 (35%)	32 (14%)	144 (46%)	20 (18%)
	Headache‡	13 (6%)	21 (9%)	11 (5%)	19 (8%)	19 (6%)	5 (5%)
Infectious AEs*	Infections and infestations	63 (28%)	80 (35%)	76 (32%)	65 (28%)	182 (58%)	63 (57%)
	Conjunctivitis	2 (1%)	11 (5%)	1 (<1%)	9 (4%)	25 (8%)	15 (14%)
	Any herpes virus infection†	9 (4%)	15 (7%)	8 (3%)	10 (4%)	25 (8%)	8 (7%)
	Non-herpetic skin infection	18 (8%)	13 (6%)	26 (11%)	13 (6%)	56 (18%)	12 (11%)
	Non-cutaneous infection	49 (22%)	69 (30%)	57 (24%)	58 (25%)	-	-

TCS: topical corticosteroids; q2w: every two weeks

* The included AEs correspond to the level of "preferred terms" (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA) terminology unless otherwise specified. Only AEs reported in at least 5% of the patients of any treatment group are included, with the exception of adverse effects with PTs related to herpes virus infection, all of which are included in this table.

†:AEs reported at the level of "high level terms" of the MedDRA terminology. ‡: AEs reported at the level of "PTs" of the MedDRA terminology in the SOLO 1 and SOLO 2 studies and at the level of "system organ classes" in the LIBERTY AD CHRONOS study.

Source: [54,55]

In general, dupilumab showed an acceptable safety profile, with a very favourable AE profile and an incidence of adverse events similar to the placebo group. The percentage of patients with an adverse event ranged from 65% to 73% (88% at 52 weeks in combination with TCS) compared with 65%-72% in the placebo group (84% at 52 weeks).

Severe adverse events or those that caused treatment discontinuation were infrequent during treatment with dupilumab (1% -2%), providing percentages similar to those in the placebo arm, with the exception of the group treated with placebo at 52 weeks, in combination with TCS (8%).

6. <u>Comparative patients-perceived outcomes (PROs)</u>: How do the results reported/perceived by patients compare with the alternatives?

The results of dupilumab reported or perceived by patients are also summarised in Table 3. The variables measure is the impact on patient health-related quality of life, using general scales (HADS, GISS) and specific dermatology/dermatitis scales (DLQI, SCORAD, POEM). Specific aspects related to the impact of the disease on the patient (level of pruritus, affected body surface area) are also measured. The results are conclusive in favour of the drug.

Table 3. Results reported/perceived by patientes of dupilumab in pivotal trials

	NCT02277743 (SOLO 1)¥		NCT02277769 (SOLO 2)¥		NCT02260986 (LIBERTY AD CHRONOS)Θ			
	Week 16		Week 16		Week 16		Week 52	
	Placebo (N=224)	Dupilumab 300 mg/q2w (N=223)	Placebo (N=236)	Dupilumab 300 mg/q2w (N=239)	Placebo +TCS (N=315)	Dupilumab 300 mg/q2w +TCS (N=319)	Placebo +TCS (N=264)	Dupilumab 300 mg/q2w +TCS (N=270)
SCORAD mean variation (%)	-29.0% ±3.2	-57.7% ±2.1	-19.7% ±2.5	-51.1% ±2.0	-31.8% ±1.55	-62.1% ±2.61	-34.1% ±1.88	-66.2% ±3.14§
DLQI mean variation	-5.3 ±0.5	-9.3 ±0.4	-3.6 ±0.5	-9.3 ±0.4	-5.3 ±0.31	-9.7 ±0.51	-5.6 ±0.36	-10.9 ±0.59§
POEM mean variation	-5.1 ±0.7	-11.6 ±0.5	-3.3 ±0.6	-10.2 ±0.5	-4.7 ±0.38	-12.4 ±0.63	-5.3 ±0.46	-13.7 ±0.75§
HADS mean variation	-3.0 ±0.7	-5.2 ±0.5	-0.8 ±0.4	-5.1 ±0.4	-3.6 ±0.34	-4.9 ±0.56¶	-3.4 ±0.40	-5.3 ±0.65§
GISS mean variation (%)	-26.4% ±3.3	-53.4% ±2.4	-17.9% ±2.5	-45.6% ±2.1	-28.2% ±1.63	-53.1% ±2.73§	-29.2% ±2.01	-58.3% ±3.30§
Pruritus NRS mean variation (%)	-26.1% ±3.0	-51.0% ±2.5	-15.4% ±3.0	-44.3% ±2.3	-28.6% ±2.03	-56.2% ±3.38	-27.1% ±2.66	-56.2% ±4.38§
BSA affected mean variation	-15.4 ±1.9	-33.4 ±1.4	-12.6 ±1.6	-30.6 ±1.3	-18.6 ±1.13	-38.6 ±1.88	-20.3 ±1.33	-41.5 ±2.19§

Obtained by the least-squares method. ¥: If not otherwise specified, p <0.001; Θ: If not otherwise specified, p<0.0001; §: Nominally significant p value; ¶: p=0.03 (No significance). TCS: topical corticosteroids; q2w: every two weeks; SCORAD: *Scoring Atopic Dermatitis;* Pruritus NRS: *Numerical-rating scale*; DLQI: *Dermatology Life Quality Index*; POEM: *Patient- Oriented Eczema Measure*; HADS: *Hospital Anxiety and Depression Scale*; GISS*: Global Individual Signs Score* BSA*: Body surface area.*
Source: [54,55]

Treatment with dupilumab was superior to placebo in reducing the symptoms and signs of AD (including pruritus and its effect on sleep), causing clinically significant reductions in anxiety/depression symptoms with better **self-perceived** quality of life. In patients treated with dupilumab, a significantly higher proportion achieved a reduction of at least 4 points in DLQI and POEM (considering the minimum clinically relevant difference) compared with those treated with placebo.

Domain: Type of health benefit of the intervention

7. Type of preventive benefit: What type of preventive gains or decrease in health risks does the intervention provide?

Dupilumab does not prevent or modify the risk of suffering from AD, nor that of its associated diseases.

8. Type of therapeutic benefit: What type of health gains does the intervention provide?

Similarly to the approved biologics for psoriasis, dupilumab provides the opportunity to control the disease in the long term (the period of time studied to date), being a safe and effective treatment [56]. Dupilumab does not cure AD, but it significantly reduces the severity of its symptoms and the extent of the affected body surface. The treatment reduces the itching felt by patients and improves their physical appearance, rest, and quality of life. In clinical trials. Additionally, it was well tolerated and demonstrated a favourable safety profile in the short and medium term.

Domain: Economic consequences of the intervention

9. Comparative cost consequences -cost of the intervention: What is the impact of the intervention on direct costs (acquisition and administration costs) compared with the alternatives?

Because dupilumab has not yet been approved in Europe, this drug has no price in Spain. As a mere approximation of its possible cost, it can be assumed that this first-in-class drug could have the same annual treatment cost as secukinumab (at an approved price, approximately 11,000 euros per patient in the maintenance phase). Cyclosporine, the only systemic drug approved for AD, lacks a dosing regimen and specific duration since, due to the variability of the process, the treatment must be individualised. According to its data sheet, the recommended daily dose of CSP ranges between 2.5 and 5 mg/kg/day divided into two oral doses, for a maximum of 8 weeks [57]. According to clinical practice, CSP can be administered for a maximum of two years [42].

10. Comparative cost consequence s-other medical costs: What is the impact of the intervention on other health costs (medical visits, hospitalisations, tests, etc.) compared with the alternatives?

No specific evidence is available for this criterion compared with the alternatives, so the score should be based on your experience and/or intuition. Documentation has shown that patients with severe AD require more direct healthcare resources (scheduled medical visits, emergency visits, medication, hospitalisations, etc.) than do less severe patients, which would translate into higher direct healthcare costs. A Spanish study (IDEA study) has reported that the economic impact is three times higher in patients with severe AD than in patients with mild AD, placing the total annual average cost at 3,397 euros per patient with severe AD (2,111 euros with moderate AD and 885 euros with mild AD). The cost of medication represents 40% of the total cost [5].

11. Comparative cost consequences -non-medical costs: What is the impact of the intervention on other non-medical costs (productivity loss, social services, psychologist, etc.) compared with the alternatives?

No specific evidence is available for this criterion compared with the alternatives, so the score should be based on your experience and/or intuition. Documentation has shown that patients with severe AD suffer a greater work productivity loss (sick leave days, reduced productivity) than less severe patients, which translates into higher indirect costs [58]. In Spain, the IDEA study, which has yet to be published, has estimated the work productivity loss per patient with AD at 157 euros per year if it is mild, 555 euros if it is moderate, and 1,142 euros if it is severe AD [5]. The work productivity loss (sick leave + lower productivity) has been quantified as more than 2,280 million euros annually in the EU-15 [31]. Therefore, improving the health status of patients with severe AD could lead to indirect cost savings.

Domain: Knowledge about the intervention

12. <u>Quality of the evidence</u>: What is the quality of the designs, validity, relevance, and completeness of the studies in the context of the intervention?

It is considered that the SOLO 1 and SOLO 2 clinical trials provide good-quality evidence. Valid instruments were used to evaluate the results, and a differential withdrawal rate was not observed [59]. Due to the recent publication of the LIBERTY AD CHRONOS trial, an external evaluation of its quality is not yet available. However, it has the same characteristics on which the Institute for Clinical and Economic Review (ICER) is based to assess quality.

13. <u>Expert consensus/Clinical practice guidelines</u>: Is the intervention (or intervention of the same kind) recommended in the usual CPGs? At what level (first line?)

In the "Update in AD. Proposed algorithm of action" [60], the authors state that in Spain, we do not have adequate therapeutic guidelines to treat patients with AD severity levels that significantly affect their health and social development. In addition, all drugs traditionally used in the treatment of severe AD, excluding CSP, such as MTX, AZA, or MMF, do so *off-label* or outside of this indication [45]. Currently, American clinical practice guidelines for the treatment and management of AD still do not include the new, recently marketed biologics (the latest version dates from 2014) [61]. In Europe, the guidelines on the diagnosis and treatment of AD in adult and paediatric patients of the ETFAD/EADV Eczema Task Force 2015, although it does not include dupilumab in the therapeutic algorithm, does make special mention of the improvements in its safety and efficacy profile[49].

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1.2 Evidence matrix of quantitative criteria for secukinumab

DRUG DESCRIPTION

Drug type/intervention category: Secukinumab (Cosentyx®) is a fully human IgG1k monoclonal antibody that binds selectively and neutralises a proinflammatory cytokine, interleukin 17ª (IL17ª), inhibiting its interaction with the IL receptor expressed in several cell types, including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines, and mediators of tissue damage, reducing the contribution of IL-17a to autoimmune and inflammatory diseases such as psoriasis [1].

Therapeutic group: Immunosuppressants, interleukin inhibitors.

Indication: Secukinumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adult candidates for systemic therapies [2]. It is also indicated, alone or in combination with methotrexate (MTX), for the treatment of active psoriatic arthritis in adult patients who have not responded adequately to previous therapies with disease-modifying antirheumatic drugs (DMARDs) [2] as well as for the treatment of active ankylosing spondylitis in adults who have not responded adequately to conventional treatment[2].

Dosage and administration: The recommended dosing regimen of secukinumab is 300 mg (two subcutaneous injections of 150 mg). It is administered on a weekly basis (weeks 0, 1, 2, and 3) in the initial phase and monthly during the maintenance phase (starting at week 4) [2].

Duration of the intervention: The available data suggest that a clinical response is usually achieved after 16 weeks of treatment. Consideration should be given to treatment discontinuation in patients who have not responded after 16 weeks of treatment. Some patients with an initial partial response may later improve by continuing treatment for more than 16 weeks [2].

Comparators: Biologic treatments in patients with moderate-to-severe plaque psoriasis. Current therapies are ustekinumab (Stelara®), etanercept (Enbrel®), infliximab (Remicade®), ixekizumab (Taltz®), and adalimumab (Humira®). Ustekinumab and etanercept are the comparators used in published direct comparator trials with secukinumab.

ECONOMIC BURDEN OF THE DISEASE

In Spain, it has been estimated that the average annual cost of a patient with psoriasis is 1,079 euros (or 1,379 euros in 2015) (including both direct and indirect costs). The average costs of moderate and severe psoriasis were approximately 1.5 (1.617 euros) and 2.5 (2.772 euros) times higher, respectively, than those of patients with mild psoriasis. Work productivity loss (17.4% of the total cost) was three times higher in patients with severe psoriasis [3,4]. Another study examining a greater range of costs (including, in addition to hospitalisations, medical visits, diagnosis and medication, surgery, emergencies, nursing, phototherapy, and patient expenses) places the total costs of patients with moderate-to-severe psoriasis at 7,452 euros per patient in 2015, of which 7% represents indirect costs [4,5]

QUANTITATIVE CRITERIA

Domain: Need for intervention

1. <u>Disease severity</u>: How severe is the disease for which the intervention is intended?

Psoriasis is a **chronic inflammatory dermatosis** associated with arthritis, which is accompanied by multiorgan involvement in severe cases. It is usually characterised by a variable clinical course, chronic or recurrent, with flares and remissions of variable duration [6]. Approximately one in three patients with psoriasis will develop psoriatic arthropathy during the course of the disease, often after the onset of cutaneous symptoms.

The appearance and distribution of psoriasis lesions is variable. Plaque psoriasis (psoriasis vulgaris) is the most common and accounts for approximately 90% of cases. The typical lesions of plaque psoriasis are well-defined erythematous papules and plaques covered with fine and pearly scales of varying size, which can be attributed to a hyperproliferation of epidermal keratinocytes in the context of an inflammatory process involving both innate and adaptive immunity [7].

Psoriasis can be classified as mild, moderate, or severe, depending on the extent and location of the lesions, the psychosocial handicap caused to the patient, impairment of the general condition, and presence or absence of arthritis [8]. Psoriasis is defined as severe when PASI >10, BSA >10%, or DLQI >10 are obtained, when the disease requires systemic treatment at some point during its progression, or when psoriatic erythroderma, an association with psoriatic arthritis, or generalised or localised pustular psoriasis is present, but with functional and psychological limitations [9].

Comorbidities: Severe psoriasis is associated with different comorbidities, the most relevant of which are those related to metabolism, which can affect the morbidity and mortality of patients. It is also associated with heart conditions [10,11], inflammatory bowel disease, obesity, depression, diabetes, or cancer [12,13]. Patients with moderate-to-severe psoriasis have a relative risk of cardiovascular disease almost three times higher than the general population [14].

Joints are affected in 30% of cases, mainly after the appearance of skin lesions [15]. Different studies have also shown a negative effect of psoriasis on quality of life, and the greater tendency towards psychiatric disorders such as depression and anxiety [16].

Quality of life: Psoriasis has an important impact on patients suffering from the disease, including physical, psychological, social, and occupational aspects [12,17,18]. The greater the extent or severity of psoriasis, the greater the negative impact is on health-related quality of life [12,17]. Severe psoriasis affects the joints, limiting mobility [8,19]. The location of the affected body area can influence patient's quality of life and psychosocial health, regardless of the extent of the affected body surface [19]. Patients with palmoplantar involvement suffer greater social constraints and greater impact on their lives than those in which other areas of the body are affected, regardless of the degree of extension [1]. Psoriasis physically and emotionally affects patients who suffer from it. In the physical sphere, 16.6% state that the disease is painful. In the psychological sphere, almost 20% state that psoriasis affects their physical appearance and generates a problem with clothing. It causes social problems for 20.3% of patients. In total, 88% of patients state that psoriasis affects their emotional well-being, and 82% that it interferes with a full life [18].

Comparison with other diseases: Patients with psoriasis suffer an impact on their health-related quality of life similar to patients with severe chronic diseases, such as cancer or cardiovascular diseases. Patients with psoriasis report mean EQ-5D scores between 0.52 and 0.90, compared with the range of 0.24 to 0.90 for cardiovascular diseases, 0.20 to 0.88 for type 2 diabetes, 0.44 to 0.86 for end-stage kidney disease, 0.66 to 0.79 for liver disease, 0.33 to 0.93 for cancer, and 0.64 to 0.89 for visual disorders [20].

2. <u>Size of the affected population</u>: What is the size of the population for which the intervention is intended?

Considering that secukinumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adult candidates for systemic treatment, the following data should be considered:

- Total prevalence of psoriasis in Spain: 2.3% [21].
- Proportion of patients with psoriasis, according to severity, in Spain: 70.5% mild, 19.1% moderate, and 10.4% severe [3].
- Proportion of patients with moderate-to-severe psoriasis under conventional or biologic systemic treatment, requiring a change in treatment: 40% [1]
- Population of Spain over 18 years old: 38,128,226 people [22].
- In Spain, the size of the affected population could amount to some 103,000 people (equivalent to a population prevalence of 27 per 10,000 people):

Population ≥18 years	Psoriasis	Moderate-severe	Non-responders to SI
	2.30%	29.50%	40.00%
38,128,226	876,949	258,700	103,480

Note: SI: systemic immunosuppression

3. <u>Unmet needs</u>: Are there many unmet needs in disease management compared with the other available alternatives? (in efficacy/effectiveness, in safety/tolerance, in health-related quality of life, in patient requirements).

The treatment of psoriasis in clinical practice aims to achieve and maintain to the greatest extent possible the clearance of the lesions in the long term. Current clinical guidelines, taking into account not only clinical aspects but also costs, recommend the use of systemic therapy with conventional drugs as the first-line treatment in most patients in whom systemic therapy is indicated [23]. The use of biologics is reserved for those patients who do not respond adequately or who have contraindications or intolerance to these therapies[24].

In severe psoriasis, there are unmet needs in its treatment, mainly due to concerns about the safety, tolerability, and efficacy of currently available therapies [25]. Added to this is the lack of patient satisfaction with the treatments [26].

Topical treatments are generally not curative and are difficult to comply with because they are usually creams or gels that are applied to the affected area, sometimes more than once a day, which can be time-consuming, in addition to other inconveniences [27]. Additionally, prolonged treatment with topical corticosteroids causes cutaneous atrophy, striae, hypopigmentation, telangiectasia, and acne. Other treatments, such as reducers, present discomforts such as a bad odour or stains on clothes, in addition to other AEs such as irritation and photosensitivity. Calcineurin inhibitors can produce itching, stinging, and local paraesthesias [28].

Conventional systemic therapies indicated for moderate-to-severe psoriasis, in the case of a good response, have a limited time of application during maintenance to avoid AEs associated with long-term treatment. The most common adverse events are infections, affecting almost 14% of treated patients, followed by alterations in additional examinations, with 12%, and gastrointestinal disorders, which account for 10% of all adverse events recorded [29]. In particular, methotrexate is hepatotoxic and causes myelosuppression; while treatment with cyclosporine is nephro- and hepato-toxic, increases the risk of arterial hypertension, and causes immunosuppression [28]. In general,

among the medical unmet needs in severe psoriasis, it is worth noting the existence of oral treatments as effective as biologics, avoiding the parenteral route; therapies for HIV, HCV, and HBV patients with a history of malignancy or CHF (degree III-IV); therapies that reduce the comorbidities associated with the disease; and therapies that effectively stop the radiological progression of joint involvement.

Regarding **biologic treatments**, not all can be classified in the same group because each one has its own mechanism of action. In general, their long-term effects are still unknown, and anti-TNF drugs are contraindicated in patients with multiple sclerosis, heart failure, or a history of malignancy[28]. According to three meta-analyses that evaluated etanercept, infliximab, adalimumab, and ustekinumab for moderate-to-severe psoriasis, all these biologics were significantly more effective than placebo. Infliximab obtained the best results in the PASI 75 response. Adalimumab and ustekinumab had better PASI 75 rates than etanercept. There were no significant differences between adalimumab and ustekinumab (RR 0.91, 95% CI 0.78-1.04) [30–32]. A systematic review of the approved systemic therapies up to 2014 (cyclosporine, methotrexate, fumaric acid esters, systemic retinoids, etanercept, infliximab, adalimumab, and ustekinumab) for moderate-to-severe psoriasis showed that, in placebo-controlled trials, infliximab was the most effective (RD 76%, 95%CI 73-79%). Adalimumab (61%, 95%CI 60-74%) and ustekinumab (67%, 95%CI 60-74%) had similar efficacies. These biologics were more effective than etanercept and all conventional treatments [33].

Domain: Comparative outcomes of the intervention

4. <u>Comparative effectiveness/efficacy</u>: How do the efficacy/effectiveness results of the intervention compare with the alternatives?
EFFECTIVENESS DATA: Not available. **EFFICACY DATA**: Four pivotal phase III trials.

Additional Information: A clinical trial is available versus ustekinumab (CLEAR), for which the results were reported after marketing authorisation of secukinumab:

- **ERASURE**: International, multicentre, placebo-controlled, randomised, double-blind, parallel-group, phase III trial in adults with chronic plaque psoriasis for at least 6 months before randomisation and moderate-to-severe psoriasis (PASI >12, IGA at least 3, and total BSA >10%), candidates for systemic therapy and poorly controlled with topical treatments, phototherapy, and/or previous systemic therapy (n = 738). Duration of 52 weeks (12 induction and 40 maintenance). Comparator: placebo induction [34–38].
- **FEATURE:** International, multicentre, placebo-controlled, randomised, double-blind, parallel-group, phase III trial in adults with chronic plaque psoriasis for at least 6 months before randomisation and moderate-to-severe psoriasis, candidates for systemic therapy (n = 177). The inclusion and exclusion criteria were similar to those of the ERASURE study. Measurement of the response at week 12. Comparator: placebo induction [34–37].
- **JUNCTURE**: International, multicentre, placebo-controlled, randomised, double-blind, parallel-group, phase III trial in adults with moderate-to-severe chronic plaque psoriasis who were poorly controlled with topical treatments, and/or phototherapy, and/or previous systemic therapy (n = 182). The inclusion and exclusion criteria were similar to those of the FEATURE study. Measurement of response at week 12 compared to placebo [37–39].
- **FIXTURE**: International, multicentre, double-blind, double-simulated, placebo-controlled, parallel-group, phase III trial in adults with moderate-to-severe chronic plaque psoriasis who were poorly controlled with topical treatments, and/or phototherapy, and/or prior systemic therapy. <u>Non-inferiority study versus etanercept</u> (subcutaneous

route): 50 mg, 2 doses per week up to week 12; 50 mg weekly at weeks 12-51. The inclusion and exclusion criteria were similar to those of the ERASURE study, excluding also those who had received previous treatment with etanercept (n = 1,306). Duration of 52 weeks [34–38].

- **CLEAR**: International, multicentre, randomised, double-blind, parallel-group, phase III trial in adults with plaque psoriasis for at least 6 months before randomisation and moderate-to-severe psoriasis, candidates for systemic therapy and poorly controlled with topical treatments, and/or phototherapy, and/or previous systemic therapy. Superiority study versus ustekinumab (subcutaneous route): initial dose of 45 mg in patients ≤100 kg and 90 mg in patients > 100 kg. The main exclusion criteria considered patients previously exposed to biologics directed to the therapeutic targets IL-17 receptor A or IL-12/IL-23 (n = 676). Duration of 52 weeks [40,41].

The main efficacy results of the five studies are summarised below:

- The main response variables used to measure the magnitude of the treatment effect were the same in the four pivotal trials: PASI 75 and IGA mod 2011 "complete clearance" or "practically complete" at week 12. The FIXTURE trial, being a non-inferiority study versus etanercept, established a delta value of 10% for the PASI 75 variable, which was transformed after the result in a superiority study. In the CLEAR trial (of superiority to ustekinumab), the main variable was PASI-90 at week 16, and the secondary variables were PASI 75 and IGA mod 2011 at week 12 and 52.

- The results obtained in the four pivotal studies for the main variable (PASI 75) between secukinumab (300 mg) versus placebo and etanercept were statistically significant ($p < 0.0001$ versus placebo and $p < 0.025$ versus etanercept):
  - FEATURE: 75.9% of patients showed an improvement with 300 mg secukinumab at week 12.
  - JUNCTURE: 86.7% of patients showed an improvement with 300 mg secukinumab at week 12.
  - ERASURE: 81.6% of patients showed an improvement with 300 mg secukinumab at week 12.
  - FIXTURE: 77.1% of patients showed an improvement with 300 mg secukinumab at week 12, compared to 44.0% improvement in patients with 50 mg etanercept twice a week.

- The proportion of patients with a response of 0 to 1 in the variable IGA was higher for 300 mg secukinumab at 12 weeks compared with placebo and etanercept (ERASURE: 65.3%, FIXTURE: 62.5% versus 27.2% with etanercept, FEATURE: 69%, and JUNCTURE: 73.3%). The proportion of patients with a response of 0 to 1 in the main variable IGA was also higher with 300 mg secukinumab at 16 and 52 weeks compared with placebo and etanercept (ERASURE: 58.2% and 60.4% at weeks 16 and 52, respectively; FIXTURE: 75.5% versus 39.3% with etanercept at 16 weeks, and 67.8% versus 37.2% with etanercept at 52 weeks, respectively). The results were statistically significant and clinically relevant in favour of secukinumab. Regarding long-term maintenance, the results showed that the effect observed at week 12 remained reasonable up to week 52.

- Secukinumab has been shown to have superior efficacy versus ustekinumab at week 16. The results obtained versus ustekinumab (CLEAR trial) for the main variable PASI 90 at week 16 were 80.1% with 300 mg secukinumab compared with 59.5% improvement in patients with ustekinumab ($p < 0.0001$). These results for superiority were maintained in the long term, with significant improvements at week 52 in PASI75, PASI90, and IGA.

5. <u>Comparative safety/tolerability</u>: How do the safety/tolerability results of the intervention compare with the alternatives?

The safety/tolerability data of secukinumab were also similar in the four pivotal clinical trials, three versus placebo (ENSURE, FEATURE, JUNCTURE) and one versus etanercept (FIXTURE) conducted at weeks 12 and 52, plus the results of the post-marketing authorisation study of secukinumab (CLEAR study) versus ustekinumab at weeks 16 and 52 (table 4, table 5).

Table 4. Comparative safety/tolerability results of secukinumab in pivotal trials

	ENSURE, FEATURE, JUNCTURE, and FIXTURE						
	12 weeks				52 weeks		
	Secukinumab 150 mg (N=692) n (%)	Secukinumab 300 mg (N=690) n (%)	Etanercept (N=323) n (%)	Placebo (N=694) n (%)	Secukinumab 150 mg (N=692) n (%)	Secukinumab 300 mg (N=690) n (%)	Etanercept (N=323) n (%)
Adverse effects (AEs)	412 (59.5)	388 (56.2)	186 (57.6)	340 (49.0)	562 (81.2)	575 (83.3)	253 (78.3)
Severe AEs	14 (2.0)	14 (2.0)	12 (1.7)	3 (0.9)	48 (6.9)	48 (7.0)	20 (6.2)
AEs that involved treatment discontinuation	5 (0.7)	10 (1.4)	6 (1.9)	10 (1.4)	21 (3.0)	25 (3.6)	12 (3.7)
Most common AEs							
Nasopharyngitis	85 (12.3)	79 (11.4)	36 (11.1)	60 (8.6)	164 (23.7)	172 (24.9)	86 (26.6)
Headache	38 (5.5)	45 (6.5)	23 (7.1)	36 (5.2)	65 (9.4)	79 (11.4)	40 (12.4)
Diarrhoea	18 (2.6)	28 (4.1)	11 (3.4)	10 (1.4)	45 (6.5)	54 (7.8)	22 (12.4)
Upper respiratory tract infection	22 (3.2)	17 (2.5)	7 (2.2)	5 (0.7)	64 (9.2)	53 (7.7)	18 (5.6)
Cough	9 (1.3)	19 (2.8)	4 (1.2)	9 (1.3)	21 (3.0)	45 (6.5)	12 (3.7)
Back pain	12 (1.7)	14 (2.0)	9 (2.8)	10 (1.4)	30 (4.3)	37 (5.4)	26 (8.1)
Hypertension	22 (3.2)	7 (1.0)	5 (1.5)	12 (1.7)	37 (5.3)	35 (5.1)	14 (4.3)
Arthralgia	20 (2.9)	9 (1.3)	12 (3.7)	17 (2.4)	38 (5.5)	34 (4.9)	23 (7.1)

Sources: [42, 37, 34].

Table 5. Comparative safety/tolerability results of secukinumab versus ustekinumab

	CLEAR			
	16 weeks		52 weeks	
	Secukinumab 300 mg (N=335) n (%)	Ustekinumab (N=336) n (%)	Secukinumab 300 mg (N=335) n (%) [Incidence rate per 100 patients-year]	Ustekinumab (N=336) n (%) [Incidence rate per 100 patients-year]
Adverse effects (AEs)	215 (64.2%)	196 (58.3%)	286 (85.4%) [280.9]	278 (82.7%) [250.1]
Severe AEs	10 (3.0%)	10 (3.0%)	30 (8.9%) [9.6]	26 (7.7%) [8.5]
Death	0	0	0	1
AEs that involved treatment discontinuation	3 (0.9%)	4 (1.2%)	10 (3.0%)	9 (2.7%)
Most common AEs				
Nasopharyngitis	23 (6.9%)	34 (10.1%)	77 (23.0%) [27.1]	83 (24.7) [31.0]
Headache	26 (7.8%)	27 (8.0%)	40 (12.0%) [13.5]	41 (12.2%) [14.2]
Upper respiratory tract infection	-	-	31 (9.2%) [10.1]	30 (8.9%) [9.9]
Arthralgia	13 (3.9%)	14 (4.2%)	25 (7.5%) [8.1]	28 (8.3%) [9.2]
Diarrhoea	14 (4.2%)	12 (3.6%)	23 (6.9%) [7.5]	24 (7.1%) [7.9]
Back pain	-	-	22 (6.6%) [7.1]	26 (7.7%) [8.5]

Source: [41]

The main safety/tolerability results of the five studies are summarised below:

- AEs associated with treatment with secukinumab are typical of other biologic therapies indicated for the treatment of psoriasis. In the five studies, the most common AEs were upper respiratory infections (most frequently nasopharyngitis and rhinitis, diarrhoea, and headache). Most adverse reactions were mild to moderate in nature [1]. A total of six deaths were reported in all patients who participated in the clinical trials of psoriasis with secukinumab. However, they did not appear to be related to the use of secukinumab and could be attributed to concomitant morbidity [42].
- The infection rate was higher in secukinumab than placebo and similar compared to etanercept [34].
- According to the FIXTURE study, the safety profile of secukinumab was similar to that of etanercept [1].

According to the CLEAR study, the safety and tolerability profile of secukinumab were similar to those of ustekinumab [41]

6. <u>Comparative patient-perceived outcomes (PROs)</u>: How do the results reported/perceived by patients compare with the alternatives?

The results of secukinumab reported or perceived by patients were also obtained from the five clinical trials mentioned above (table 6), three versus placebo (ENSURE, FEATURE, JUNCTURE), one versus etanercept (FIXTURE), and one versus ustekinumab (CLEAR).

Table 6. Results reported/perceived by patients at week 12

	ERASURE			**FIXTURE**			**FEATURE**		**JUNCTURE**		**CLEAR**	
	Secuk. 150 mg (N=244)	**Secuk**. 300 mg (N=245)	**Placebo** (N=246)	**Secuk**. 300 mg (N=323)	**Etaner**. (N=323)	**Placebo** (N=324)	**Secuk**. 300 mg (N=58)	**Placebo** (N=59)	**Secuk**. 300 mg (N=60)	**Placebo** (N=61)	**Secuk**. 300 mg (N=331)	**Ustek**. (N=333)
DLQI* % patients with response 0-1.	46.1¥	58.8¥	10.3	56.7¥†	34.5	6.6	54.7¥	7.4	74.6¥	15.3	219 (66.2%)§	188 (56.5%)
EQ-5D Initial **pain/discomfort ****	22.1% (70.8%)	26.2% (72.8%)	18.9% (28.4%)									
EQ-5D Pain/discomfort % var$^{\theta}$				-	-	-	+24.7%	+6.8%	+14.3%	0%	-	-
EQ-5D Pain/discomfort Var$^{\theta}$	-	-	-	+22.3	+14.4	+2.2	-	-	-	-	-	-

*The 0-1 response is defined as one in which the disease does not affect the quality of life of the patients. **Refers to treated patients who did not show pain/discomfort. $^{\Theta}$Percentage or absolute variation from the value reached at the start of treatment compared with the value at week 12 in the pain/discomfort category. ¥p <0.005 compared with placebo. †p <0.001 compared with etanercept. §p = 0.0109 compared with ustekinumab. Source:[42].

The following statements summarize the main results perceived or reported by patients in these five studies:

- Patient quality of life was assessed using the DLQI questionnaire (dermatological quality of life index)—where a score above 10 correlates with a significant impact on quality of life—and the EuroQol-5D-3L questionnaire.

- In the ERASURE trial, the percentage of patients with DLQI between 0 and 1 (the disease does not affect quality of life) was 58.8% at week 12 and 66.3% at week 52 for the group treated with secukinumab, compared with 10.3% for the placebo group at 12 weeks ($p < 0.001$) [1].
- In the FIXTURE trial, the percentage of patients with DLQI between 0 and 1 at week 12 was 56.7% for the secukinumab group, compared with 34.5% for patients treated with etanercept ($p < 0.001$). At week 52, the percentages increased to 69.7% for the secukinumab group and 46.9% for the etanercept group, demonstrating clinically relevant differences [1].
- In the CLEAR trial, the percentage of patients with DLQI between 0 and 1 at week 12 was 66.2% for the secukinumab group versus 56.5% for ustekinumab. At week 52, the results improved significantly, showing a percentage of patients whose disease did not affect their quality of life of 71.6% for the secukinumab group and 59.2% for the ustekinumab group [41].

In the CLEAR trial, secukinumab was also significantly more effective than ustekinumab in the five dimensions of the EuroQol-5D-3L questionnaire. Secukinumab advanced 14 points in the mobility dimension (versus 11 points for ustekinumab) between baseline and week 52, 8 points in self-care (versus 4), 30 points in daily activities (versus 20), 45 points in pain/discomfort (versus 38), and 34 points in depression/anxiety (versus 30) [41].

Domain: Type of health benefit of the intervention

7. Type of preventive benefit: What type of preventive gains or decrease in health risks does the intervention provide?

Secukinumab does not prevent or modify the risk of suffering from psoriasis.

8. Type of therapeutic benefit: What type of health gains does the intervention provide?

Secukinumab does not cure psoriasis, but it has demonstrated a robust and reliable high efficacy in adult patients with moderate-to-severe plaque psoriasis who were previously treated with phototherapy, topical treatment, and/or systemic therapy, including biologics. Its safety profile is favourable in the short and medium term, similar to other biologics.

Domain: Economic consequences of the intervention

9. Comparative cost consequences -cost of the intervention: What is the impact of the intervention on direct costs (acquisition and administration costs) compared with the alternatives?

The average cost of the intervention is around €11,000 per patient per year (price financed for the maintenance phase). Considering that there is a biosimilar approved for etanercept, the annual cost of the treatment with secukinumab was about €4,000 higher per patient than the treatment with etanercept and €342 lower than the treatment with ustekinumab[1].

10. Comparative cost consequences -other medical costs: What is the impact of the intervention on other healthcare costs (medical visits, hospitalisations, tests, etc.) compared with the alternatives?

No specific evidence is available for this criterion in comparison to the alternatives, so the score should be based on particular experience and/or intuition.

It has been estimated that the mean direct healthcare costs (including medication) of a patient with moderate-to-severe psoriasis in Spain amount to approximately 6,953 euros per year [4,5]. According to data from another study, the direct costs associated with a patient with severe psoriasis are estimated to be 2,012 euros per year, which is 53% more than those that associated with moderate psoriasis (1,314 euros) [3,4].

In the United States, it is estimated that the direct healthcare costs of patients with moderate-to-severe psoriasis are US$ 8,015 per year (excluding medicines), which is almost 50% more than "controls" with this disease (US$ 4,990). Fifty-eight percent of these healthcare costs correspond to medical consultations, followed by hospitalisation costs (33%) [43].

11. <u>Comparative cost consequences -non-medical costs</u>: What is the impact of the intervention on other non-medical costs (productivity loss, social services, psychologist, etc.) compared with the alternatives?

In Spain, the work productivity loss of patients with severe psoriasis has been estimated to amount to 760 euros per year (from 2015), which represents 27% of the total cost per patient. For moderate psoriasis, indirect costs per patient amount to 313 euros (19% of the total) and for mild psoriasis 151 euros (13% of the total) [3,4].

Patients treated with secukinumab showed statistically significant improvements in two of the three work productivity variables contemplated in WPAI-PSO (work productivity and activity impairment questionnaire-psoriasis) and in the variable of overall impairment of activities of daily living, which is also contemplated in the same questionnaire[41]. These findings could imply a potential reduction of indirect and direct non-medical costs associated with moderate-to-severe psoriasis.

Figure 1. Percentage reductions in impairment on the WPAI_PSO from baseline to week 52

Source: [41] †p<0,01

Domain: Knowledge about the intervention

12. <u>Quality of the evidence</u>: What is the quality of the designs, validity, relevance, and completeness of the studies in the context of the intervention?

<u>FEATURE and JUNCTURE trials</u>[1]: They have very similar designs. The baseline characteristics of the patients were similar in the treatment groups, which were comparable. One possible limitation when comparing the results between studies would be that they include both patients who received biologic pre-treatment as well as biologic naive patients. They are studies of superiority with intention-to-treat analysis, which is appropriate. The chosen control group (placebo) was not the most appropriate when there was a possibility of a comparison versus active treatment. The results of both trials were measured after 12 weeks of treatment.

<u>ERASURE and FIXTURE trials</u>[1]: These trials have very similar designs. The control group (etanercept) in the FIXTURE study is suitable as a comparator because it is one of the active treatments. The study of the main efficacy variables was performed by intention-to-treat analysis, as well as that of the safety variables. Few patients continued to receive placebo after week 12, which limits the comparison during the maintenance period, and secondary efficacy variables in this group were not evaluated. In both studies, the results of efficacy and safety variables were available at 12 and 52 weeks, providing evidence in the medium term, unlike the JUNCTURE and FEATURE trials.

<u>CLEAR trial</u>[41]: The arms of the study were comparable at baseline, the authors used valid instruments to evaluate the results, and a differential withdrawal rate was not observed [44]. In the CLEAR trial, the patients were naive to biologic treatment, favouring a somewhat different profile from the pivotal studies and justifying the better response observed both for secukinumab compared with the pivotal trials and other reference drugs.

13. <u>Expert consensus/ Clinical practice guidelines</u>: Is the intervention (or intervention of the same kind) recommended in the usual CPGs? At what level (first line?)

Based on the data on quality, safety, and efficacy, the European Committee for Medicinal Products for Human Use (CHMP) considered the benefit/risk ratio of secukinumab as favourable in patients with moderate-to-severe plaque psoriasis for whom systemic therapy is indicated, recommending the marketing authorisation of Cosentyx® [42].

In July 2015, NICE published a Technology appraisal guidance on secukinumab for the treatment of moderate-to-severe plaque psoriasis [45], in which it is recommended as a treatment option when the disease is severe (defined as PASI ≥10 and DLQI >10) and has not responded to standard systemic therapies (e.g., cyclosporine, methotrexate, and PUVA) or when these treatments are contraindicated or the patient cannot tolerate them.

According to the assessment report for secukinumab [46], it is considered as a therapeutic alternative with a new mechanism of action, which provides high efficiency clearance of skin lesions and has been shown to be superior to some of the drugs available for second-line treatment.

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Supplementary material 2. Criteria definitions and scales

CRITERIA	DEFINITIONS
QUANTITATIVE CRITERIA	
NEED FOR INTERVENTION	
DISEASE SEVERITY	Severity of the health condition of patients treated with the proposed intervention (or severity of the health condition that is to be prevented) with respect to mortality, disability, function, impact on quality of life, clinical course (i.e., acuteness, clinical stages). ***Scoring scale:*** ☐*5 Very severe* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 Not severe*
SIZE OF THE AFFECTED POPULATION	Number of people affected by the condition (treated or prevented by the proposed intervention) among a specified population at a specified time; can be expressed as annual number of new cases (annual incidence) and/or proportion of the population affected at a certain point of time (prevalence). ***Scoring scale****:* ☐*5 X > 500/10,000* ☐*4 X < 500/10,000* ☐*3 X < 100/10,000* ☐*2 X < 10/10,000* ☐*1 X < 5/10,000 (rare)* ☐*0 X < 2/100,000 (ultra rare)*
UNMET NEEDS	Shortcomings of comparative interventions in their ability to prevent, cure, or ameliorate the condition targeted; also includes shortcomings with respect to safety, patient reported outcomes and convenience. ***Scoring scale****:* ☐*5 Many unmet needs* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No unmet needs*

CRITERIA	DEFINITIONS
COMPARATIVE OUTCOMES OF THE INTERVENTION (EXTENT OF BENEFIT)	
COMPARATIVE EFFECTIVENESS	Capacity of the proposed intervention to produce a desired (beneficial) change in signs, symptoms or course of the targeted condition above and beyond beneficial changes produced by alternative interventions. Includes efficacy and effectiveness data, as available. ***Scoring scale:*** ☐*5 Much better than comparator (positive contribution)* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No difference* ☐*-1* ☐*-2* ☐*-3* ☐*-4* ☐*-5 Much worse than comparator (negative contribution)*
COMPARATIVE SAFETY / TOLERABILITY	Capacity of the proposed intervention to produce a reduction in intervention-related harmful or undesired health effects compared to alternative interventions. ***Scoring scale:*** ☐*5 Much better than comparator (positive contribution)* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No difference* ☐*-1* ☐*-2* ☐*-3* ☐*-4* ☐*-5 Much worse than comparator (negative contribution)*

CRITERIA	DEFINITIONS
COMPARATIVE PATIENT REPORTED OUTCOMES (PROS)	Capacity of the proposed intervention to produce beneficial changes in patient-reported outcomes (PROs) (e.g., quality of life) above and beyond beneficial changes produced by alternative interventions; also includes improvement in convenience to patients. ***Scoring scale:*** ☐*5 Much better than comparator (positive contribution)* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No difference* ☐*-1* ☐*-2* ☐*-3* ☐*-4* ☐*-5 Much worse than comparator (negative contribution)*
TYPE OF HEALTH BENEFIT OF THE INTERVENTION	
TYPE OF PREVENTIVE BENEFIT	Disease risk reduction provided by the proposed intervention at the population-level (e.g., prevention, reduction in disease transmission, reduction in the prevalence of risk factors). Public health perspective. ***Scoring scale:*** ☐*5 Eradication* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No preventive benefit*
TYPE OF THERAPEUTIC BENEFIT	Nature of the clinical benefit provided by the proposed intervention at the patient-level (e.g., symptom relief, prolonging life, cure). ***Scoring scale:*** ☐*5 Cure* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No therapeutic benefit*

CRITERIA	DEFINITIONS
ECONOMIC CONSEQUENCES OF THE INTERVENTION	
COMPARATIVE COST CONSEQUENCES – COST OF INTERVENTION	Net cost of covering the intervention (excluding other spending). This represents the differential between expected expenditures for the proposed intervention and potential cost savings that may result from replacement of other intervention(s) currently covered by the health plan. Limited to cost of intervention (e.g., acquisition cost, implementation and maintenance cost). ***Scoring scale:*** ☐*5 Substantial savings (positive contribution)* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No change in spending* ☐*-1* ☐*-2* ☐*-3* ☐*-4* ☐*-5 Substantial additional expenditures (negative contribution)*
COMPARATIVE COST CONSEQUENCES – OTHER MEDICAL COSTS	Impact of the intervention on other medical costs (excluding intervention cost, such as hospitalization, specialist consultations, adverse events costs, long-term care, etc). ***Scoring scale:*** ☐*5 Substantial savings (positive contribution)* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No change in spending* ☐*-1* ☐*-2* ☐*-3* ☐*-4* ☐*-5 Substantial additional expenditures (negative contribution)*

CRITERIA	DEFINITIONS
COMPARATIVE COST CONSEQUENCES – NON-MEDICAL COST	Impact of the intervention on non-medical costs (excluding intervention cost and other medical costs) such as disability costs, social services, lost productivity, caregiver time, etc. ***Scoring scale:*** ☐*5 Substantial savings (positive contribution)* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 No change in spending* ☐*-1* ☐*-2* ☐*-3* ☐*-4* ☐*-5 Substantial additional expenditures (negative contribution)*
KNOWLEDGE ABOUT THE INTERVENTION	
QUALITY OF EVIDENCE	Extent to which evidence on the proposed intervention is relevant to the decisionmaking body (in terms of population, disease stage, comparator interventions, outcomes etc.) and valid with respect to scientific standards (i.e., study design etc.) and conclusions (agreement of results between studies). This includes consideration of uncertainty (e.g., conflicting results across studies, limited number of studies & patients). Consistent and complete reporting of evidence is a pre-requisite to assess validity. ***Scoring scale:*** ☐*5 Highly relevant and valid* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 Not relevant and/or invalid*

CRITERIA	DEFINITIONS
EXPERT CONSENSUS/CLINICAL PRACTICE GUIDELINE RECOMMENDATIONS (CPGS)	Concurrence of the proposed intervention (or similar alternatives) with the current consensus of experts on what constitutes state-of-the-art practices in the management of the targeted health condition; guidelines are usually developed via an explicit process and are intended to improve clinical practice. ***Scoring scale:*** ☐*5 Strong recommendation for intervention above all other alternatives* ☐*4* ☐*3* ☐*2* ☐*1* ☐*0 Not recommended*
CONTEXTUAL CRITERIA	
NORMATIVE CONTEXTUAL CRITERIA	
MANDATE AND SCOPE OF THE HEALTHCARE SYSTEM	Alignment of the intervention with the mandate/scope of the healthcare system. The goal of healthcare is to maintain normal functioning. The mission and scope of health plans/systems derive from this principle. **Positive**: aligned with mandate and scope **Negative**: in potential disagreement with mandate and scope
PRIORITIES OF THE POPULATION AND ACCESS	Alignment of the intervention with current priorities of health system/plan. Priorities for specific groups of patients are defined by societies/decisionmakers and reflect their moral values. Such considerations are aligned with the principle of fairness, which considers treating like cases alike and different cases differently and often gives priority to those who are worst-off (theory of justice). **Positive**: aligned with established priorities **Negative**: in potential disagreement with established priorities
COMMON GOAL AND SPECIFIC INTERESTS	Pressures or barriers from groups of stakeholders or individuals are often part of the context surrounding healthcare interventions. Being aware of pressures and interests at stake and how they may affect decisionmaking helps ensure that decisions are fair-minded. **Positive**: aligned with the common goal **Negative**: in potential disagreement with the common goal
ENVIRONMENTAL IMPACT	The extent to which the production, use or implementation of the intervention causes environmental damage. **Positive**: aligned with the protection of the environment **Negative**: in potential disagreement with the protection of the environment

CRITERIA	DEFINITIONS
FEASIBILITY OF THE CONTEXTUAL CRITERIA	
OPPORTUNITY COSTS & AFFORDABILITY	Consideration of the medical resources that may be forgone (opportunity costs) if the intervention is implemented and whether the healthcare system can afford implementing the intervention. Both opportunity cost and affordability considerations require a financial/budgeting exercise. Opportunity cost and affordability can be considered at the system/institution level and at the patient level. **Positive**: savings, low opportunity cost **Negative**: high opportunity cost
SYSTEM CAPACITY & APPROPRIATE USE OF THE INTERVENTION	The capacity of a healthcare system to implement the intervention and to ensure its appropriate use depends on its infrastructure, organization, skills, legislation, barriers and risks of inappropriate use. Such considerations include mapping current systems and estimating whether the use of the intervention under scrutiny requires additional capacities (note: if available, economic data on these aspects could be included under the economic criterion of the MCDA model). **Positive**: aligned with system capacity and appropriate use **Negative**: in potential disagreement with system capacity and appropriate use
POLITICAL, HISTORICAL AND CULTURAL CONTEXT	The political, historical and cultural context may influence the value of an intervention with respect to specific political situations and overall priorities (e.g., priority for innovation) as well as habits, traditions and precedence. **Positive**: aligned with political, historical & cultural context **Negative**: in potential disagreement with political, historical & cultural context

Supplementary material 3. Evidence matrix of qualitative criteria. EVIDEM contextual tool

1. Evidence matrix of qualitative criteria for dupilumab

Normative contextual criteria

1. ***Mandate and scope of the health system:*** *Is the use of dupilumab in severe AD aligned with the mandate and scope of the National Health System?*

Evidence: According to Law 16/2003 of 28 May, on cohesion and quality of the National Health System (NHS), the common objective of public health administrations is to ensure citizens the right to health protection and to guarantee equity, quality and social participation. The efforts of the system should be oriented towards the anticipation of health problems or towards effective solutions to these problems, evaluating the benefit of clinical actions, and incorporating only those that provide an added value to the improvement of health.

Researching on health constitutes a strategic vector for the policies of promotion and coordination of R&D and innovation in Spain, which must consider, as fundamental aspects, (a) research on the most prevalent diseases; (b) clinical research on human diseases; (c) public health and health services; (d) rehabilitation and development of assisted environments aimed at addressing chronicity; (e) rare diseases; (f) biological bases of the disease; and (g) the development of nanomedicine and personalised medicine in which the challenge is to treat the individual and not the disease [1].

2. ***Population priorities and access****: Is the use of dupilumab aligned with the current specific priorities of the NHS (e.g., isolated areas, priority diseases, age groups, specific therapeutic groups)?*

Evidence: Skin diseases are not a specific priority of the NHS per se. According to a study published in Spain on the relationship between health research funded by the NHS and disease burden, skin diseases, together with some neuropsychiatric diseases (e.g., alcohol abuse, migraines, bipolar disorders, depression), some specific cancers (e.g., oral, pharyngoesophageal, lung), accidents and unintentional injuries, or sexually transmitted diseases were the causes that had lower allocation for research funds for each DALY averted [2].

3. ***Common goal and specific interests:*** *Are there pressures or barriers by interest groups or individuals in the context surrounding the health intervention? Being aware of the pressures and interests at stake and how they can affect decision-making helps ensure that decisions are fair.*

No evidence is available for this criterion.

4. ***Environmental impact****: To what extent does the production or use of the intervention cause environmental damage?*

There is no information on the possible environmental impact of dupilumab.

Feasibility of contextual criteria

5. ***Opportunity cost and affordability:*** *Does the use of dupilumab imply a significant shift in the use of NHS resources? Consideration of health resources that are not invested in other interventions (opportunity costs) if the intervention is implemented, and whether the health system can afford to implement the intervention (affordability).*

No evidence is available for this criterion.

6. ***System capacity and appropriate use of the intervention:*** *Is the NHS trained (at the organisational, technical, legal levels, etc.) to ensure the proper use of dupilumab?*

Evidence*:* The administration of dupilumab does not require a special process or equipment, specific skills for its management, nor additional legal requirements than those required by the drug regulatory rules [3,4]

7. ***Political, historical, and cultural context:*** *Can it influence the value of an intervention compared to specific political situations and general priorities (for example, priority for innovation), as well as habits, traditions, and precedents?*

Evidence*:* Innovation is a priority of the health system. RD-L 1/2015 of July 25, 2015 (Article 92) establishes the following: "For the decision to fund new medicines, in addition to the corresponding cost-effectiveness analysis and budgetary impact, the component of innovation will be taken into account for indisputable therapeutic advances by modifying or improving the course of the disease, the prognosis and outcome of the intervention, and its contribution to the sustainability of the NHS, if, for the same health outcome, it contributes positively to the Gross Domestic Product" [5].

Dupilumab is considered an innovative therapy. It offers a significant therapeutic advance in the treatment of AD. Unlike the available systemic therapies, it profoundly changes the therapeutic paradigm and long-term management of AD. Similar to the approved biologics for psoriasis, dupilumab seems to offer the opportunity for long-term disease control, being in general effective and safe [6]. Recently, it was granted a breakthrough therapy designation by the FDA [7], and NICE has allowed an early access programme for dupilumab (to date, only eight drugs have received approval for this type of programme, six of which are in the oncology field) [8]. According to the Early Access to Medicines Scheme (EAMS) Scientific Opinion of the United Kingdom, dupilumab produces a significant reduction in the severity and extension of eczema lesions and an improvement in sleep and quality of life [3].

2. Evidence of qualitative criteria for secukinumab

Normative contextual criteria

1. ***Mandate and scope of the health system****: Is the use of dupilumab in severe AD aligned with the mandate and scope of the NHS?*

Evidence: According to Law 16/2003 of 28 May, on cohesion and quality of the National Health System (NHS), the common objective of public health administrations is to ensure citizens the right to health protection and to guarantee equity, quality and social participation. The efforts of the system should be oriented towards the anticipation of health problems or towards effective solutions to these problems, evaluating the benefit of clinical actions, and incorporating only those that provide an added value to the improvement of health.

Researching on health constitutes a strategic vector for the policies of promotion and coordination of R&D and innovation in Spain, which must consider, as fundamental aspects, (a) research on the most prevalent diseases; (b) clinical research on human diseases; (c) public health and health services; (d) rehabilitation and development of assisted environments aimed at addressing chronicity; (e) rare diseases; (f) biological bases of the disease; and (g) the development of nanomedicine and personalised medicine in which the challenge is to treat the individual and not the disease [1].

2. ***Population priorities and access****: Is the use of dupilumab aligned with the current specific priorities of the NHS (e.g., isolated areas, priority diseases, age groups, specific therapeutic groups)?*

Evidence: Skin diseases are not per se a specific priority of the NHS. According to a study published in Spain on the relationship between health research funded by the NHS and disease burden, skin diseases, together with some neuropsychiatric diseases (e.g., alcohol abuse, migraines, bipolar disorders, depression), some specific cancers (e.g., oral, pharyngoesophageal, lung), accidents and unintentional injuries, or sexually transmitted diseases had lower allocations for research funds for each DALY averted [2].

3. ***Common goal and specific interests:*** *Are there pressures or barriers by interest groups or individuals in the context surrounding the health intervention? Being aware of the pressures and interests at stake and how they can affect decision-making helps ensure that decisions are fair.*

No evidence is available for this criterion.

4. **Environmental impact:** *To what extent does the production, use, or implementation of the intervention cause environmental damage?*

There is no information on the possible environmental impact of treatment with secukinumab.

Feasibility of contextual criteria

5. ***Opportunity cost and affordability:*** *Does the use of secukinumab represent a significant shift in the use of NHS resources? Consideration of health resources that are not invested in other interventions (opportunity costs) if the intervention is implemented, and whether the health system can afford to implement the intervention (affordability).*

No evidence is available for this criterion.

6. ***System capacity and appropriate use of the intervention:*** *Is the NHS trained (at the organisational, technical, legal levels, etc.) to ensure the proper use of dupilumab?*

Evidence: The administration of secukinumab does not require a special process or equipment, particular skills for its management, or additional legal requirements from those required by drug regulatory rules [910].

7. ***Political, historical, and cultural context:*** *Can it influence the value of an intervention compared with specific political situations and general priorities (e.g., priority for innovation), as well as habits, traditions, and precedents?*

Evidence: Innovation is a priority of the health system. RD-L 1/2015 of July 25, 2015 (Article 92) establishes the following: "For the decision to fund new medicines, in addition to the corresponding cost-effectiveness and budgetary impact analyses, the component of innovation will be taken into account for indisputable therapeutic advances by

modifying or improving the course of the disease, the prognosis and outcome of the intervention, and its contribution to the sustainability of the NHS, if, for the same health outcome, it contributes positively to the Gross Domestic Product" [5].

The introduction of biological therapies in the treatment of psoriasis with a new mechanism of action represents a new era in the history of the treatment of this condition. Secukinumab is unanimously recommended by the FDA and the EMA for its strong efficacy and safety results for the treatment of moderate-to-severe psoriasis [11].

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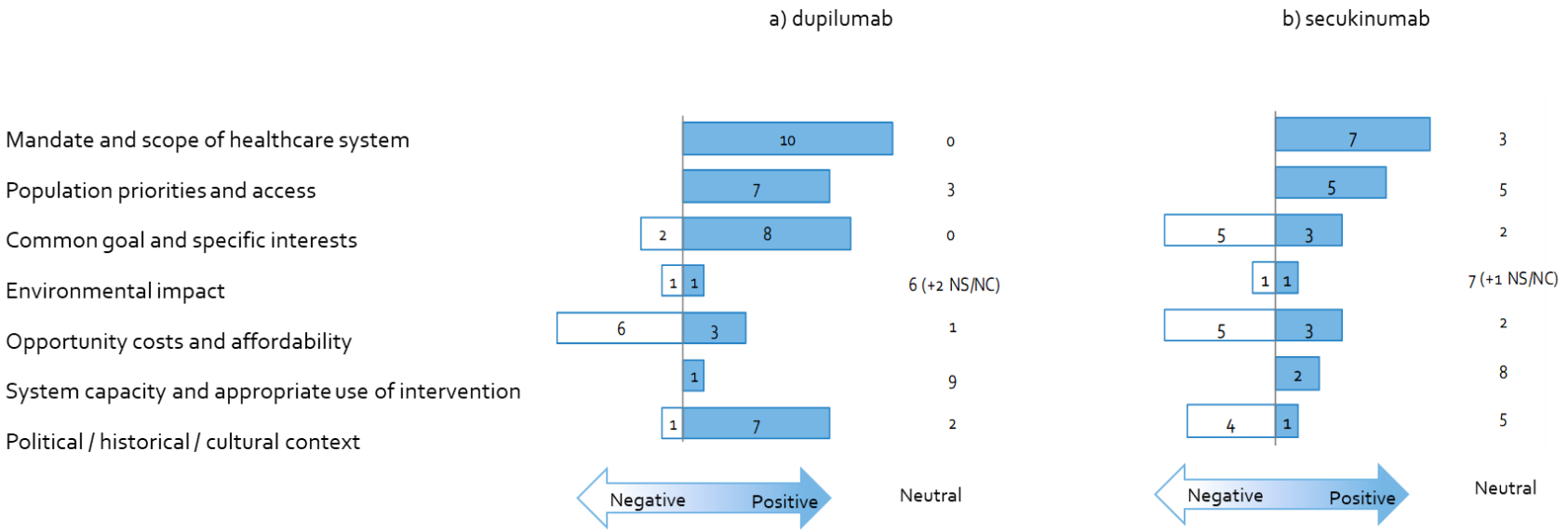
Supplementary material 4. Impact of contextual criteria

Figure 2. Impact of contextual criteria on the appraisal of dupilumab and secukinumab assigned by the advisory committee*



*Measured in terms of number of panellists' opinions (positive, neutral or negative) assigned to each EVIDEM qualitative criterion.