# New Medicine Recommendation
# Secukinumab (Cosentyx▼) for treatment of Palmoplantar Psoriasis

**Recommendation: RED**

Secukinumab is recommended for the treatment of moderate to severe palmoplantar psoriasis that has not responded (refractory) to at least two standard systemic treatments and photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications.

Medicine is supplied by the hospital for the duration of the treatment course.

Primary care initiation or continuation of treatment is not recommended unless exceptional circumstances such as specialist GP.

Red medicines are those where primary care prescribing is not recommended. These treatments should be initiated by specialists only and prescribing retained within secondary care. They require specialist knowledge, intensive monitoring, specific dose adjustments or further evaluation in use. If however, a primary care prescriber has particular specialist knowledge or experience of prescribing a particular drug for a particular patient it would not always be appropriate for them to expect to transfer that prescribing responsibility back to secondary care. There should be a specific reason and a specific risk agreement, protocol and service set up to support this.

Primary care prescribers may prescribe RED medicines in exceptional circumstances to patients to ensure continuity of supply while arrangements are made to obtain on going supplies from secondary care.

Novartis, the company holding the marketing authorisation for secukinumab (Cosentyx▼), have confirmed that the use of secukinumab to treat a patient with moderate to severe plaque psoriasis with hand and foot involvement is within licence. However, the use of secukinumab to treat palmoplantar psoriasis only would be considered outside of licence.

**Summary of supporting evidence**

**Psoriasis**

- Four phase III studies (**FIXTURE**[1], **ERASURE**[1], **FEATURE**[2] and **JUNCTURE**[3]) recruited adults with moderate-to-severe plaque psoriasis diagnosed at least six months previously who had a psoriasis area and severity index (PASI) score of at least 12, a modified (2011) investigator's global assessment (IGA) score of at least 3 and involvement of at least 10% of their body surface area. Their psoriasis was poorly controlled with topical treatments, phototherapy, systemic therapy (including biologics) or a combination of these. Randomisation was stratified by body weight, <90kg versus ≥90kg, in all trials and also by geographical region in FIXTURE and ERASURE. In all studies, co-primary endpoints (PASI 75 and modified (2011) IGA 0/1 at week 12) were achieved by significantly more patients in the secukinumab 300mg groups than in the placebo groups. In the FIXTURE study, co-primary endpoints were achieved by significantly more patients in the secukinumab 300mg group than in the etanercept group.
- In the FIXTURE and ERASURE studies, 84% (210/249) and 80% (161/200) of patients who achieved a PASI 75 response at week 12 maintained this at week 52 by continuing treatment with secukinumab 300mg. Corresponding figures for modified (2011) IGA 0/1 response were



 

80% (161/202) and 74% (119/160). In the FIXTURE study, these were significantly greater than proportions of week-12 responders maintaining PASI 75 and modified (2011) IGA 0/1 responses at week 52 with the comparator, etanercept: 72% (103/142) and 57% (50/88), respectively.

- Pooled analyses of data to 52 weeks from the ERASURE, FIXTURE and SCULPTURE studies indicate that PASI 75 response rate at week 52 was 77% (605/784) and 55% (179/323) in the secukinumab 300mg and etanercept groups and modified (2011) IGA 0/1 response rates were 63% (495/784) and 37% (120/323), respectively. Response rates for these outcomes with secukinumab reached their plateau at week 16 and declined slightly thereafter.
- In the four pivotal studies, Dermatology Life Quality Index (DLQI) was significantly improved at week 12 with secukinumab 300mg compared to placebo, with mean decreases (improvements) from baseline of -10.4 to -11.6 compared to -1.1 to -1.9 in the placebo groups and -7.9 in the etanercept group of the FIXTURE study

**Palmoplantar Psoriasis**

- The investigational program for secukinumab for palmoplantar psoriasis included **GESTURE**,[21] a double-blind, randomized, placebo controlled, parallel-group multicentre Phase 3b study
- Both secukinumab doses (150mg / 300mg) were superior to placebo at week 16 with respect to a ppIGA (palmoplantar IGA) 0/1 response. Overall, 33.3% of subjects on secukinumab 300 mg, 22.1% on secukinumab 150 mg, and 1.5% on placebo ($P < 0.0001$ and $P = 0.0002$, respectively vs. placebo) achieved this endpoint. Both secukinumab doses exhibited consistently higher percentages of ppIGA 0/1 responders compared to placebo over time to week 16, starting as early as week 2 for secukinumab 300 mg.
- Across all measures secukinumab 300 mg showed the greatest efficacy. Similar results were observed with multiple imputation data at week 16, with 39.3% of subjects on secukinumab 300 mg, 23.1% on secukinumab 150 mg, and 1.5% on placebo achieving a ppIGA 0/1 response ($P<0.0001$ and $P = 0.0002$, respectively vs placebo).
- In subjects receiving secukinumab 300 mg that had previously failed biologics, ppIGA 0/1 response rate remained similar to the overall population (33.3%).
- The reduction in ppPASI (palmoplantar PASI) from baseline to week 16 was consistently greater with secukinumab compared with placebo. At week 16, ppPASI reduction from baseline was significant, with secukinumab 300 mg (-54.5%) and 150 mg (-35.3%) compared with placebo (- 4.0%; $P<0.0001$ and $P = 0.0006$, respectively).
- At baseline, skin problems had a very large effect on subjects' lives (median DLQI 13-14). At week 16, the percentage of subjects achieving a DLQI score of 0/1, indicating no impact of skin problems on their lives, was significantly higher with secukinumab 300 mg (26.6%) and 150 mg (16.9%) compared with placebo (1.5%, $P< 0.0001$ and $P <0.005$, respectively).
- Palmoplantar Quality-of-Life Instrument (ppQLI) captured more health-related quality of life (HRQoL) information because it is specific to aspects relevant for palmoplantar psoriasis. It showed that the percentage of subjects experiencing no difficulty due to involvement of both palms and soles increased from 0% at baseline to 12.5% and 10.8% at week 16 for secukinumab 300 mg and 150 mg, respectively, and did not change for placebo.
- At baseline, HRQoL was overall more impaired due to psoriasis on the palms than on the soles. As a result of psoriasis of the palms, 50%-60% of subjects at baseline reported moderate-to-extreme hand pain, work limitation, and social limitation, as well as feeling embarrassed and less confident. Due to psoriasis of the soles, almost 50% of subjects reported moderate-to extreme pain/inability to walk and work. At week 16, these percentages were halved with secukinumab 300 mg. With the Subject Global Assessment (SGA), subjects reported a median improvement in HRQoL after treatment for palmoplantar psoriasis: 55.4%, 29.6%, and 14.0% for secukinumab 300 mg, 150 mg, and placebo, respectively, at week 16.

| |
|---|
| EQ-5D also revealed significant health impairment of subjects at baseline, with improvements being observed with both doses of secukinumab at week 16. |

**Details of Review**

| |
|---|
| Name of medicine (generic & brand name): Secukinumab (Cosentyx▼) |
| Strengths and forms:<br>150 mg solution for injection in pre-filled syringe<br>150 mg solution for injection in pre-filled pen |
| Dose and administration:<br>The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg. |
| BNF therapeutic class / mode of action: Chapter 10, Musculoskeletal system, Arthritis<br>Secukinumab (Cosentyx▼) is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence treatment with secukinumab reduces erythema, induration and desquamation present in plaque psoriasis lesions.<br>Serum levels of total IL-17A (free and secukinumab-bound IL-17A) are initially increased in patients receiving secukinumab. This is followed by a slow decrease due to reduced clearance of secukinumab-bound IL-17A, indicating that secukinumab selectively captures free IL-17A, which plays a key role in the pathogenesis of plaque psoriasis. |
| Licensed indication(s):<br>Secukinumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. |
| Proposed use:<br>Moderate to severe palmoplantar psoriasis that has not responded (refractory) to at least two standard systemic treatments and photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. |
| Course and cost:<br>300mg every week for 5 doses, then maintenance 300mg every month, review treatment if no response within 16 weeks of initial dose. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks.<br>Cost – PAS scheme available for when secukinumab used within licence i.e. moderate to severe plaque psoriasis with palmoplantar involvement. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of secukinumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that |

this patient access scheme does not constitute an excessive administrative burden on the NHS.[4] The company has confirmed that the PAS scheme would also be available for the treatment of palmoplantar psoriasis alone

Current standard of care/comparator therapies:

Topical agents such as coal tar products, salicylic acid and corticosteroids may be used initially for mild to moderate psoriasis. However, systemic treatment is required for severe, resistant, unstable or complicated forms of psoriasis, and it should be initiated only under specialist supervision. Standard systemic drugs for psoriasis include acitretin and drugs which affect the immune response e.g. ciclosporin and methotrexate. Other biologics e.g. etanercept, adalimumab, infliximab and ustekinumab can be used for severe plaque psoriasis that has not responded (refractory) to at least two standard systemic treatments and photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications.

**Relevant NICE guidance:**

Secukinumab for treating moderate to severe plaque psoriasis Technology appraisal guidance [TA350] Published date: 22 July 2015[4]

Secukinumab is recommended, within its marketing authorisation, as an option for treating adults with plaque psoriasis only when:

- the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
- the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long‑wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them
- the company provides secukinumab with the discount agreed in the patient access scheme.

Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these people. An adequate response is defined as either:

- a 75% reduction in the PASI score from when treatment started (PASI 75) or
- a 50% reduction in the PASI score (PASI 50) and a 5‑point reduction in DLQI from when treatment started.

**Disease Background**

Psoriasis is one of the most common human skin diseases affecting 2 to 3% of the general population. It is characterized by increase in epidermal thickness, hyperkeratosis, parakeratosis, dilated blood vessels, and dense clusters of inflammatory T-cells and dendritic cells in the dermis, and neutrophils and CD8+ T-cells in the epidermis. IL-17A directly activates in synergy with other cytokines (such as TNFα, IFNγ or IL-22) keratinocytes and dermal fibroblasts to produce cytokines (e.g. IL-6, TNFα, IL-1β, IL-20 family cytokines, GM-CSF), chemokines (CXCL1, CXCL2, CCL20, CXCL8/IL-8) and anti-microbial peptides. This leads to the recruitment of inflammatory cells such as neutrophils and lymphocytes (e.g. Th17 cells) into the psoriatic lesion thereby maintaining and amplifying local inflammation.

Approximately 80-90% of psoriasis patients have chronic plaque psoriasis, characterized by recurrent exacerbations and remissions of thickened, erythematous, scaly patches of skin.

Patients with moderate to severe disease represent approximately 15% to 25% of plaque psoriasis patients and generally require systemic therapy.

The treatment of moderate-to-severe psoriasis, or skin involving more than 10% body surface area (1% body surface area is equivalent to one whole hand), requires systemic agents.[5]

Palmoplantar psoriasis is plaque psoriasis involving the palms and soles. Studies have shown that up to 40 percent of patients with plaque psoriasis have some form of palmoplantar involvement.[6] The prevalence of palmoplantar psoriasis varies widely in different studies, ranging from 2.8%[7] to 40.9%.[8]

Palmoplantar psoriasis can occur as part of a more generalized plaque-type condition, or it may be limited to the palms of the hands and the soles of the feet. It is a chronic, recurring condition and is characterized by a few different symptoms:

- The appearance of red patches of skin topped with scales typical of psoriasis on the palms and elsewhere on the body
- Thickening and scaling of the skin accompanied with the formation of deep, painful fissures on the palms and soles
- Palmoplantar pustulosis - the appearance of deep, yellowish pustules (rare)

Palmoplantar sores may appear as typical psoriasis plaques or as more unified, less obviously inflamed thickenings of the skin called acquired keratodermas.

Palmoplantar psoriasis can make it difficult to carry out everyday activities such as walking.

The location of symptoms also makes it harder to keep the lesions clean and to hide them. This can lead to embarrassment and social anxiety.

Palomoplantar psoriasis is associated with disproportionately greater pain, functional limitations, and significant impairment of health-related quality of life.[9] Compared to plaque psoriasis involving other regions, those with palmoplantar psoriasis suffer from more discomfort and disability.[10]

It is generally recognized that palmoplantar psoriasis poses a treatment challenge.[11] Therapies that achieve a certain level of response in other parts of the body often perform relatively poorly in the palmoplantar regions. Patients with palmoplantar involvement but little plaque psoriasis elsewhere on the body are less likely to participate in pivotal trials for new systemic therapies because these trials usually require a body surface area (BSA) of 10 percent or greater.

Few trials have examined the effect of systemic therapies on palmoplantar psoriasis.[12, 13] These studies uniformly showed that the currently available systemic medications yield lower efficacy in palmoplantar psoriasis than in generalized psoriasis. Biologics have shown better efficacy than other treatment options,[14, 15, 16] however, the efficacy achieved with biologics in treating palmoplantar psoriasis is markedly lower than that achieved by these agents in psoriasis on other parts of the body.

**Current treatment options**

Due to the thick stratum corneum of the palmoplantar regions, the search for effective topical treatments has been significantly more difficult than other forms of psoriasis. Current topical treatments for mild to moderate plaque psoriasis include phototherapy, coal tar, corticosteroids and tazarotene ointment; however, if there is moderate to severe disease then systemic treatment is warranted.

Adalimumab (TA146), etanercept (TA 103), infliximab (TA134) , ustekinumab (TA180) and secukinumab (TA 350) have all been reviewed and accepted for use in psoriasis by LMMG - Psoriasis: LMMG Biologic Commissioning Pathway Sept 2016[17]

In TA350 (Secukinumab for treating moderate to severe plaque psoriasis), secukinumab is recommended, within its marketing authorisation, as an option for treating adults with plaque psoriasis only when:

- the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10

- the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long‑wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them
- the company provides secukinumab with the discount agreed in the patient access scheme.

These pre-requisites also exist for adalimumab, etanercept and ustekinumab with infliximab being restricted for use in patients with very severe psoriasis, i.e.

- The disease is very severe as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18.
- The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant to or has a contraindication to these treatments.

Therefore, in relation to the NICE guideline, patients with severe palmoplantar psoriasis might not qualify for treatment with secukinumab (or any of the other biologics) as they may have little plaque psoriasis elsewhere on the body and therefore will not have a PASI score of greater than 10.

The British Association of Dermatologists guidelines for biologic therapy for psoriasis (2017)[18] states that biologic therapy should be offered to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated and the psoriasis has a large impact on physical, psychological or social functioning (for example, a DLQI or cDLQI of >10 or clinically relevant depressive or anxiety symptoms) and one or more of the following disease severity criteria apply:

- the psoriasis is extensive (defined as BSA >10%, or a PASI ≥10, or at least 'moderate' on physician's global assessment)
- **the psoriasis is severe at localised sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, <u>palms, soles</u>, flexures and genitals)**

**Summary of efficacy data in proposed use:**

Palmoplantar psoriasis has rarely been studied in clinical trials, which may explain why there is no clear treatment algorithm and has been recognized as one of the top priorities in psoriasis research by the International Psoriasis Council.[19] The data that does exist often comes from research with heterogeneous patient populations or small sample sizes and/or from a subgroup/post-hoc analysis from trials in which palmoplantar psoriasis was not the main focus of research.

**<u>Plaque Psoriasis</u>**

Psoriasis Area and Severity Index (PASI) is the most widely used tool for the measurement of severity of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).

The investigator global assessment (IGA) is another common approach used in clinical practice. This approach takes into consideration the clinical presentation of the disease from the physician's perspective, using five categories of severity, 0 (Clear -No signs of psoriasis. Post-inflammatory hyperpigmentation may be present), to 4 (Severe - Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions).

Four phase III studies (FIXTURE[1], ERASURE[1], FEATURE[2] and JUNCTURE[3]) recruited adults with moderate-to-severe plaque psoriasis diagnosed at least six months previously who had a psoriasis area and severity index (PASI) score of at least 12, a modified (2011) investigator's

global assessment (IGA) score of at least 3 and involvement of at least 10% of their body surface area.

Their psoriasis was poorly controlled with topical treatments, phototherapy, systemic therapy (including biologics) or a combination of these. Randomisation was stratified by body weight, <90kg versus ≥90kg, in all trials and also by geographical region in FIXTURE and ERASURE.

Patients were equally assigned to placebo; secukinumab 150mg or 300mg (two 150mg) subcutaneous (SC) injections at weeks 0, 1, 2, 3, 4 and then every 4 weeks to week 48. In the FIXTURE study, patients could also be randomised to etanercept 50mg SC injection twice weekly for 12 weeks then once weekly to week 51. Patients in the placebo groups not achieving at least a 75% improvement in PASI score (PASI-75 response) at week 12 were re-randomised in a 1:1 ratio and treated from week 12 with secukinumab 150mg or 300mg SC injections in the dose regimen detailed previously.

The co-primary outcomes were proportions of patients achieving, at week 12, a PASI 75 response and a modified (2011) IGA 0/1 response, which comprised an IGA score of 0 (clear) or 1 (almost clear) and a reduction of at least 2 points from baseline. These were assessed using a stratified Cochran-Mantel-Haenszel test in all randomised patients, with missing data input as non-response. In all studies, co-primary endpoints (PASI 75 and modified (2011) IGA 0/1 at week 12) were achieved by significantly more patients in the secukinumab 300mg groups than in the placebo groups. In the FIXTURE study, co-primary endpoints were achieved by significantly more patients in the secukinumab 300mg group than in the etanercept group. In the FIXTURE and ERASURE studies, 84% (210/249) and 80% (161/200) of patients who achieved a PASI 75 response at week 12 maintained this at week 52 by continuing treatment with secukinumab 300mg. Corresponding figures for modified (2011) IGA 0/1 response were 80% (161/202) and 74% (119/160). In the FIXTURE study, these were significantly greater than proportions of week-12 responders maintaining PASI 75 and modified (2011) IGA 0/1 responses at week 52 with etanercept: 72% (103/142) and 57% (50/88), respectively.

Pooled analyses of data to 52 weeks from the ERASURE, FIXTURE and SCULPTURE[20] studies indicate that PASI 75 response rate at week 52 was 77% (605/784) and 55% (179/323) in the secukinumab 300mg and etanercept groups and modified (2011) IGA 0/1 response rates were 63% (495/784) and 37% (120/323), respectively. Response rates for these outcomes with secukinumab reached their plateau at week 16 and declined slightly thereafter.

In the four pivotal studies, Dermatology Life Quality Index (DLQI) was significantly improved at week 12 with secukinumab 300mg compared to placebo, with mean decreases (improvements) from baseline of -10.4 to -11.6 compared to -1.1 to -1.9 in the placebo groups and -7.9 in the etanercept group of the FIXTURE study.

In a double-blind phase III study (SCULPTURE) with the same inclusion criteria as the four pivotal studies described previously, 966 adults were randomised with stratification for body weight (<90kg or ≥90kg) and geographic region to secukinumab 300mg or 150mg SC at weeks 0, 1, 2, 3, 4 and 8. Those achieving a PASI 75 response at week 12 were re-randomised to their assigned dose of secukinumab every four weeks starting at week 12 (fixed-interval dosing group) or to receive placebo until they lost their PASI 75 response and at least 20% of their maximum PASI gain, then they received secukinumab weekly for 4 weeks then every 4 weeks until PASI 75 response was regained (start-of-relapse group). The study primarily assessed non-inferiority to the fixed-interval dosing group of the start-of-relapse group using a 15% margin for maintenance of PASI 75 at week 52 (in the fixed-interval group) and at week 40 or 52 (for start of relapse group who did not require and who did require retreatment at week 40, respectively). With secukinumab 300mg, PASI 75 response was maintained by 78% (169/216) and 68% (147/217) of patients in the respective groups. Non-inferiority of the start-of-relapse dosing to fixed-interval dosing was not demonstrated as the difference between the groups was -10% (lower bound of CI -19%) with secukinumab 300mg.

**Palmoplantar Psoriasis**

The investigational program for secukinumab for palmoplantar psoriasis included **GESTURE**[21], a double-blind, randomized, placebo controlled, parallel-group multicentre Phase 3b study.

The primary objective of the study was to assess the percentage of patients achieving palmoplantar psoriasis Investigator's Global Assessment (ppIGA) score of 0/1 (i.e., clear or almost clear/minimal and a reduction of at least 2 points from baseline on the ppIGA scale) at Week 16. The ppIGA scale was based on the IGA modified version 2011,[22] specifically applied to the palms and soles, (palmoplantar investigator global assessment).

Secondary objectives included the evaluation of ppIGA and Palmoplantar Psoriasis Area and Severity Index (ppPASI) over time from baseline to week 16 comparing treatment groups with placebo. The ppPASI was based on the PASI[23] but applied only to the palms and soles. Subject-reported outcomes included the Dermatology Life Quality Index (DLQI),[24] Palmoplantar Quality-of-Life Instrument (ppQLI),[25] Subject Global Assessment (SGA) of disease activity, and EuroQoL 5-Dimension Health Status Questionnaire (EQ- 5D).[26] The ppQLI assesses relevant dimensions affected by palmoplantar psoriasis: pain/discomfort, functionality, and social/activity limitations, and the SGA assesses subjects' well-being, from very poor (0 mm) to very good (100 mm). Safety and tolerability were evaluated by adverse events (AE), laboratory and vital sign assessments, and physical examinations.

205 patients were randomised to one of the three study groups, secukinumab 300 mg, secukinumab 150 mg, or placebo. Approximately 92% of subjects completed the 16-week treatment period. Eligible subjects were randomized 1:1:1, to secukinumab 300 mg, secukinumab 150 mg, or placebo delivered subcutaneously.

Eligible subjects were ≥18 years old with moderate-to-severe palmoplantar psoriasis (ppIGA score of ≥3 [on a 5-point scale]) and at least one additional plaque outside of the palms and soles to confirm the diagnosis of plaque psoriasis (nearly 3 out of 4 subjects had a BSA<10%). Subjects must have had disease previously inadequately controlled by topicals, phototherapy, and/or systemic therapy. Subjects with forms of psoriasis other than plaque were excluded. Previous exposure to secukinumab or other drugs directly targeting IL-17A or the IL-17 receptor were prohibited. During the study, no concomitant use of any other psoriasis treatments was allowed.

Results - Efficacy

All subjects had moderate to severe palmoplantar psoriasis with the majority (72.2%) having a BSA <10%. 58.5% of subjects were previously exposed to nonbiologic systemic therapies; 10.7% were exposed to biologics with the majority failing previous biologic therapy (7.8%).

Both secukinumab doses were superior to placebo at week 16 with respect to a ppIGA 0/1 response. 33.3% of subjects on secukinumab 300 mg, 22.1% on secukinumab 150 mg, and 1.5% on placebo ($P < 0.0001$ and $P = 0.0002$, respectively vs. placebo) achieved this endpoint.

Across all measures secukinumab 300 mg showed the greatest efficacy. Similar results were observed with multiple imputation data at week 16, with 39.3% of subjects on secukinumab 300 mg, 23.1% on secukinumab 150 mg, and 1.5% on placebo achieving a ppIGA 0/1 response ($P<0.0001$ and $P = 0.0002$, respectively vs. placebo).

In subjects receiving secukinumab 300 mg that had previously failed biologics, ppIGA 0/1 response rate remained similar to the overall population (33.3%).

At week 16, ppPASI reduction from baseline was significant, with secukinumab 300 mg (-54.5%) and 150 mg (-35.3%) compared with placebo (-4.0%; $P<0.0001$ and $P = 0.0006$, respectively).

At baseline, skin problems had a very large effect on subjects' lives (median DLQI 13-14). At week 16, the percentage of subjects achieving a DLQI score of 0/1 was significantly higher with

secukinumab 300 mg (26.6%) and 150 mg (16.9%) compared with placebo (1.5%, P< 0.0001 and P <0.005, respectively).

ppQLI scores showed that the percentage of subjects experiencing no difficulty due to involvement of both palms and soles increased from 0% at baseline to 12.5% and 10.8% at week 16 for secukinumab 300 mg and 150 mg, respectively, and did not change for placebo.

At baseline, HRQoL was overall more impaired due to psoriasis on the palms than on the soles. As a result of psoriasis of the palms, 50%-60% of subjects at baseline reported moderate-to-extreme hand pain, work limitation, and social limitation, as well as feeling embarrassed and less confident. Due to psoriasis of the soles, almost 50% of subjects reported moderate-to extreme pain/inability to walk and work. At week 16, these percentages were halved with secukinumab 300 mg. With the SGA, subjects reported a median improvement in HRQoL of 55.4%, 29.6%, and 14.0% for secukinumab 300 mg, 150 mg, and placebo, respectively, at week 16. EQ-5D also revealed significant health impairment of subjects at baseline, with improvements being observed with both doses of secukinumab at week 16.

Safety

The proportion of subjects experiencing at least one AE was slightly higher with secukinumab 300 mg and 150 mg (58.0% and 64.7%, respectively) than with placebo (50.0%).The most common AEs across all groups were headache, nasopharyngitis, and upper respiratory tract infection. The incidence of serious AEs (SAEs) was slightly higher with secukinumab 150 mg compared with secukinumab 300 mg and placebo (5.9%, 2.9%, and 2.9%, respectively). All SAEs were nonfatal and single events. No major cardiac events or opportunistic infections were reported.

**Overall conclusions on the clinical efficacy**

The GESTURE study met its primary objective. Both doses of secukinumab were superior to placebo in ppIGA 0/1 response, with secukinumab 300 mg consistently showing the highest efficacy. The one-third of subjects who received secukinumab 300 mg achieved clear or almost clear palms and soles (or ppIGA 0/1) at week 16 with clear differentiation from placebo as early as week 2. At week 16, palmoplantar disease improved on average by 55%, based on ppPASI.

Over one quarter of subjects taking secukinumab 300 mg reported that skin problems had no effect on their lives at week 16 (DLQI 0/1). HRQoL, as impacted by palmoplantar psoriasis, improved overall by 55% (as measured by SGA), and an absence of any difficulty due to palms and soles at week 16 was reported by 12.5% of subjects on secukinumab 300 mg (by ppQLI). The number of subjects with moderate-to extreme pain and work limitations due to palmoplantar psoriasis was halved in the same period.

Previously, the strongest evidence for treatment with biologics came from a study with adalimumab in moderate-to severe palmoplantar psoriasis. In this study, adalimumab treatment resulted in 15 of 49 subjects (31%) achieving clear or almost clear palms and soles versus 1 of 23 (4%) on placebo.[27] In another smaller, controlled trial, 3 of 12 (25%) patients on infliximab and 1 of 12 (8.3%) on placebo had clear or almost clear palms and soles at week.[28]

Ustekinumab in an open-label, non-placebo-controlled single-centre study involving 20 patients showed a 35% Palmoplantar Physician Global Assessment (ppPGA) 0/1 response at week 16.[29]

In addition to these studies, there are several subgroup/ post-hoc analyses, which are limited by the fact that palmoplantar psoriasis was not the primary focus of the trials. In the largest post-hoc analysis of apremilast, 22 of 57 patients (38.6%) versus 8 of 26 (30.8%) with placebo achieved a ppPGA 0/1 response at week 16.[30] This placebo response is unusually high given the slowly progressing natural course of palmoplantar psoriasis.

**Summary of safety data**

The SPC[31] for secukinumab (Cosentyx▼) states it has the potential to increase the risk of infections. In clinical studies, infections have been observed in patients receiving Cosentyx. Most of these were mild or moderate upper respiratory tract infections such as nasopharyngitis and did not require treatment discontinuation.

Related to its mechanism of action, non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies (3.55 per 100 patient years for secukinumab 300 mg versus 1.00 per 100 patient years for placebo).

No increased susceptibility to tuberculosis was reported from clinical studies, however, secukinumab should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of secukinumab in patients with latent tuberculosis

Caution should be exercised when prescribing secukinumab to patients with Crohn's disease as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both secukinumab and placebo groups.

Live vaccines should not be given concurrently with secukinumab.

In psoriasis studies, the safety and efficacy of secukinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.

**Table of Adverse events for secukinumab (Cosentyx▼)**[31]

| Incidence of Event | Adverse Event |
|---|---|
| **Very Common (≥1/10)** | Upper respiratory tract infections |
| **Common (≥1/100 to <1/10)** | Oral herpes, Rhinorrhoea, Diarrhoea |
| **Uncommon (≥1/1,000 to <1/100)** | Oral candidiasis, Tinea pedis, Otitis externa, Neutropenia, Conjunctivitis, Urticaria |
| **Rare (≥ 1/10,000 to ≤ 1/1,000)** | Anaphylactic reactions |

**Strengths and limitations of the evidence:**

Strengths:

- GESTURE was a double-blind, randomized, placebo controlled, parallel-group multicentre Phase 3b study.
- GESTURE was specifically designed to evaluate efficacy/ safety of secukinumab in treating palmoplantar psoriasis.
- 205 patients were randomized to one of the three study groups. Approximately 92% of subjects completed the 16-week treatment period.

Limitations:

- GESTURE is the only Phase 3b trial whose primary objective was to evaluate the efficacy/ safety of secukinumab in treating palmoplantar psoriasis.
- No active comparator arm included in the GESTURE study only placebo.
- Trial only 16 weeks in duration, therefore long term data are lacking.

**Prescribing and risk management issues:**

This medicinal product is subject to additional monitoring▼.

After proper training in subcutaneous injection technique, patients may self-inject secukinumab (Cosentyx▼) if a physician determines that this is appropriate. However, the physician should ensure appropriate follow-up of patients.

NICE TA 350 states secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks, (licence and trial data looks at review of treatment duration at 16 weeks).

**Commissioning considerations:**

**Anticipated patient numbers and net budget impact**

According to NICE, 18,600 people in England may be eligible for treatment with secukinumab for psoriasis each year. This equates to 35 people per 100,000 population.[32]

In 2016, the population of Lancashire was estimated at 1,485,042[33] this equates to 520 potential psoriasis patients eligible for treatment with secukinumab.

The number of psoriasis patients suffering from palmoplantar psoriasis who may potentially be eligible for treatment with secukinumab will be smaller, with the prevalence of palmoplantar psoriasis ranging from 2.8%[7] (14 patients) to 40.9%[8] (212 patients) in the different studies.

Some of the patients with palmoplantar disease may already be treated with secukinumab for severe plaque psoriasis if they meet the NICE criteria and so the expected number of patients requiring treatment solely for palmoplantar psoriasis might be reduced from the above estimate (14 -212 patients)

**Associated additional costs or available discounts:**

The company holding marketing authorisation have confirmed the PAS currently available, will also apply when used solely for palmoplantar psoriasis (outside of licence). The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

**Productivity, service delivery, implementation:**

Secukinumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which it is indicated.

After proper training in subcutaneous injection technique, patients may self-inject secukinumab.

Secukinumab (Cosentyx) 150 mg solution for injection is supplied in a single-use pre-filled syringe or pen for individual use and must be stored in a refrigerator (2°C - 8°C) and protected from light.

**Innovation, need, equity:**

Secukinumab offers a different mechanism of action to the other NICE‑recommended biological treatments (TNF‑alpha inhibitors), and some patients experience complete clearance of disease.

In GESTURE, the largest randomised, controlled trial in palmoplantar psoriasis, secukinumab demonstrated the greatest efficacy to date for treating this difficult to treat condition.

The NICE appraisal committee (Secukinumab for treating moderate to severe plaque psoriasis Technology appraisal guidance [TA350])[4], heard from clinical experts that clinicians use both the Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI) when monitoring disease and choosing who to offer biological therapies. This is because of the requirements outlined in existing NICE guidance for biological treatments, and that 'severe' disease is defined as a PASI of 10 or more, and a DLQI of more than 10. However, the Committee also heard that these measures do not identify everyone who might benefit from treatment, for example, people with limited disease but in high impact areas (such as the

hands, feet and genitals), or people with anxiety and depression because of their condition – there is therefore currently an unmet need.

Grading of evidence (based on SORT criteria):

| Levels | Criteria | Notes |
|---|---|---|
| Level 1 | Patient-oriented evidence from:<br>high quality randomised controlled trials (RCTs) with low risk of bias<br>systematic reviews or meta-analyses of RCTs with consistent findings | High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%) |
| Level 2 | Patient-oriented evidence from:<br>clinical trials at moderate or high risk of bias<br>systematic reviews or meta-analyses of such clinical trials or with inconsistent findings<br>cohort studies<br>case-control studies | |
| Level 3 | Disease-oriented evidence, or evidence from:<br>consensus guidelines<br>expert opinion<br>case series | Any trial with disease-oriented evidence is Level 3, irrespective of quality |



Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR

## References


[1] Secukinumab in Plaque Psoriasis — Results of Two Phase 3 Trials ; Langley R et al: N Engl J Med 2014; 371:326-338 http://www.nejm.org/doi/full/10.1056/NEJMoa131425 [Accessed online July 2017]

[2] Secukinumab administration by prefilled syringe maintains efficacy in moderate to severe plaque psoriasis over 100 weeks: Results of the FEATURE trial. Blauvelt A et al: J Am Acad Dermatol Volume 74, Issue 5, Supplement 1, Page AB270 May 2016 http://www.jaad.org/article/S0190-9622(16)01172-5/fulltext . [Accessed online July 2017]

[3] Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). Paul C et al: J Eur Acad Dermatol Venereol. 2015 Jun;29(6):1082-90.

[4] Secukinumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA350] Published date: 22 July 2015 https://www.nice.org.uk/guidance/ta350/chapter/2-The-technology

[5] Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009;61(3):451–485.

[6] Kumar B, Saraswat A, Kaur I. Palmoplantar lesions in psoriasis: a study of 3065 patients. Acta Derm Venereol. 2002;82(3):192–195.

[7] Lomholt G. Psoriasis: prevalence, spontaneous cause and genetics. Copenhagen: GEC, 1963

[8] Farber EM, Nall ML. Natural history of psoriasis in 5600 patients. Dermatologica 1974; 148: 1–18

[9] Chung J, Callis Duffin K, Takeshita J, et al. Palmoplantar psoriasis is associated with greater impairment of health related quality of life compared with moderate to severe plaque psoriasis. J Am Acad Dermatol. 2014;71(4):623–632.

[10] Pettey AA, Balkrishnan R, Rapp SR, et al. Patients with palmoplantar psoriasis have more physical disability and discomfort than patients with other forms of psoriasis: implications for clinical practice. J Am Acad Dermatol. 2003;49(2):271–275.

[11] Kragballe K. Management of difficult to treat locations of psoriasis. Scalp, face, flexures, palm/soles and nails. Curr Probl Dermatol. 2009;38:160–171.

[12] Bissonnette R, Poulin Y, Guenther L, et al. Treatment of palmoplantar psoriasis with infliximab: a randomized, double-blind placebo-controlled study. J Eur Acad Dermatol Venereol. 2011;25(12):1402–1408.

[13] Janagond AB, Kanwar AJ, Handa S. Efficacy and safety of systemic methotrexate vs. acitretin in psoriasis patients with significant palmoplantar involvement: a prospective, randomized study. J Eur Acad Dermatol Venereol. 2013;27(3):e384–e389.

[14] Au SC, Madani A, Alhaddad M, Alkofide M, Gottlieb AB. Comparison of the efficacy of biologics versus conventional systemic therapies in the treatment of psoriasis at a comprehensive psoriasis care center. J Drugs Dermatol. 2013;12: 861-866.

[15] Gelfand JM, Wan J, Callis Duffin K, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. Arch Dermatol. 2012;148:487-494.

[16] Takahashi H, Iinuma S, Tsuji H, Honma M, Iizuka H. Biologics are more potent than other treatment modalities for improvement of quality of life in psoriasis patients. J Dermatol. 2014; 41:686-689.

[17]Psoriasis: LMMG Biologic Commissioning Pathway Sept 2016. http://www.lancsmmg.nhs.uk/download/guidelines/Psoriasis%20biologics%20pathway.pdf

[18] British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. Smith C H et al: Br J Dermatol. 2017 May 17.

[19] Strober BE, Griffiths CE, O'Dell SJ, Tebbey PW, Barker JN, International Psoriasis C. Prioritizing the global research agenda in psoriasis: an International Psoriasis Council Delphi consensus exercise. Br J Dermatol. 2016;174:212-215.

[20] Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). Mrowietz U et al: J Am Acad Dermatol. 2015 Jul;73(1):27-36

[21] Secukinumab shows significant efficacy in palmoplantar psoriasis: Results from GESTURE, a randomized controlled trial. Gottlieb A et al: J Am Acad Dermatol Volume 76, Number 1, January 2017. http://www.jaad.org/article/S0190-9622(16)30612-0/fulltext#sec1.1 [Accessed online June 2017]

[22] Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: aA modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat. 2015;26:23-31.

[23] Weisman S, Pollack CR, Gottschalk RW. Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. J Dermatolog Treat. 2003;14:158-165.

[24] Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210-216.

[25] Farley E, Masrour S, McKey J, Menter A. Palmoplantar psoriasis: a phenotypical and clinical review with introduction of a new quality-of-life assessment tool. J Am Acad Dermatol. 2009;60: 1024-1031.

[26] EuroQol G. EuroQol a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199-208.

[27] Leonardi C, Langley RG, Papp K, et al. Adalimumab for treatment of moderate to severe chronic plaque psoriasis of the hands and feet: efficacy and safety results from REACH, a randomized, placebo-controlled, double-blind trial. Arch Dermatol. 2011;147:429-436.

[28] Bissonnette R, Poulin Y, Guenther L, Lynde CW, Bolduc C, Nigen S. Treatment of palmoplantar psoriasis with infliximab: a randomized, double-blind placebo-controlled study. J Eur Acad Dermatol Venereol. 2011;25:1402-1408.

[29] Au SC, Goldminz AM, Kim N, et al. Investigator-initiated, open-label trial of ustekinumab for the treatment of moderate-to-severe palmoplantar psoriasis. J Dermatolog Treat. 2013;24:179-187.

[30] Robert Bissonnette; Jennifer Cather; Phoebe Rich; Alan Menter; Carlos Ferrandiz; Mark Goodfield; ChiaChi Hu ERMDMS. Efficacy of apremilast, an oral phosphodiesterase 4 inhibitor, for palmoplantar psoriasis in patients with moderate to severe plaque psoriasis in phase 2 and phase 3 (ESTEEM) trials. 73rd Annual Meeting of the American Academy of Dermatology. San Francisco, CA 2015.

[31] Summary of product characteristics Secukinumab (Cosentyx): https://www.medicines.org.uk/emc/medicine/29848 [Accessed online July 2017]

[32] NICE costing template for TA350 Secukinumab for treating moderate to severe plaque psoriasis July 2015 https://www.nice.org.uk/guidance/ta350/resources/costing-statement-pdf-428628637

[33] Lancashire County Council: Mid-year Population Estimates http://www.lancashire.gov.uk/lancashire-insight/population-and-households/population/mid-year-population-estimates.aspx [ accessed online July 2017]