A personalised and systematically designed adherence intervention improves photoprotection in adults with Xeroderma Pigmentosum (XP): Results of the XPAND randomised controlled trial

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Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement: This research has been approved by London – West London & GTAC Research Ethics Committee 17/LO/2110.

Patient consent: Written patient consent for publication was obtained.

What is already known about this topic?

- Xeroderma Pigmentosum (XP) is a rare genetic disorder characterised by multiple skin cancers from early childhood.
- Photoprotection against UVR is the only way for people with XP to prevent skin and eye cancers.
- We have recently identified the psychosocial determinants of poor photoprotection in XP.
- No intervention has previously been designed or tested to improve photoprotection in people with XP**.**

What does this study add?

- Demonstrates that a personalised adherence intervention, designed by systematically mapping change strategies to the determinants of poor photoprotection, improves photoprotection, reducing the dose of UVR reaching the face.

- Photoprotection improves without impairing emotional wellbeing.
- Reducing the time spent outside is as important as improving the photoprotection used when outside.
- Mood, automaticity, confidence, and perceived importance of photoprotection are psychological mechanisms that may contribute to improving photoprotective behaviour in XP.

Abstract

Background: Poor adherence to photoprotection in Xeroderma Pigmentosum (XP) increases morbidity and shortens lifespan due to skin cancers.

Objective: To test a highly personalised intervention (XPAND) to reduce the dose of ultraviolet radiation (UVR) reaching the face in adults with XP, designed using known psychosocial determinants of poor photoprotection.

Methods: A two-arm parallel group randomised controlled trial, including patients with sub-optimal photoprotection to receive XPAND or a delayed intervention control arm that received XPAND the following year. XPAND comprises seven one-to-one sessions targeting photoprotection barriers (e.g., misconceptions about UVR) supported by personalised text messages, activity sheets, and educational materials incorporating behaviour change techniques. The primary outcome, mean daily UVR dose-to-face across 21 days in June-July 2018, was calculated by combining UVR exposure at the wrist with a face photoprotection activity diary. Secondary outcomes were UVR dose-to-face across 21 days in August 2018, time spent outside, photoprotective measures used outside, mood, automaticity, confidence-to-photoprotect. Financial costs and quality-adjusted life years (QALYs) were calculated.

Results: 16 patients were randomised, 13 provided sufficient data for primary outcome analysis. The XPAND group (n=8) had lower mean daily UVR dose-to-face [0.03 SED (SD 0.02] compared to control (n=7) [0.36 SED (SD 0.16)] (adjusted difference=-0.25, p<0.001, Hedge's

g=2.2). No significant between-group differences were observed in time spent outside, photoprotection outside, mood, or confidence. The delayed intervention control showed improvements in UVR dose-to-face (adjusted difference=-0.05, Hedge's g=-0.1) , time outside (adjusted difference=-69.9, Hedge's g=-0.28), and photoprotection (adjusted difference=-0.23, Hedge's g=0.45), after receiving XPAND. XPAND was associated with lower treatment costs (£-2642; 95% CI: -£8715 to £3873) and fewer QALYs (-0.0141; 95% CI: -0.0369 to 0.0028).

Conclusions: XPAND was associated with a lower UVR dose-to-face in XP patients and was cost-effective.

Introduction

Xeroderma Pigmentosum (XP) is a rare recessive disease involving an impaired response to ultraviolet radiation (UVR), which induces DNA damage[1]. This substantially increases the risk of skin and eye cancers resulting in an average life expectancy of 32 years, with 60% of premature deaths resulting from metastatic cutaneous malignancies[2]. Photoprotection from UVR in daylight is the main means of preventing the cancers: staying indoors as much as possible and using protective clothing and broad-spectrum SPF50 sunscreen when outside. Most XP skin cancers (80%) are on the face, head and neck, so face protection is critical,[3] ideally achieved by wearing a legionnaire-style cap with a UVR-protective transparent film at the front, or wide-brimmed hat, glasses and face-buff/scarf[4]. We previously identified that photoprotection of the face is poor in one-third of patients, and that the extreme photoprotection restricts daily activities and impairs emotional wellbeing[5,6,7,8,9].

Following our previous studies[5-9,] we specifically targeted the psychosocial determinants of poor photoprotection for each patient to create a highly personalised intervention to improve photoprotection in adults with XP[10,19] (XPAND – 'Enhancing XP Photoprotection Activities – New Directions'). XPAND was informed by studies of non-XP high risk skin cancer patients [11], psychological theory [12,13,14] and designed for delivery by healthcare professionals without specialist psychological training.

The rarity of XP (136 known patients with XP in the UK) necessitated a Randomised Controlled Trial (RCT) with a delayed-intervention control group design. Our novel UVR exposure measurement methodology[7] enabled intensive longitudinal data capture and maximised statistical power by the number of observations recorded per patient[7]. The primary objective was to investigate whether the average daily UVR dose-to-face was reduced after XPAND compared to the control. We assessed whether change persisted across 21 consecutive days 3 months later, measured effects on psychological variables, and investigated the impact of the intervention in the delayed intervention control group. Cost-utility analysis assessed the cost effectiveness of incorporating XPAND into routine care.

Materials and Methods

Study design

A phase-II, assessor-blind, two-armed parallel group RCT compared participants who received the XPAND intervention in May-June 2018 to a delayed-intervention control group, who then received XPAND a year later; both groups continued to receive their routine care. Intervention and measurement periods were chosen to control for seasonal differences in environmental UVR. Ethical approval: West London & GTAC National Research Ethics Committee

(17/LO/2110). Trial registration: ClinicalTrials.gov NCT03445052. The trial protocol[15] and a process evaluation[16] are published elsewhere.

Recruitment

Eligible participants (≥16 years) were recruited from the National XP Service at Guy's and St Thomas' NHS Foundation Trust. They had previously been identified in formative research[5,6,7] as having poor photoprotection according to

i) Scores of <20 on the Adherence to Facial Photoprotection questionnaire[17]

ii) Anything other than 'excellent' or 'very good' recorded on the daily UVR protection diary and the Daily Photoprotection Scale (DPS)[5].

iii) Having 'resistant' or 'integrated' mode of adjustment associated with lower photoprotection[6].

Exclusion criteria were cognitive impairment, current clinical depression or anxiety, being unable to speak or understand spoken or written English. Potential participants were sent an invitation letter and informed consent was obtained during a home visit.

Randomisation and Masking

Participants were 1:1 randomised to receive XPAND in 2018 or 2019. The delayed-intervention group acted as controls for the 2018 analysis of the primary outcome. Equal allocation to both groups employed a random allocation sequence for all participants, using a computer programme with fixed block sizes of 4 stratified by sunburn phenotype to balance those with a genetic complementation group associated with an exaggerated versus a normal sunburn response[18]. Related participants were randomised as a cluster to avoid group contamination. Two of the participants were related and therefore we randomised the first participant recruited and then allocated the next to the same intervention group, accounting for these as a

cluster where possible in analyses (e.g, random effect). The trial statistician and XP clinical team were blinded to group allocation.

Procedure

Participants completed baseline assessments for 21-days in April 2018 (t0), which were repeated for 21 days in June-July 2018 (t1) after the main XPAND sessions, and after a booster session in August 2018 (t2). Participants completed the daily diary of face photoprotection and rating of psychological factors, and wore the UVR wrist dosimeter (SunSaver 3, Bispebjerg Hospital, Copenhagen, Denmark)[7] continuously from the start of the first assessment period (t0) until the end of the August assessment period (t2). Participants completed additional self-report measures once at the start of each 21-day period and 6 months after XPAND (December 2018, t3). The delayed-intervention control group additionally followed a similar protocol of assessments and measurements at equivalent times in 2019 (t4,5,6).

XPAND intervention

XPAND was delivered by one of two psychologists or by a trained research nurse, following a manual. Each patient received a personalised intervention, with content that addressed their photoprotection barriers (e.g., misconceptions about UVR). XPAND comprised seven 1:1 sessions, supported by a consumer-styled magazine containing articles incorporating behaviour change techniques (BCTs), personalised text messages, activity sheets, and educational materials. Details of XPAND are in Figure 1[15] and published elsewhere[10,19.]

Outcomes

Primary outcome: Average daily UVR dose-to- face (SED) across 21 consecutive days in June-July 2018 (t1)

The UVR dose-to-face was calculated as the product of the dose of UVR recorded at the wrist by the dosimeter, and the 'protection factor' of the facial photoprotection behaviours recorded in the daily UVR protection diary (supplementary Figure 1)[7]. For time spent outside during the day, participants recorded the face photoprotection used for each 15-minute period (wearing a face visor, hat, hoodie worn-up, glasses, face scarf or face buff, applying sunscreen or lip block). Methodological details are provided elsewhere[7,15].

Secondary outcomes

i) Average daily UVR dose-to-face across 21 consecutive days in August 2018 (t2)

ii) Average daily total UVR exposure during t1, t2

iii) Average daily total time outside during daytime (6am -10pm) t1, t2

iv) Average daily total time outside when UVR levels are highest (11am–3pm) t1, t2

v) Average daily proportion of time spent outside during which face photoprotection using clothing was 'very good' or 'excellent' t1, t2

vi) Average daily number of times sunscreen was applied irrespective of time outside during each of the 21-day periods t1, t2

vii) Average daily measures of psychological factors (single items) rated 0-10 (higher scores are more favourable) (t1, t2): a) mood, b) extent to which photoprotection activities are done without having to think about it consciously ('automaticity'), c) self-efficacy to manage barriers to photoprotection ('confidence'); d) prioritisation of photoprotection ('importance')

Tertiary outcomes

Self-report measures: *Health-related quality of life* (EQ-5D-5L[20]); *Emotional well-being* (Short-form Warwick Edinburgh Mental Well-Being Scale SWEMBS[21]) (α=.75); *Automaticity of photoprotection activities* (Self-Report Behavioural Automaticity Index SRBAI[22]) (α =.98); *Self-efficacy to photoprotect* (Photoprotection self-efficacy questionnaire, PhotoSEQ[15] using clothing (α =.88) and sunscreen (α =.93); *Photoprotection outdoors* (Brief Photoprotection Adherence Questionnaire, BPAQ[15]).

Fidelity

A proportion (40%) of the 101 session recordings were evaluated and independent assessors judged whether treatment elements were fully completed, partially completed, or not completed for sessions 1 and 6, and a random selection of follow-up sessions. Interrater-agreement assessed by Gwet's agreement coefficients (91, .76, .84, .83; 95% CI = 81%-85%) was good.

Sample size

A sample size of 10 participants per group with 21 daily observations per participant was required to provide 80% power for a two-sided test of means between groups at 5% significance level to detect a clinically meaningful reduction of 0.10 SED/day in UVR dose-to-face. Recruitment was lower than the target sample size (*n*=16) but was considered sufficient to continue by the trial steering committee, based on providing 80% power of the study to detect a similar reduction in UVR dose-to-face of 0.12 SED/day.

Statistical Analysis

Data were analysed using Stata version 16.1 statistical software. Daily UVR exposure and daily self-report assessments were analysed, following a modified intention-to-treat framework, using linear mixed-effects models with patient as a random effect to account for repeated observations within individuals. Treatment group and assessment period were included as dummy-coded variables. Group-by-period interaction terms allowed for the estimate of treatment effect to vary across time points. Average daily UVR dose-to-face during the baseline period, sunburn phenotype, and daily environmental UVR from the nearest Public Health England monitoring station were included as covariates to adjust for baseline differences between groups for these variables. A first-order autoregressive structure was specified to further account for anticipated relation within residuals over time. Given anticipated issues with heteroscedasticity of the residuals, heteroscedasticity robust standard errors were estimated using the Huber-White sandwich estimator. This approach provides standard errors corrected for violation of distribution assumptions (e.g., skew). On days where dosimeter data were not available or diary assessments not reported, these days were not included in the model. Treatment effect estimates are therefore under the assumption that these data are missing at random. Days where the dosimeter was likely not worn but a diary entry completed indicating that the participant had not gone outside that day were included in the analysis assuming the SED was 0. Sensitivity analyses for the 'missing at random' assumption for the primary outcome imputed missing days with the mean of the participants' daily assessments across the assessment period.

A similar approach using linear mixed-effects models was used to estimate between-group differences in June-July 2018 and August 2018 for the self-report measures assessed once at the beginning of each period. Due to the number of observations being up to 2 per participant,

no additional residual structure was estimated. Since these analyses were underpowered, no significance testing was applied, and estimates are reported as point estimates with 95% CIs.

Planned exploratory analyses were also undertaken for the delayed intervention control group by comparing the June-July 2018 and 2019 assessments for this group. Linear mixed-effects models, with a random intercept and autoregressive error structure, were estimated for each outcome including data from all available periods with period included as a dummy-coded variable. The pre-post difference for periods t5 versus t1, with heteroscedasticity robust standard errors, was estimated as an indicator of treatment effect.

Economic analysis

The economic analyses are indicative of potential cost-effectiveness as the small sample size does not allow for generalisable findings. The cost of the intervention is predominantly therapist time and unit cost of a psychologist. Development costs were not included as it was assumed that these would tend to zero as more patients received the intervention. 'Other service use' was measured using an adapted version of the *Client Service Receipt Inventory*[23] which recorded contacts with health and social care services over the six months prior to baseline and t3 interviews. Costs were calculated by combining the service use data with unit cost information[24,25].

Quality-adjusted life years (QALYs) accrued over the period from baseline to t3 were derived from the *EQ-5D-5L* combined with tariffs. Area under the curve methods were used assuming a linear change between t0 and t3. Cost and QALY differences between the two groups at t3 were estimated using regression models with baseline cost or EQ-5D-5L score used as an independent variable along with the group identifier. In the case of the intervention having

higher costs and producing more QALYs than 'treatment as usual alone', an incremental cost effectiveness ratio (ICER) was produced, defined as the difference in costs divided by the difference in QALYs.

Results

Recruitment and attrition

Forty eligible patients were identified and 16 (43%) consented to participate (Figure 2). Attrition was minimal: one participant from the delayed-intervention group left the study after the baseline assessment. Twelve participants received all seven sessions, two had sessions six and seven combined for logistical reasons, and one had five short sessions. The analysis sample for the primary outcome involved 13 participants due to 2 faulty dosimeters, providing a total of 492 useable days, across the June and August 2018 reporting periods where dosimetry was available and daily UVR protection diary data recorded (78% complete; see supplementary Table 1 and supplementary Figure 2. & 3). The analysis sample consisted of 11 participants providing data across both periods, one providing data only in June, and one providing usable data only in August. Where analyses relied on the diary only, the analysis sample included 15 participants providing a total of 540 useable days (86%).

Baseline demographic and clinical characteristics of the sample by group are shown in Table 1. The patients were predominantly white (62.5%) and male (62.5%) with a mean age of 44.3 years (SD=15.7). Most participants (62.5%) belonged to the three XP complementation groups (C, E, V)[18] that do not cause abnormal sunburn responses. Baseline levels of daily UVR dose-to-face were lower in the intervention group than in the control (M=0.04, SE=0.02; M=0.27, SE=0.03). Randomisation did not achieve good balance between the groups on several key

outcome variables at baseline (see Table 2). Those randomised to the intervention group described protection as more automatic, were more confident that they could achieve good protection, and thought protection was more important, than those in the delayed-intervention control.

Treatment effect on primary outcome (June-July 2018)

As shown in Table 2, the XPAND intervention group had significantly lower mean daily UVR dose-to-face (M=0.03, SD=0.02) than the delayed-intervention control group at the June 2018 (primary outcome) post-intervention assessment (M=0.36, SD=0.16; adjusted difference = -.25 SED, p<.001; large effect size Hedge's g=2.2). This difference was maintained at the August 2018 follow-up (intervention: M=0.04, SD=0.03; control: M=0.28, SE=0.08; adjusted difference = -0.19 SED, *p*<.001; Hedge's g=-1.4).

Treatment effect on secondary outcomes

Total UVR exposure was also lower in the intervention group at the June 2018 post-intervention assessment (intervention: M=0.07, SD=0.05; control: M=0.58, SD=0.19; adjusted difference=-0.30 SED, *p*<.001) and at the August 2018 follow-up (intervention: M=0.08, SD=0.05; control: M=0.42, SD=0.26; adjusted difference = -0.30, *p*<.001).

Based on 540 daily observations for 15/ 16 randomised patients, there were no significant differences observed for proportion of time spent outside during which face photoprotection was 'very good' or 'excellent', average daily frequency of sunscreen application, confidence in ability to photoprotect, automaticity of photoprotection, perceived importance of photoprotection, or mood. Effect sizes were small, favouring the intervention (Table 2; Figure 3).

Tertiary outcomes

Observed means and estimated mean differences between groups for patient-reported outcomes using standardised scales completed once at the end of each reporting period are shown in Supplementary table 2. Differences for quality-of-life, emotional wellbeing, self-efficacy (confidence) for wearing photoprotective clothing and automaticity were small and non-significant. Self-efficacy for applying sunscreen was higher for the intervention group across t1 and t2 (adjusted difference = -0.46, $p<.05$). Differences for the adherence behaviour subscales were small to medium in favour of the intervention, but only significant for sunscreen application frequency (adjusted difference = -1.25, $p<.05$).

Exploratory delayed-intervention control group outcomes

We assessed within-person changes in the delayed-intervention control group between the June 2018 and June 2019 assessment periods (Table 2.). Although effect sizes favoured the intervention, no statistically significant differences were observed for the mean daily UVR dose-to-face (adjusted difference=-0.05, Hedge's g=-0.1), total UVR exposure (adjusted difference= -.05 Hedge's g=-0.10), time outside (adjusted difference=-69.9, Hedge's g=-0.28), proportion of time outside with 'very good' or 'excellent' facial photoprotection (adjusted difference=0.23, Hedge's g=0.45), or the number of times sunscreen was applied (adjusted difference=0.27, Hedge's g=0.28). Statistically significant differences were observed in favour of the intervention for daily self-reported ratings of mood (adjusted difference=0.8, Hedge's g=0.4), automaticity (adjusted difference=0.55, Hedge's g=0.21), confidence (adjusted difference=-0.58, Hedge's g=0.23, and importance of photoprotection (adjusted difference=-0.78, Hedge's g=0.32).

Treatment effects were consistent with intention-to-treat sample, in sensitivity analyses which excluded cases without dosimetry/diary data/fewer sessions. No trial-related adverse events were recorded.

Fidelity

Facilitator adherence to the XPAND intervention was high, with an average of 85% treatment fidelity achieved across sessions (S) (S1: 92%, 95%CI = 90%-94%; S2-5: 78%, 95%CI 73%-83%; S6: 86%, 95%CI 83%-90%).

Economic analysis

Resource use information was collected 9 months after baseline assessment for both intervention and delayed intervention control. Full details of resource use are provided in Supplementary Table 3. After adjusting for baseline costs, the intervention group had costs that were on average £2642 lower than for 'treatment as usual' alone (95% CI -£8715 to £3873). The intervention group accrued on average 0.714 QALYs over the period from baseline to t3 compared with 0.699 for the control group. After adjusting for baseline quality of life, the intervention group accrued 0.014 fewer QALYs (95% CI, -0.037 to 0.003). The ICER was £187,376 for treatment as usual compared to the intervention. Over a 15-year period it was estimated that the intervention would result in fewer cases of cancer.

Discussion

Participants who received XPAND had a significantly lower UVR dose-to-face compared to controls. The size of the effect was large, which would be expected to reduce morbidity and mortality from facial skin cancers. The small sample prevented full mediational analysis, and

there were no differences between groups on daily measures of psychological process variables, but the results suggest that perceptions of importance of photoprotection, self-efficacy to photoprotect, and automaticity are potential mechanisms of change underlying improvements in photoprotection behaviour. Receipt of XPAND had a positive impact on UVR dose-to-face without diminishing emotional wellbeing.

The economic evaluation showed that health-related quality of life and hence QALYs were similar between the two groups, although slightly lower in the intervention group. Costs were much lower in the intervention group; however, neither difference was statistically significant. Based on the difference in mean costs and QALYs (adjusted for baseline), we conclude that the intervention was the most cost-effective option.

Strengths and limitations

The XPAND intervention was based on formative research, which identified the psychological drivers of photoprotection specific to the XP population[4] and then systematically mapped evidenced-based BCTs to these drivers[10]. The primary limitation of the study was the small sample and the failure of randomisation to balance baseline differences in dose-to-face between groups. Although statistical analysis adjusted for baseline levels, we could not ascertain the true effect size. Failure of randomisation in small samples is a known pitfall of rare disease trial design[26]. The delayed-intervention control arm aided interpretation of the between-groups findings and increased confidence that XPAND was effective.

Future research

We recommend XPAND is trialled in a larger group of international XP patients, with an extended duration of follow-up. High adherence rates suggest that the daily measures are acceptable to participants, consistent with findings in other patient groups[27,28]. UVR dose-to-face measurements highlighted how UVR protection requires reduction in the *quantity* of exposure alongside better photoprotection *during* exposure. We consider that an adapted version of XPAND may be a promising new approach to improving photoprotection in the many patients who do not have XP who are at high risk of skin cancer[29]. Despite extensive efforts, poor photoprotection has proven hard to improve in melanoma and non-melanoma skin cancer patients[30,31]

Despite the challenges of evaluating an intervention in an extremely rare disease, our findings show that receipt of XPAND was associated with a lower UVR dose-to-face, and exploratory analysis pointed to the psychological mechanisms responsible. The intervention was cost-effective and did not impair emotional wellbeing, thus justifying service implementation.

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Figure legends

Figure 1: The structure of the XPAND intervention

Figure 2. Participant flow through the study

Figure 3. Adjusted mean daily dose to face (SED) for the (primary outcome) at assessment t1 and t2, with 95% confidence interval

Table 1. Baseline sample characteristics by treatment group, 2018

	XPAND intervention group (n=8)	Delayed intervention control group (n=8)	Total
Demographic factors			
Gender, N (%)			
Female	3 (37.5)	3 (37.5)	6 (37.5)
Male	5 (62.5)	5 (62.5)	10 (62.5)
Age, M (SD)	39.9 (15.3)	48.8 (15.9)	44.3 (15.7)
Ethnicity, N (%)			
Caucasian	5 (62.5)	5 (62.5)	10 (62.5)
Asian[1]	3 (37.5)	3 (37.5)	6 (37.5)
Clinical factors and Quality of life			
Self-reported age at diagnosis, M (SD)	16.1 (17.0)	38.1 (7.4)	27.1 (17.0)
Age of lab molecular diagnosis from medical notes, M (SD)	36.1 (14.9)	44.5 (15.3)	40.3 (15.2)
Propensity to burn, N (%)			
Burner	3 (37.5)	3 (37.5)	6 (37.5)
Non-burner	5 (62.5)	5 (62.5)	10 (62.5)
History of previous cancer, N (%)			
Yes	5 (62.5)	5 (62.5)	10 (62.5)
No	3 (37.5)	3 (37.5)	6 (37.5)
XP complementation group, N (%)			
A	1 (12.5)	3 (37.5)	4 (25.0)
C	3 (37.5)	0	3 (18.8)
E	1 (12.5)	2 (25.0)	3 (18.8)
F	2 (25.0)	0	2 (12.5)
V	1 (12.5)	3 (37.5)	4 (25.0)
Quality of life (EQ-5D-5L), M (SD)	0.9 (0.1)	0.8 (0.1)	0.9 (0.1)

Notes. *delayed intervention control N=6. N=total; M=mean; SD=standard deviation. [1]Asia ethnicity includes Pakistani, Bangladeshi, Iranian, Saudi Arabian.

Table 2. Treatment effects on primary outcome and secondary outcomes

Variable		XPAND intervention group			Delayed intervention control group			Adjusted mean difference					
	Period	N	Mean	SD	N	Mean	SD	Mean diff	SE	p	95%ll	95%ul	Hedge's g
Daily dose to face (SED)	Apr18*	6	0.03	0.03	7	0.26	0.17						
	Jun18	5	0.03	0.02	7	0.43	0.17	-0.25[a]	0.05	<0.0001	-0.35	-0.15	-2.21
	Aug18	5	0.04	0.03	7	0.33	0.20	-0.20[a]	0.05	<0.0001	-0.29	-0.10	-1.40
	Apr19	0			7	0.14	0.07						
	Jun19	0			7	0.41	0.27	-0.05[b]	0.08	0.542	-0.19	0.10	-0.12
Daily total (SED)	Apr18	6	0.05	0.05	7	0.36	0.21						
	Jun18	5	0.07	0.05	7	0.58	0.19	-0.30[a]	0.06	<0.0001	-0.42	-0.18	-2.01
	Aug18	5	0.08	0.05	7	0.42	0.26	-0.24[a]	0.06	<0.0001	-0.36	-0.11	-1.20
	Apr19	0			7	0.21	0.07						
	Jun19	0			7	0.56	0.32	-0.05[b]	0.09	0.588	-0.22	0.13	-0.10
Daily minutes outside (daylight hours)	Apr18	6	75.95	42.93	7	356.43	163.48						
	Jun18	5	105.57	65.83	7	274.41	150.86	-51.11[a]	81.03	0.528	-209.92	107.70	0.33
	Aug18	5	123.57	38.28	7	280.20	177.17	-43.52[a]	73.90	0.556	-88.36	101.311	0.32
	Apr19	0			7	237.65	124.03						

	Jun19	0			7	227.65	131.92	-69.90[b]	48.31	0.148	-164.59	24.78	-0.28
Daily high-risk minutes outside (11am-3pm)	Apr18	6	27.26	15.65	7	127.52	68.92						
	Jun18	5	21.86	18.84	7	71.29	45.18	-23.80[a]	23.15	0.304	-69.18	21.58	-0.53
	Aug18	5	41.05	14.05	7	87.82	66.20	-27.34[a]	24.54	0.265	-75.43	20.75	-0.54
	Apr19	0			7	76.43	49.57						
	Jun19	0			7	68.50	48.06	-21.32[b]	16.26	0.190	-53.19	10.54	-0.20
Daily proportion time outside photoprotection very good/excellent	Apr18	6	0.68	0.32	7	0.29	0.41						
	Jun18	6	0.67	0.38	7	0.34	0.35	0.06[a]	0.11	0.546	-0.27	0.15	0.11
	Aug18	8	0.68	0.34	7	0.34	0.43	0.01[a]	0.10	0.897	-0.21	0.18	0.02
	Apr19	0			7	0.31	0.44						
	Jun19	0			7	0.61	0.37	0.23[b]	0.13	0.065	-0.01	0.48	0.45
Daily number times sunscreen applied	Apr18	6	1.03	0.51	7	1.32	0.37						
	Jun18	7	0.98	0.65	7	1.40	0.56	-0.33[a]	0.27	0.213	-0.86	0.19	-0.34
	Aug18	8	1.04	0.62	7	1.24	0.24	-0.18[a]	0.21	0.389	-0.59	0.23	-0.23
	Apr19	0			7	1.04	0.46						
	Jun19	0			7	1.66	0.54	0.27[b]	0.20	0.161	-0.11	0.66	0.28
Mood	Apr18	6	7.81	0.89	7	6.77	1.47						

	Jun18	7	8.47	1.47	7	7.23	1.40	0.20[a]	0.49	0.686	-0.77	1.17	0.09
	Aug18	8	8.38	1.50	7	7.38	1.33	0.01[a]	0.56	0.984	-1.09	1.11	0.00
	Apr19	0			7	6.88	1.78						
	Jun19	0			7	8.23	1.21	0.80[b]	0.28	0.005	0.25	1.35	0.40
Automaticity of protection	Apr18	6	8.29	1.36	7	6.30	1.97						
	Jun18	7	8.07	2.62	7	6.86	2.01	-0.93[a]	0.95	0.329	-2.79	0.94	-0.24
	Aug18	8	7.51	3.28	7	7.18	1.89	-1.71[a]	1.13	0.130	-3.94	0.51	-0.38
	Apr19	0			7	6.51	2.60						
	Jun19	0			7	7.88	1.58	0.55[b]	0.18	0.003	0.19	0.90	0.21
Confidence in protection	Apr18	6	7.21	3.07	7	6.21	1.83						
	Jun18	7	8.36	1.93	7	6.86	1.95	0.76[a]	0.56	0.175	-0.34	1.86	0.25
	Aug18	8	8.11	2.19	7	7.21	1.81	0.12[a]	0.47	0.790	-0.80	1.04	0.04
	Apr19	0			7	6.42	2.43						
	Jun19	0			7	7.99	1.29	0.58[b]	0.28	0.041	0.02	1.13	0.23
Importance of protection	Apr18	6	9.06	0.77	7	6.88	1.87						
	Jun18	7	8.82	1.64	7	7.11	1.87	-0.24[a]	0.69	0.727	-1.59	1.11	-0.09
	Aug18	8	8.60	1.80	7	7.40	1.71	-0.65[a]	0.77	0.395	-2.15	0.85	-0.23
	Apr19	0			7	6.57	2.52						
	Jun19	0			7	8.27	1.42	0.78[b]	0.28	0.006	0.22	1.33	0.32

Note: [a] difference is adjusted mean difference between XPAND group and delayed intervention control group at same time point; [b] difference is adjusted mean difference for delayed intervention control compared to same time period in previous year

* These observations are prior to the group receiving the XPAND intervention.

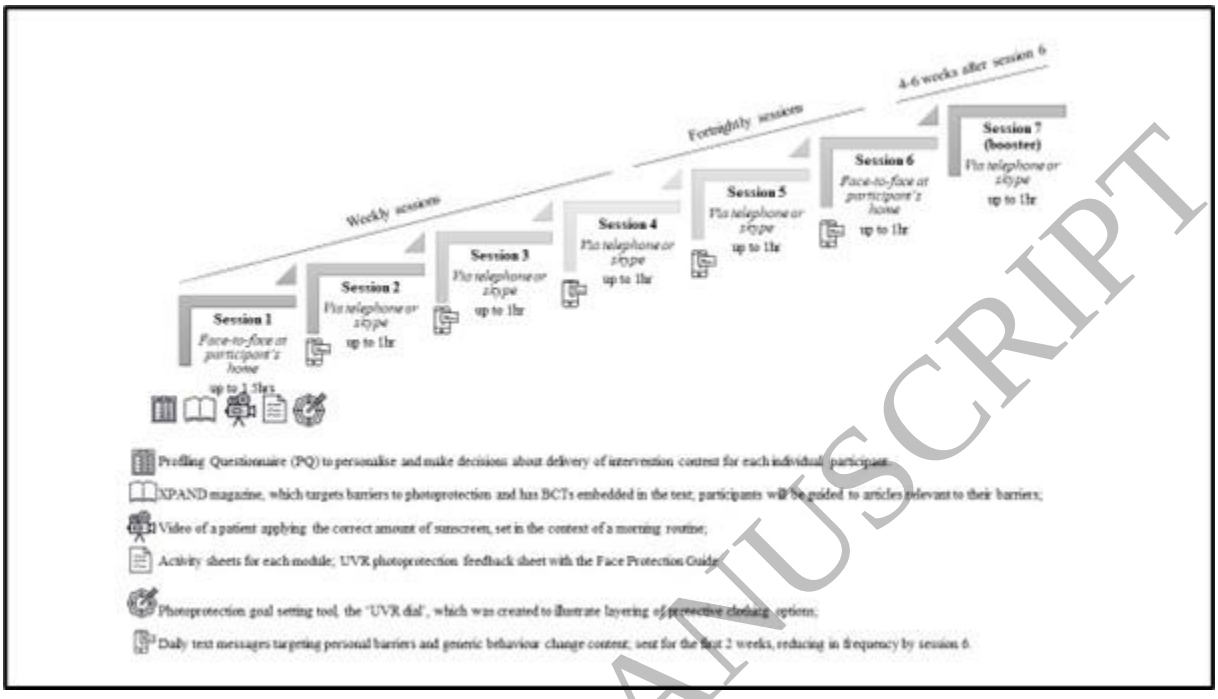
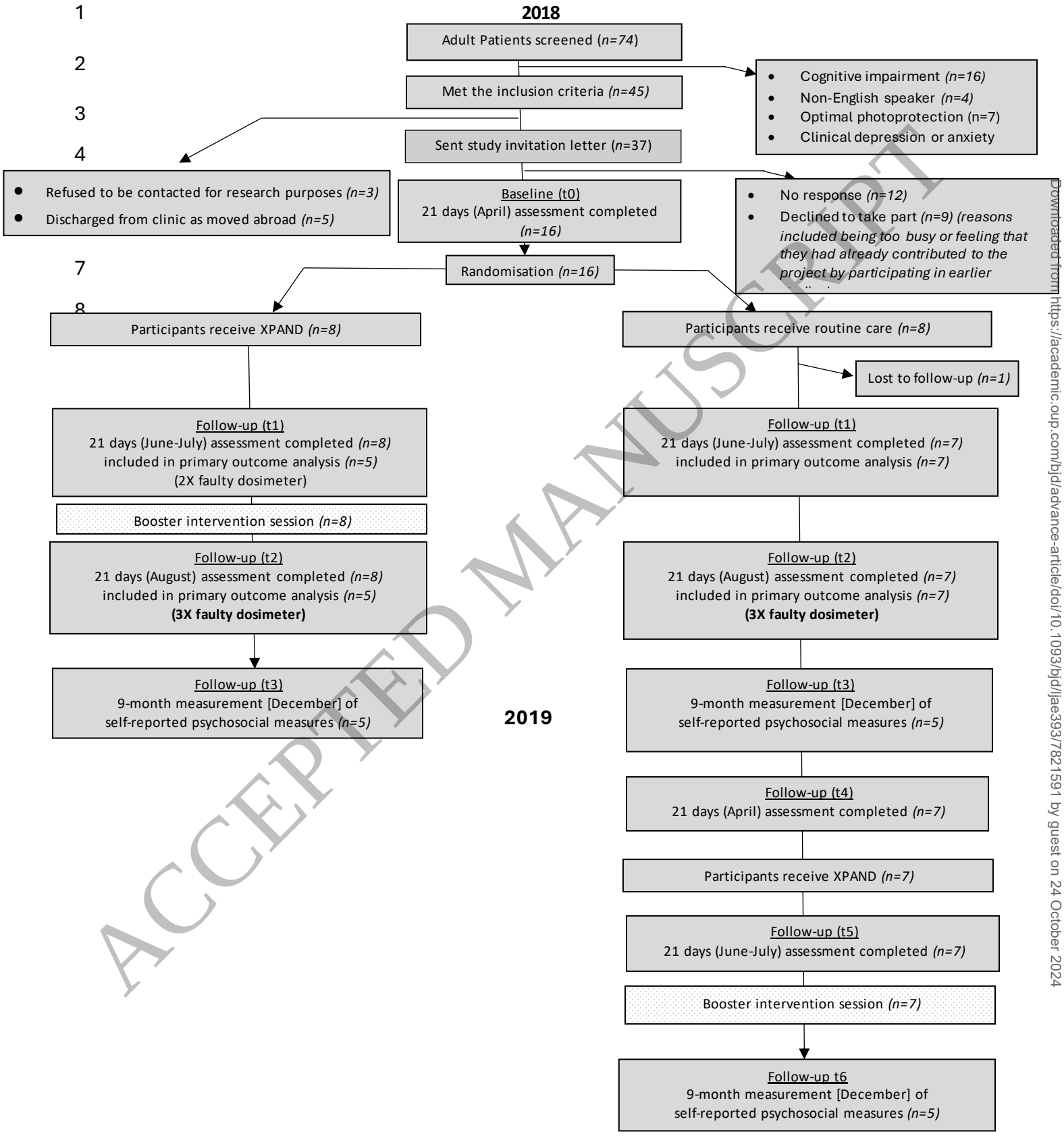


Figure 1
160x90 mm (x DPI)



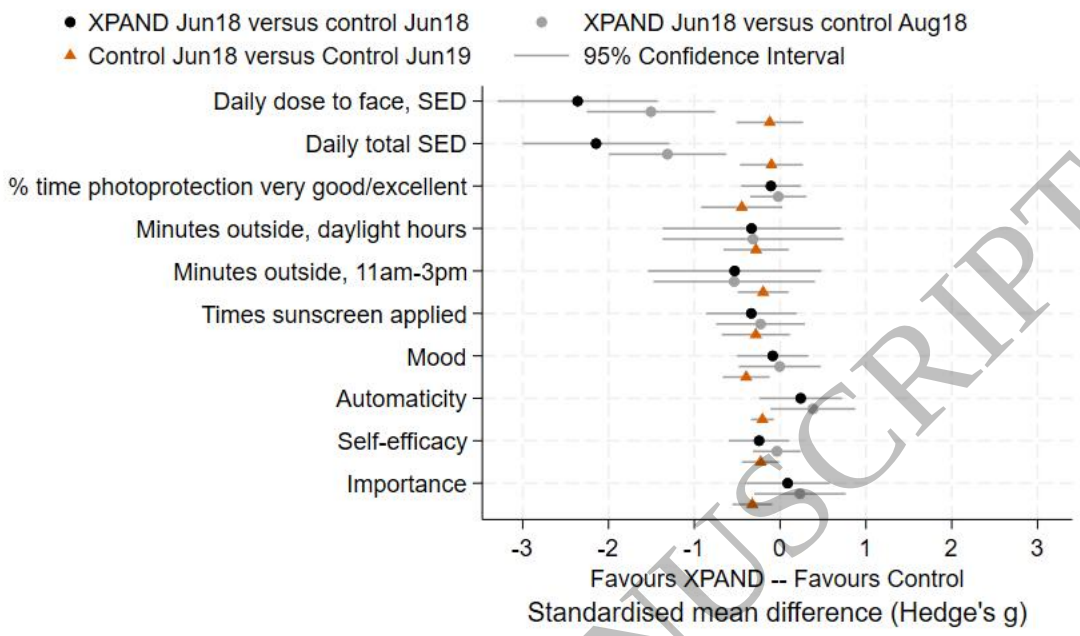


Figure 2
152x91 mm (x DPI)

Consistent safety profile with over 8 years of real-world evidence, across licensed indications[1–3]

Cosentyx® secukinumab

1,000,000 patients treated globally, and counting across indications[4]

150+ clinical trials across indications[5]

8+ years of real-world evidence, worldwide across indications[1–3]

8 indications[1–3]

Click here to visit our HCP portal and learn more

Real-world evidence shows a consistent safety profile with long-term use of Cosentyx over 6 years[6,7]

No trend toward increased AE rates over time (pooled PsA, AS, PsO):*[6]

AEs of select interest (EAIR per 100 PY)	1 year	2 years	3 years	4 years	5 years	6 years	Cumulative rate
Serious infections Cases	2.0 n=149	1.7 n=475	0.7 n=649	1.3 n=1,841	1.3 n=2,285	1.1 n=2,226	1.3 n=8,719
Malignant or unspecified tumours Cases	0.2 n=15	0.2 n=50	0.2 n=225	0.3 n=422	0.3 n=520	0.3 n=573	0.3 n=1,896
MACE Cases	0.2 n=15	0.1 n=39	0.2 n=151	0.2 n=238	0.2 n=264	0.1 n=287	0.2 n=1,031
Total IBD Cases	0.2 n=12	0.2 n=46	0.2 n=185	0.3 n=340	0.2 n=312	0.1 n=261	0.2 n=1,291
Exposure (PY)	7450	28,549	93,744	137,325	182,024	212,636	680,470

No trend towards increased rates of malignancy, MACE or IBD over time[6]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[1,2] Refer to the prescribing information for a summary of adverse events.

Adapted from Novartis Data on File. 2021.[6]

Refer to the Cosentyx Summary of Product Characteristics for full details, dosing and administration, including special populations.

Cosentyx is indicated for the treatment of moderate to severe **PsO** in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active **PsA** in adult patients (alone or in combination with methotrexate) when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active **AS** in adults who have responded inadequately to conventional therapy; active **nr-axSpA** with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active moderate to severe **HS** (acne inversa) in adults with an inadequate response to conventional systemic HS therapy; active **ERA** in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active **JPsA** in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[1,2]

Prescribing information, adverse event reporting and full indication can be found on the next page.

*Successive time periods of PSUR shown with cumulative rate: 26 Dec 2014 to 25 Dec 2015; 26 Dec 2015 to 25 Dec 2016; 26 Dec 2016 to 25 Dec 2017; 26 Dec 2017 to 25 Dec 2018: 26 Dec 2018 to 25 Dec 2019; 26 Dec 2019 to 25 Dec 2020.[6]

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; EIAR, exposure-adjusted incidence rate; ERA, enthesitis-related arthritis; HCP, healthcare professional; HS, hidradenitis suppurativa; IBD, inflammatory bowel disease; JPsA, juvenile psoriatic arthritis; MACE, major adverse cardiac event; nr-axSpA, non-radiographic axial spondyloarthritis; PsA, psoriatic arthritis; PsO, plaque psoriasis; PY, patient year.

References: 1. Cosentyx® (secukinumab) GB Summary of Product Characteristics; **2.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **3.** European Medicines Agency. European public assessment report. Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed August 2024]; **4.** Novartis Data on File. Secukinumab – Sec008. 2023; **5.** ClinicalTrials.gov. Search results for 'secukinumab', completed, terminated and active, not recruiting trials. Available at: https://clinicaltrials.gov/search?term=Secukinumab,&aggFilters=status:com [Accessed August 2024]; **6.** Novartis data on file. Cosentyx Periodic Safety Update Report (PSUR); 26 December 2019 – 25 December 2020. 22 February 2021; **7.** Deodhar A, et al. Arthritis Res Ther 2019;21(1):111.

NOVARTIS

UK | August 2024 | FA-11239622

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity*: Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 284832 | May 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity*: Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 290802 | June 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com