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# Validation of a questionnaire for central nervous system aspects of joint pain: the CAP questionnaire

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## Abstract

**Background:** Neuropathic-like pain, fatigue, cognitive difficulty, catastrophizing, anxiety, sleep disturbance, depression and widespread pain associate with a single factor in people with knee pain. We report the Central Aspects of Pain questionnaire (CAP) to characterize this across painful musculoskeletal conditions.

**Methods:** CAP was derived from the 8-item CAP-Knee questionnaire, and completed by participants with joint pain in the Investigating Musculoskeletal Health and Wellbeing survey. Subgroups had OA, back pain or FM. Acceptability was evaluated by feedback and data missingness. Correlation coefficients informed widespread pain scoring threshold in relation to the other items, and evaluated associations with pain. Factor analysis assessed CAP structure. Intraclass Correlation Coefficient (ICC) between paper and electronic administration assessed reliability. Friedman test assessed score stability over 4 years in people reporting knee OA.

**Results:** Data were from 3579 participants (58% female, median age 71 years), including subgroups with OA ($n = 1158$), back pain ($n = 1292$) or FM ($n = 177$). Across the three subgroups, ≥10/26 painful sites on the manikin scored widespread pain. Reliability was high [ICC = 0.89 (95% CI 0.84–0.92)] and CAP scores fit to one- and two-factor model, with a total CAP score that was associated with pain severity and quality (r = 0.50–0.72). In people with knee pain, CAP scores were stable over 4 years at the group level, but displayed significant temporal heterogeneity within individual participants.

**Conclusions:** Central aspects of pain are reliably measured by the CAP questionnaire across a range of painful musculoskeletal conditions, and is a changeable state.

**Keywords:** pain, epidemiology, osteoarthritis, lower back pain, fibromyalgia, nociplastic pain, central sensitization

**Rheumatology key messages**

- The Central Aspects of Pain (CAP) questionnaire reliably measures a construct associated with pain across a range of musculoskeletal conditions.
- The CAP questionnaire is a candidate measurement tool for nociplastic pain in musculoskeletal conditions.

## Introduction

Chronic pain is a symptom shared across many musculoskeletal conditions, even when disease management has been optimized. Musculoskeletal pathology is an important treatment target, but often does not adequately explain pain or its persistence. Processing of nociceptive signals in the spinal cord can increase pain severity, exacerbated by inadequate descending inhibitory control from the brainstem. Central sensitization is an increased responsiveness of CNS neurons to a standardized nociceptive input. Changes in brain connectivity might explain increased emotional components of pain. Pain, increased by these neuronal mechanisms, both in severity and distribution, beyond that explained by musculoskeletal pathology, has been called 'nociplastic' [1]. Measurement of these CNS aspects of pain is a prerequisite for understanding their mechanistic underpinning, and their ability to predict future pain and responses to treatment.

Chronic pain is associated with CNS dysfunction across several domains, depression, anxiety, catastrophizing, impaired cognitive function, sleep disturbance and fatigue [2]. Chronic musculoskeletal pain may take on neuropathic-like characteristics, and may spread beyond index sites [3]. Scores from questionnaires that capture these symptoms correlate

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with each other, and with quantitative sensory testing (QST) indices of central sensitization [4]. Although it is challenging to measure mechanisms via questionnaire, these shared associations might indicate diverse consequences of pain or a more general CNS dysfunction. We previously reported a questionnaire measuring central aspects of knee pain (Central Aspects of Pain Knee, CAP-Knee) which was designed with the aim to predict outcomes and stratify patients [5]. CAP-Knee comprises eight self-reported items associated with depression, anxiety, catastrophizing, cognition, sleep, fatigue and a body pain manikin.

No 'gold standard' exists for measuring central sensitization or nociplastic pain, providing challenges for questionnaire validation. Both QST and questionnaires depend on self-report, acknowledging that pain is a subjective experience. Objectivity is maximized by validated and standardized questionnaires and nociceptive stimuli in QST. Various QST modalities reflect different pain mechanisms, such as spinal sensitization (Temporal Summation) or descending inhibitory or facilitatory control of nociceptive transmission (Conditioned Pain Modulation). Different QST modalities sometimes only weakly correlate with each other [6], underlining the heterogeneous CNS mechanisms that modulate pain. In the absence of a 'gold standard', measurement tools are validated against multiple (and sometimes differing) criteria, which, in turn, inform interpretation of measured outcomes.

The CAP-Knee questionnaire measures a unitary overarching factor that was associated with sensitivity, as measured by pressure pain detection thresholds (PPT) distal to the index knee [7]. It predicted persistent pain in a cohort of people with knee pain more strongly than did any individual characteristic measured by questionnaires from which CAP-Knee items were derived [8]. We here refer to that underlying factor as Central Aspects of Pain factor (CAPf). Identification of CAPf is consistent with (although not proof of) a condition of CNS dysfunction in people with nociplastic pain.

That self-reported symptoms can be used to measure aspects of CNS pain processing is supported by data using other questionnaires. Widespread pain distribution is associated with pain severity and QST evidence of central pain sensitivity [9]. Pain distribution is addressed by questionnaires such as the 9-item Central Sensitization Inventory (CSI9) [10, 11] and 8-item Somatic Symptom Scale (SSS8) [12], each of which addresses frequently co-existing medically unexplained symptoms, and is also associated with QST evidence of central pain sensitivity [13–15]. Pain distribution items addressing widespread or specific body site pain comprise five (55%) of the items in CSI9, and five (63%) items in SSS8. Unlike CSI9 and SSS8, CAP-Knee was derived in a musculoskeletal pain population, and addresses a broader range of cognitive and affective factors, each of which has been associated with QST evidence of central pain sensitivity [5]. In general, measures of individual characteristics have been less strongly associated with QST evidence of central pain sensitivity than are composite measures. In particular, pain distribution may be less strongly associated with QST evidence of central pain sensitivity than are other items associated with CNS function [7]. CAP-Knee contains only one (13%) pain distribution item. CAP-Knee [5] and CSI9 [16] behave as unidimensional measurement tools, and the multiple factor structure of SSS8 does not preclude it being recommended as a single summated score [12]. All of these questionnaires have shown validity and utility, and might provide useful clinical information in future studies.

Central aspects of pain are shared between people with different diagnoses, and different index joints. We have presented preliminary evidence that a CAPf may be identified in low back pain [19], as well as knee pain. CAP-Knee has some items that might be specific to knee pain; four out of eight items refer to the knee, and the widespread pain item is classified by 'other pain below the waist'. Minor adaptations, referring to the index joint(s) rather than knee, might lead to a CAPf instrument for use across musculoskeletal conditions.

We here describe the CAP questionnaire, developed through modification of CAP-Knee, for use assessing central aspects of pain across painful musculoskeletal conditions. We evaluated acceptability, reliability and validity of CAP, in people with musculoskeletal pain, and in diagnostic subgroups with OA, back pain or FM.

## Methods

### Participants

Participants were selected from the Investigating Musculoskeletal Health and Wellbeing (IMHW) survey [20]. The IMHW is a community-based study recruiting people from the East Midlands region of the UK who were at risk of frailty, disability or musculoskeletal conditions. IMHW received favourable ethical opinion from London Central Research Ethics Committee #18/LO/0870. Recruitment to IMHW was from multiple sources detailed elsewhere [20], mostly from primary care. Recruitment to IMHW was continuous (could occur at any time) but follow-up questionnaires were dispatched in three waves, approximately annually. For validation analyses of the CAP questionnaire, data were from consecutive participants ($n = 3579$) who participated in IMHW follow up wave 2, each of whom returned a questionnaire that incorporated CAP between September 2020 and September 2021.

A nested subgroup was invited to participate in the reliability sub-study of paper questionnaires first ($n = 168$) or electronic questionnaires first ($n = 69$), then, up to 2 weeks after the questionnaires had been returned, were subsequently invited to complete electronic or paper questionnaires, respectively.

In order to examine stability or change in CAPf over time, baseline questionnaires were used from all waves. Baseline and follow up wave 1 questionnaires incorporated CAP-Knee, and waves 2 and 3 used CAP. CAP-Knee only captured data when people reported knee pain [5], and therefore only people who cited their knee as their index joint were included in this longitudinal analysis.

### CAP questionnaire

CAP was modified from the CAP-Knee questionnaire [5]. The 4 CAP-Knee items that made no reference to 'knee' were retained unmodified (widespread pain, depression, fatigue and anxiety) [5]. The remaining four CAP items replaced 'knee' with 'joint' (catastrophizing, cognition, sleep and neuropathic-like pain). The lead question was re-worded to 'Please select the response that best describes how you have felt over the PAST WEEK. Joint pain may be due to pain in any of your joints, such as fingers, wrist, toes, knees, hips, etc. Please tick one box only per statement and try not to leave any statements blank'. The final paper and electronic

(see Supplement 1, available at *Rheumatology* online) versions of CAP were reviewed by people with lived experience of musculoskeletal conditions.

### Demographic and clinical details

Morbidities were self-reported using tick boxes and free text. Participants reported index joint pain with the question 'over the past 4 weeks, where was your most bothersome joint pain or aching feeling?' Joint pain severity was recorded from 0 to 10 with the question 'over the past 4 weeks, how intense was your average pain or average aching feeling in your most bothersome joint, where 0 is "no pain" and 10 is "pain as bad as could be"?' Pain qualities were recorded using the full-length McGill Pain Questionnaire and its subscales for sensory, affective and evaluative pain [21]. The deciles of the English Index of Multiple Deprivation from 2019 (IMD2019) [22] were retrieved from postcodes [23].

### Statistical analysis

Most analyses were performed in the cross-sectional sample of people with joint pain in wave 2, and also in each of the three subgroups of participants with self-reported diagnoses of OA, back pain or FM. Correlation analysis identified the number of 26 body sites shaded on a pain manikin that most strongly associated with CAPf scores (derived from seven of eight CAP items, manikin excluded). This was similar to the derivation of the widespread pain item from the CAP-Knee, when widespread pain items were correlated with QST [7].

Confirmatory Factor Analysis (CFA) for one- and two-factor models were performed. Model fit was examined using indices where values close to 1.0 showed good fit (Comparative Fit Index and Tucker–Lewis Index), plus the root mean square error of approximation and standardized root mean square residual, where values close to 0 indicated better fit [24]. As each item's data were ordinal, the diagonally weighted least squares/weighted least squares mean and variance adjusted method was used as estimator [25]. When $n < 200$, CFA was not performed [24].

Engagement with CAP was assessed by satisfaction survey, and by recording the frequency of missing data. Patterns of missingness were assessed by the association with participant. Reliability was determined in 200 participants who completed paper version and electronic questionnaires. Reliability was determined as Intraclass Correlation Coefficient (ICC). Cronbach's alpha was derived to assess internal consistency.

Convergent validity of CAP was assessed by correlation coefficients against pain. Minimal important difference (MID) was estimated as 0.5 s.d. [26].

To inform missing items strategies, the impact of imputing missing data was modelled using data from complete questionnaires. CAP scores were calculated from all items ('true' CAP score), and from seven of the eight items, in separate models in which the same item was removed from all questionnaires. CAP scores were imputed with the average (rounded integer) of the remaining seven items. Scores were also examined when two items were removed, and imputed using the mean integer. When two items were removed, they were selected to represent the most likely combinations to skew or bias the imputed CAP data. Median [interquartile range (IQR)] and Bland–Altman plots were derived to compare true CAP scores and imputed data.

Heterogeneity between time points was assessed by non-parametric Friedman's test. This tested whether the difference in CAP between longitudinal time points for individuals differed from zero, indicative of a variable trait. Changes between time points for each individual were classified as being greater than the minimum important difference for CAP, numerical rating scale (NRS) for pain and McGill Pain Questionnaire total score.

Statistical analyses used R with lavaan, ltm and irr packages. Heterogeneity between timepoints was assessed using SPSS version 26 (IBM, Chicago, MI, USA).

## Results

A total of 4130 people had returned IMHW questionnaires in IMHW follow up wave 2 at the time of the study (see Supplement 2, available at *Rheumatology* online), and the study population that reported joint pain ($n = 3579$) is shown in Table 1. People with joint pain reported diagnoses of OA ($n = 1158$), back pain ($n = 1292$) or FM ($n = 177$). Median pain scores were highest in the FM subgroup.

Participants reported high satisfaction with the CAP questionnaire for both paper and electronic versions, with 92% indicating that it was easy to follow and 99% that they would be happy to complete the questionnaire again. Nine percent of participants (330/3579) did not complete all CAP items; 4% (147/3579) of people omitted two or more items; and 5% (183/3579) omitted one item. Neuropathic-like pain was the most frequently omitted item ($n = 195$, 5%). Missing items were associated with slightly lower McGill questionnaire sensory pain scores [median (IQR), 8 (4, 12) *vs* 8 (5, 14), $P = 0.006$] and older age [median (IQR), 74 (69, 80) *vs* 70 (66, 76) years, $P < 0.001$], and were not significantly associated with joint pain severity NRS [6 (4, 8) *vs* 6 (4, 7), $P = 0.485$], sex (9% female *vs* 10% male, $P = 0.248$) or social deprivation rank [IMD2019 decile; 8 (6, 9) *vs* 7 (5, 9), $P = 0.127$].

A common criterion across diagnoses for widespread pain was sought. More widespread pain, defined using a range of thresholds from 5 to 15 out of 26 painful sites on the body manikin, was significantly associated with modified CAP scores derived from the remaining seven items (Fig. 1). Ten or more out of 26 painful sites provided a convergent threshold across diagnostic groups.

CAP score distribution was unimodal within those who reported joint pain, and included all possible scores (0–16, Fig. 2). Floor [$n = 50$ (1%) when CAP = 0] and ceiling [$n = 15$ (0.4%) when CAP = 16] effects were not substantial (Fig. 2). Median (IQR) baseline CAP scores were: IMHW, 6 (3, 9); OA 7 (4, 9); back pain, 7 (5, 11); and FM, 11 (8, 13). The 0.5 s.d. for baseline CAP scores was 1.8, to give an estimate for MID of 2 points [26].

CFA indicated that each item could contribute to a single factor model with good fit. Data also fitted well to a two-factor model which showed very high covariance (0.87–0.90) between the two factors (Table 2). Items were therefore summated for a total score. High reliability was demonstrated between paper and electronic CAP questionnaires, with ICC = 0.89 (95% CI 0.84–0.92) and Cronbach's alpha for CAP items = 0.79 (95% CI 0.78–0.80).

CAP was positively associated with NRS joint pain ($r = 0.66$, $P < 0.0001$), McGill sensory scale ($r = 0.52$, $P < 0.0001$) and other measures of pain quality (Fig. 3). For people with OA, back pain or FM, the correlation coefficients with NRS joint pain were 0.62, 0.62 and 0.72, respectively;

**Table 1.** Description of the people reporting joint pain

| Variable | Participants with joint pain | OA | Back pain | FM | Reliability and feedback subgroup | Longitudinal analysis group |
|---|---|---|---|---|---|---|
| | Median (IQR) or % | Median (IQR) or % | Median (IQR) or % | Median (IQR) or % | Median (IQR) or % | Median (IQR) or % |
| *N* | 3579 | 1153 | 1292 | 177 | 200 | 2155 |
| Age, years | 71 (66, 77) | 72 (66, 77) | 71 (65, 76) | 67 (55, 74) | 70 (65, 74) | 71 (63, 77) |
| Female, % | 60 | 70 | 64 | 86 | 56 | 57 |
| White race, % | 97 | 98 | 97 | 95 | 100 | 94 |
| BMI, kg/m$^2$ | 27.1 (24.2, 30.6) | 27.6 (24.8, 31.4) | 27.4 (24.7, 31.0) | 28.5 (26.0, 32.9) | 26.9 (24.2, 30.2) | 28.2 (25.1, 32.0) |
| Area deprivation, IMD2019 decile | 7 (5, 9) | 7 (5, 9) | 7 (5, 9) | 6 (4, 9) | 8 (6, 10) | 7 (5, 9) |
| Joint pain severity, 0–10 | 6 (4, 7) | 6 (5, 8) | 7 (5, 8) | 7 (6, 8) | 5 (4, 7) | 6 (5, 8) |
| McGill total, 0–78 | 12 (7, 21) | 15 (9, 25) | 16 (9, 26) | 22 (14, 36) | 12 (6, 18) | 13 (7, 23) |
| McGill sensory, 0–42 | 8 (4, 14) | 10 (6, 15) | 10 (6, 16) | 13 (9, 20) | 8 (4, 13) | 9 (5, 15) |
| McGill affective, 0–14 | 0 (0, 2) | 1 (0, 2) | 1 (0, 3) | 2 (0, 6) | 0 (0, 1) | 1 (0, 2) |
| McGill evaluative, 0–5 | 2 (1, 3) | 2 (1, 4) | 2 (1, 4) | 3 (1, 4) | 2 (1, 3) | 2 (0, 3) |

Description of the people reporting joint pain. IMD2019 English Area Deprivation decile ranges from 1 (worst) to 10 (least). IQR: interquartile range; IMD2019: English Index of Multiple Deprivation from 2019.

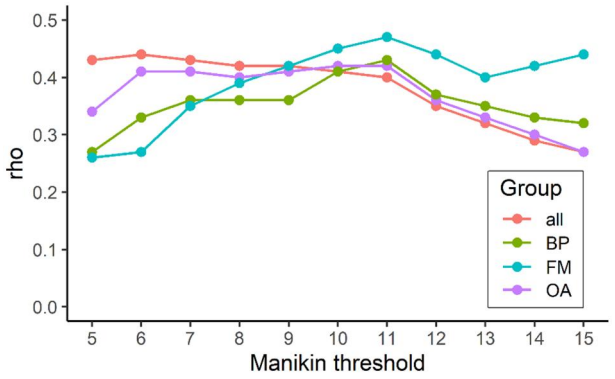


**Figure 1.** Comparisons of correlation coefficients between different manikin region counts and CAPf. CAPf was estimated using a modified CAP derived by summation of seven out of eight items, excluding manikin. Spearman's rho values represent associations between seven manikin widespread pain criteria (using thresholds ranging from 5 to 15 out of 26 regions) and CAPf (derived from the remaining seven items). Rho values converged across diagnostic groups with a manikin threshold of 10 (10 or more sites assessed as widespread pain) (rho = 0.41 for complete sample, 0.42 for OA, 0.41 for back pain and 0.45 for FM). Subsequently, a threshold of ≥10/26 painful sites on the manikin was selected to score people as exhibiting widespread pain (score = 2), and ≤9/26 painful sites to score as not widespread pain (score = 0) for calculating CAPf. CAP: Central Aspects of Pain; CAPf: Central Aspects of Pain factor; all: complete sample; BP: back pain

and with McGill sensory subscale were 0.51, 0.52 and 0.65, respectively.

The distribution of participants' responses to CAP items is shown in Fig. 4. Complete CAP data had items sequentially removed and imputed. Median imputed CAP was identical to the original when a single item was removed, except with removal of the fatigue item (median imputed CAP 1 point lower, Supplements 3 and 4, available at *Rheumatology* online). Where two items were removed, imputed scores often deviated from true scores by 2 points (see Supplement 5, available at *Rheumatology* online).

CAPf stability over time was investigated in participants with knee pain. Supplement 2, available at *Rheumatology* online, shows participant numbers across data collection waves. Median (IQR) CAP scores were similar between waves [baseline, 8 (5, 11), $n = 2137$; wave 1 (1 year), 8 (5, 11), $n = 766$; wave 2 (2 years), 9 (6, 12), $n = 681$; and wave 3 (4 years), 9 (7, 12), $n = 533$]. The median (IQR) changes between time points within each participant were; baseline to wave 1, 0 (–2, 2), $n = 761$; wave 1–2, 0 (–1, 2), $n = 404$; and wave 2–3, 0 (–1, 2), $n = 275$. Significant changes in CAP were found within individuals over time (Friedman test; $\chi^2 = 210.131$, 3 df, $P < 0.001$, $n = 461$). The frequency of changes in CAP that were greater than the minimum important difference are shown in Supplements 6 and 7, available at *Rheumatology* online, with >50% displaying an important change at each measurement.

## Discussion

We here report the 8-item CAP questionnaire, derived from the CAP-Knee questionnaire, and show that its measurement is consistent with CAPf across diverse, chronically painful musculoskeletal conditions. CAP was acceptable to participants, in both paper and electronic versions, with low item missingness. A threshold of ≥10/26 painful sites shaded on the body manikin best assessed widespread pain. CAP score distributions were unimodal with a calculated MID of 2 points. Single missing items can be imputed from an individual's score for the remaining seven items. CAP scores associated both with pain severity and pain quality. CAP scores were highly repeatable over a period of weeks and showed little variability over 3 years at the group level, but displayed significant and clinically important temporal heterogeneity within individuals. We here extend our previous findings in people with knee pain, to show that CAPf displays generalizable validity in people with pain at single or multiple index joints.

Chronic pain is both a sensory and emotional experience, resulting from the integration of mechanisms within the

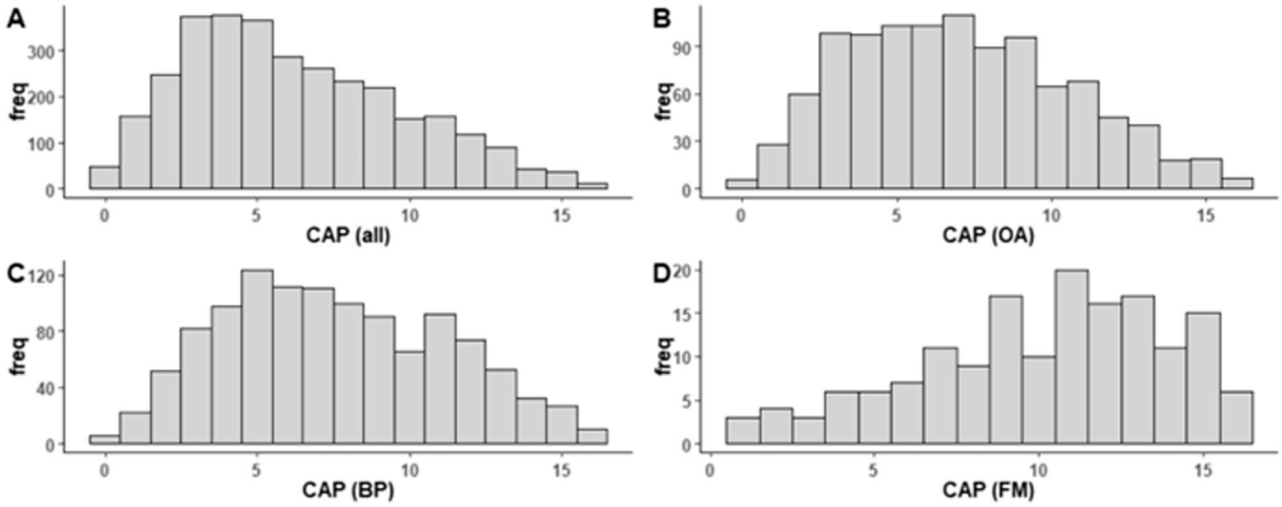


**Figure 2.** Distribution of CAP scores. Distributions of CAP scores for whole population. CAP score distributions were positively skewed in the subgroups with OA or back pain, and negatively skewed in people with FM. (**A**) All [skewness = 0.52 (95% CI 0.46, 0.58), kurtosis = 2.53 (95% CI 2.43, 2.65)]. (**B**) OA [skewness = 0.52 (95% CI 0.46, 0.57), kurtosis = 2.39 (95% CI 2.26, 2.54)]. (**C**) Lower back pain [skewness = 0.24 (95% CI 0.15, 0.32), kurtosis = 2.22 (95% CI 2.11, 2.34)]. (**D**) FM [skewnesss = –0.51 (95% CI –0.77, –0.27), kurtosis = 2.51 (95% CI 2.16, 3.09)]. CAP: Central Aspects of Pain; all: complete sample; BP: back pain

peripheral and central nervous systems. Our current findings are consistent with previous evidence that self-reported characteristics of neuropathic-like pain quality, pain distribution beyond a site of tissue injury, fatigue, cognitive difficulty, catastrophizing, anxiety, sleep disturbance and depression, each is associated with pain severity in people with musculoskeletal pain [7, 27]. Furthermore, each of these characteristics has been associated with reduced PPTs distal to chronically painful knees [7, 28–30]. Reduced pain detection thresholds distant or distal to a site of pathology may indicate central sensitization [31], and central pain processing might influence how musculoskeletal pain is experienced or reported.

Widespread pain distribution is associated with greater pain severity, and evidence of central pain sensitivity [32, 33]. Several methods have been used to classify or measure pain distribution. The ACR developed the Widespread Pain Index (WPI), which became a classification criterion for FM [34, 35]. Other authors have used number of body sites on a pain manikin [19]. CAP-Knee selected 'other pain below the waist' as being most closely associated with low PPT distal to an index knee [5]. In people with knee pain, WPI displayed only weak correlation with PPT. Our approach to the widespread pain item was designed to maximize CAP internal consistency. Across different diagnoses a threshold of ≥10/26 painful sites provided a consistently high correlation with CAPf, despite these conditions being characterized by different pain distributions.

We minimized changes to CAP-Knee when developing CAP in order to build on our previous research that maximized associations with PPT, and that was comprehensible to people with pain [5]. Where the index site is knee, CAP performs as expected, and our current findings confirm it is consistent with a unitary scale. Ninety-one percent of returned questionnaires included responses to all eight items. Missing CAP items were similar across sex and socioeconomic strata, suggesting broad acceptability. Small but statistically significant higher item missingness was found with older participants, and those with lower McGill sensory pain scores. It is possible that older people with less severe pain might have difficulty assigning values to pain-associated characteristics, especially if pain were sporadic or not viewed as a major problem. Our data imputation findings lead us to propose that a single missing item can be replaced by rounded mean integer imputation from the remaining seven items. Two or more items were missing within a single returned questionnaire in 4% of responses, and when modelled data manipulation from complete responses resulted in divergence between true and imputed CAP scores frequently greater than the MID (2 points). Caution therefore should be exercised in producing CAP scores if fewer than seven items are completed. Detailed scoring instructions for CAP are given in Supplement 1, available at *Rheumatology* online.

CAP scores displayed convergent validity through their associations with pain severity and quality, including the sensory subscale of the McGill Pain Questionnaire. These associations were observed across diagnostic groups, and were strongest in those with FM and weakest in OA, consistent with previous evidence that central aspects of pain are more predominant in FM than in OA [36].

Our data fitted well to both one- and two-factor models, with very high co-correlation in all analyses between factors in the two-factor model. Both models appear consistent with a scale derived by summation of all eight items, which might measure an overarching aspect of pain. Results of the two-factor CFA would be consistent with subscales within CAP and would also indicate a reduced comparability between CAP and CAP-Knee. However, further research would need to determine whether a two-factor structure were replicated in other populations, and to investigate the biological meaning of a subscore based on cognition, catastrophizing and sleep items. We previously referred to a unitary factor underlying CAP-Knee as 'Central Mechanisms Trait'. However, we here show that CAP scores, although stable over periods of weeks, show frequent changes over 3 years. The factor measured by CAP and CAP-Knee therefore appears to be a changeable state, rather than an intrinsic trait in people with knee pain. That CAP-Knee scores predicted pain outcomes suggests a causal mechanistic interpretation [8], but it is also

**Table 2.** Factor loadings for confirmatory factor analysis

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **All data** | | | | | | | |
| | One factor | | | | Two factors | | |
| CFI | 0.980 | | | | 0.991 | | |
| TLI | 0.972 | | | | 0.987 | | |
| RMSEA (95% CI) | 0.065 | (0.058 to 0.071) | | | 0.044 | (0.037 to 0.051) | |
| SRMR | 0.046 | | | | 0.033 | | |
| Covariance (S.E.) between factors | Not applicable | | | | 0.866 | (0.012) | |
| | Standardized estimate | S.E. | *P* | Factor | Standardized estimate | S.E. | *P* |
| Neuropathic-like | 0.61 | 0.018 | <0.001 | Factor 1 | 0.64 | 0.019 | <0.001 |
| Fatigue | 0.67 | 0.014 | <0.001 | Factor 1 | 0.71 | 0.014 | <0.001 |
| Depression | 0.42 | 0.018 | <0.001 | Factor 1 | 0.44 | 0.019 | <0.001 |
| Anxiety | 0.70 | 0.017 | <0.001 | Factor 1 | 0.74 | 0.018 | <0.001 |
| Widespread pain | 0.65 | 0.021 | <0.001 | Factor 1 | 0.68 | 0.022 | <0.001 |
| Sleep | 0.71 | 0.010 | <0.001 | Factor 2 | 0.72 | 0.013 | <0.001 |
| Catastrophizing | 0.80 | 0.010 | <0.001 | Factor 2 | 0.81 | 0.010 | <0.001 |
| Cognition | 0.87 | 0.009 | <0.001 | Factor 2 | 0.90 | 0.009 | <0.001 |
| **OA** | | | | | | | |
| | One factor | | | | Two factors | | |
| CFI | 0.981 | | | | 0.991 | | |
| TLI | 0.973 | | | | 0.987 | | |
| RMSEA (95% CI) | 0.061 | (0.050 to 0.071) | | | 0.043 | (0.030 to 0.056) | |
| SRMR | 0.046 | | | | 0.036 | | |
| Covariance (S.E.) between factors | Not applicable | | | | 0.871 | (0.021) | |
| | Standardized estimate | S.E. | *P* | Factor | Standardized estimate | S.E. | *P* |
| Neuropathic-like | 0.57 | 0.032 | <0.001 | Factor 1 | 0.60 | 0.033 | <0.001 |
| Fatigue | 0.69 | 0.023 | <0.001 | Factor 1 | 0.73 | 0.024 | <0.001 |
| Depression | 0.48 | 0.029 | <0.001 | Factor 1 | 0.51 | 0.030 | <0.001 |
| Anxiety | 0.67 | 0.031 | <0.001 | Factor 1 | 0.70 | 0.032 | <0.001 |
| Widespread pain | 0.63 | 0.034 | <0.001 | Factor 1 | 0.66 | 0.035 | <0.001 |
| Sleep | 0.69 | 0.023 | <0.001 | Factor 2 | 0.71 | 0.024 | <0.001 |
| Catastrophizing | 0.78 | 0.019 | <0.001 | Factor 2 | 0.80 | 0.019 | <0.001 |
| Cognition | 0.86 | 0.017 | <0.001 | Factor 2 | 0.88 | 0.018 | <0.001 |
| **Back pain** | | | | | | | |
| | One factor | | | | Two factors | | |
| CFI | 0.985 | | | | 0.990 | | |
| TLI | 0.978 | | | | 0.985 | | |
| RMSEA (95% CI) | 0.056 | (0.044 to 0.068) | | | 0.046 | (0.034 to 0.058) | |
| SRMR | 0.042 | | | | 0.036 | | |
| Covariance (S.E.) between factors | Not applicable | | | | 0.903 | (0.020) | |
| | Standardized estimate | S.E. | *P* | Factor | Standardized estimate | S.E. | *P* |
| Neuropathic-like | 0.61 | 0.029 | <0.001 | Factor 1 | 0.63 | 0.030 | <0.001 |
| Fatigue | 0.67 | 0.024 | <0.001 | Factor 1 | 0.69 | 0.025 | <0.001 |
| Depression | 0.55 | 0.027 | <0.001 | Factor 1 | 0.57 | 0.028 | <0.001 |
| Anxiety | 0.69 | 0.026 | <0.001 | Factor 1 | 0.71 | 0.027 | <0.001 |
| Widespread pain | 0.61 | 0.033 | <0.001 | Factor 1 | 0.63 | 0.033 | <0.001 |
| Sleep | 0.66 | 0.023 | <0.001 | Factor 2 | 0.67 | 0.024 | <0.001 |
| Catastrophizing | 0.76 | 0.019 | <0.001 | Factor 2 | 0.77 | 0.019 | <0.001 |
| Cognition | 0.86 | 0.015 | <0.001 | Factor 2 | 0.88 | 0.016 | <0.001 |

Comparison of CFA standardized loadings for one- and two-factor models of CAP. The two-factor model consisted of items loading onto either factor 1 (items for neuropathic-like, fatigue, cognition, depression and anxiety) or loading onto factor 2 (items for cognition, sleep and catastrophizing). Populations consisted of all participants with joint pain and CAP data ($n = 3177$), OA ($n = 1052$) or back pain ($n = 1151$). The number of people who self-reported FM ($n = 177$) was insufficient for analysis. CFI: Comparative Fit Index; TLI: Tucker–Lewis Index; RMSEA: root mean square error of approximation; SRMR: standardized root mean square residual; CAP: Central Aspects of Pain.

possible that scores can represent consequences of pain. We therefore here refer to a CAPf in order to avoid mechanistic overinterpretation of our findings. CAP is not a direct measure of central sensitization or neuropathy. Indeed, central sensitization may be a heterogeneous condition that results from multiple discrete mechanisms within the brain and spinal cord. Central sensitization in humans cannot be measured by any single 'gold standard' tool, and further research

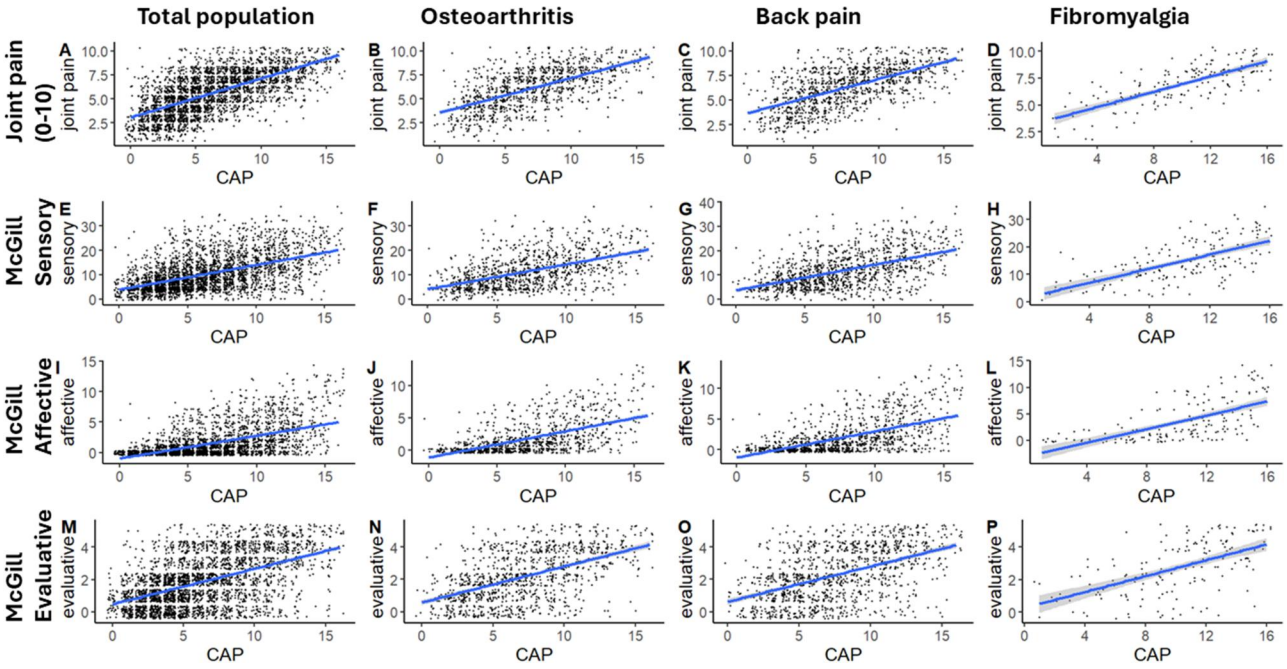


**Figure 3.** Convergent validation of CAP questionnaire by correlation with pain scales. Scatterplots of CAP *vs* pain scales. (**A**, **E**, **I**, **M**) Total study population; CAP *vs* joint pain, McGill sensory, McGill affective, McGill evaluative scales. (**B**, **F**, **J**, **N**) OA population; CAP *vs* joint pain, McGill sensory, McGill affective, McGill evaluative scales. (**C**, **G**, **K**, **O**) Back pain population; CAP *vs* joint pain, McGill sensory, McGill affective, McGill evaluative scales. (**D**, **H**, **L**, **P**) FM population; CAP *vs* joint pain, McGill sensory, McGill affective, McGill evaluative scales. Linear line of best fit (95% CI) shown for each comparison. Correlation coefficients (p) for each panel were (A) 0.66 (<0.001), (B) 0.62 (<0.001), (C) 0.62 (<0.001), (D) 0.72 (<0.001), (E) 0.52 (<0.001), (F) 0.52 (<0.001), (G) 0.52 (<0.001), (H) 0.65 (<0.001), (I) 0.57 (<0.001), (J) 0.58 (<0.001), (K) 0.58 (<0.001), (L) 0.63 (<0.001), (M) 0.52 (<0.001), (N) 0.52 (<0.001), (O) 0.50 (<0.001), (P) 0.57 (<0.001). CAP: Central Aspects of Pain

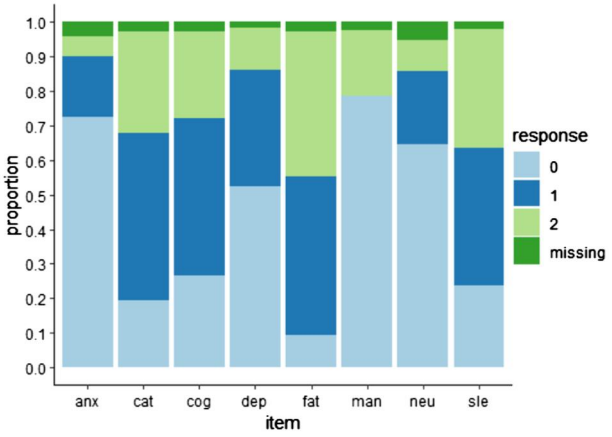


**Figure 4.** Distribution of item responses. Frequency of item responses, are represented as a proportion of total, including missing data. Responses 0 = never, 1 = sometimes, 2 = often and always. Anx: anxiety item; cat: catastrophizing item; cog: cognition item; dep: depression item; fat: fatigue item; man: widespread pain (manikin) item; neu: neuropathic-like pain item; sle: sleep item

should define relationships between CAP and discrete aspects of central pain sensitivity.

Recent attention has focused upon nociplastic pain—'pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain' [1]. Nociplastic pain can occur alongside neuropathy or musculoskeletal pathology. Classification of nociplastic pain requires evidence of pain hypersensitivity, and symptoms of sleep disturbance, fatigue and cognitive problems [37]. We show that these symptoms are associated with CAPf, as were lower pressure pain detection thresholds [7], indicative of pain hypersensitivity. CAPf might therefore be an index of nociplasticity. However, multiple mechanisms might contribute to nociplasticity, and CAP might measure each of these only partially. Variations in CAPf over time within individuals suggests the potential to be modifiable and therefore could be developed and validated as a potential target for treatment. Research is also underway examining alternative self-report questionnaires, such as CSI9, SSS8 and the Keele STarT MSK Tool, which might also represent treatment targets or predictive tools. Studies comparing different instruments in different populations with chronic pain are warranted [38].

Our study has several strengths, but also several limitations. This study did not directly demonstrate the ability of CAP to measure or classify pain mechanisms. CAP displayed convergent validity against measures of pain, but use alongside other indices of nociplastic pain mechanisms, such as QST, might further improve its clinical value. Future work might assess whether CAP can show utility over and above other instruments or QST modalities. The study population was almost entirely white British with or at risk of musculoskeletal pain or frailty. We did not undertake assessments to confirm self-reported diagnoses. We did not investigate all musculoskeletal conditions. The generalizability of our findings requires further investigation. We confirmed factor structures for subgroups with OA or low back pain, but our FM subgroup was of insufficient size. However, consistency of our findings across three different diagnostic groups, and in the total study population,

strongly implies that CAP could show similar properties in other conditions. CAPf was associated with pain severity, supporting its identification as a pain-related characteristic. However, CAP scores might be confounded by nociceptive or neuropathic pain severity. Pain severity is not readily adjusted out of statistical models without the possibility of introducing bias. CAP was developed to explore mechanistic aspects of musculoskeletal pain that might have prognostic or predictive value. As such it might complement, rather than replace, existing questionnaires that have been designed to address patient concerns about their pain, its impact on their lives or their overall well-being. Factors additional to central pain sensitivity can influence pain prognosis, and CAP might complement prognostic tools such as the Keele STarT MSK Tool [17, 18] by identifying possible contribution to prognosis from central aspects of pain.

In conclusion, we report the CAP questionnaire as a possible measurement tool for nociplastic pain. Future research should test the mechanistic underpinning of CAP, and its ability to predict future pain and responses to treatment.

## Supplementary material

Supplementary material is available at *Rheumatology* online.

## Data availability

Data requests can be addressed to D.A.W., e-mail: David.walsh@nottingham.ac.uk.

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*Ethics*: Investigating Musculoskeletal Health and Wellbeing (IMHW) received favourable ethical opinion from London Central Research Ethics Committee #18/LO/0870. The analyses described in this manuscript were secondary data analyses that did not require additional ethical opinion.

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Original Article

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# Are you using a treatment that addresses all 6 key manifestations of PsA?

**The key clinical manifestations of PsA are joints, axial, skin, enthesitis, dactylitis and nails.[1]**


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**68%** of patients achieved **ACR50** with Cosentyx® (secukinumab) at **Year 1** (observed data)[2]

Results from ULTIMATE (N=166). The primary endpoint of GLOESS mean change from baseline vs placebo at Week 12 was met (−9 vs −6, p=0.004)[2,3]

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## Skin clearance in PsO:

**55%** of patients achieved **PASI100** at **Week 52** with Cosentyx 300 mg AI (secondary endpoint, observed data, N=41)[4]

Results from MATURE. The co-primary endpoints PASI 75 and IGA mod 2011 0/1 at Week 12 were met for Cosentyx 300 mg (N=41) vs placebo (N=40), (95% vs 10% and 76% vs 8% respectively, p<0.0001)[4]

## Axial joint relief in PsA:

**69%** of patients achieved **ASAS40** at **Week 52** with Cosentyx 300 mg (secondary endpoint, observed data, N=139)[1]

Results from MAXIMISE. The primary endpoint of ASAS20 with Cosentyx 300 mg (N=164) vs placebo (N=164) at Week 12 was met (63% vs 31% respectively, p<0.0001)[1]

**Cosentyx is the first and only, fully human biologic that directly blocks IL-17A regardless of its source[5–10]**

**8 years**

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The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[5,6]

**Cosentyx licensed indications in rheumatology:** Cosentyx is indicated for the treatment of active psoriatic arthritis in adult patients (alone or in combination with methotrexate) when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis 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; moderate to severe plaque psoriasis in children and adolescents from the age of 6 years, and adults who are candidates for systemic therapy; active enthesitis-related 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 juvenile psoriatic arthritis in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[5,6]

ULTIMATE (N=166), a multicentre, randomised, double-blind, placebo-controlled, 52-week Phase III trial in patients with PsA. Patients were randomly assigned to receive either weekly subcutaneous Cosentyx (300 mg or 150 mg according to the severity of psoriasis) or placebo followed by 4-weekly dosing thereafter. The primary outcome of mean change in the ultrasound GLOESS from baseline to Week 12 was met (−9 vs −6; p=0.004).[2,3]
MATURE (N=122), a 52-week, multicentre, double-blind, randomised, placebo-controlled, Phase III trial in patients with PsO. Eligible patients were randomised to Cosentyx 300 mg or placebo. The co-primary endpoints were PASI75 and IGA mod 2011 0/1 responses at Week 12. The study met the co-primary endpoints: PASI75 and IGA mod 2011 0/1 response at Week 12 were met for Cosentyx 300 mg vs placebo (95% vs 10% and 76% vs 8% respectively, p<0.0001).[4]
MAXIMISE (N=498) a double blind, placebo-controlled, multicentre, Phase IIIb study in patients with PsA. Patients were randomised in a 1:1:1 ratio to receive Cosentyx 300 mg, 150 mg or placebo. The primary endpoint of the proportion of patients achieving and ASAS20 response with Cosentyx 300 mg at Week 12 vs placebo was met (63% vs 31% respectively, p<0.0001).[1]

ACR, American College of Rheumatology; AI, auto-injector; ASAS, Assessment of SpondyloArthritis International Society; BASDAI, Bath; ankylosing spondylitis disease activity index; EULAR, European Alliance of Associations for Rheumatology; GLOESS, Global EULAR and OMERACT synovitis score; IGA mod 2011 0/1, investigator global assessment modified 2011 0/1; OMERACT, outcome measures in rheumatology; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; PsO, plaque psoriasis.

**References: 1.** Baraliakos X, et al. *RMD open* 2019;5:e001005; **2.** Conaghan PG, et al. Poster 253. *Rheumatology* 2022;61(Suppl1). DOI:10.1093/rheumatology/keac133.252; **3.** D'Agostino MA, et al. *Rheumatology* 2022;61:1867–1876; **4.** Sigurgeirsson B, et al. *Dermatol Ther* 2022;35(3):e15285; **5.** Cosentyx® (secukinumab) GB Summary of Product Characteristics; **6.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **7.** Lynde CW, et al. *J Am Acad Dermatol* 2014;71(1):141–150; **8.** Fala L. *Am Health Drug Benefits* 2016;9(Special Feature):60–63; **9.** Schön M & Erpenbeck L. *Front Immunol* 2018;9:1323; **10.** Gorelick J, et al. *Practical Dermatol* 2016;12:35–50; **11.** European Medicines Agency. European public assessment report. Medicine overview. Cosentyx (secukinumab). Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed May 2024].

NOVARTIS

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

UK | May 2024 | 425034

## 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.

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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) 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.

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**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