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Prodromal symptoms of rheumatoid arthritis in a primary care database: variation by ethnicity and socioeconomic status

Alexander d'Elia* ¹, Aliaksandra Baranskaya ², Shamil Haroon ³, Ben Hammond ³, Nicola J Adderley ^{3,4}
Krishnarajah Nirantharakumar ^{3,4}, Joht Singh Chandan ³, Marie Falahee ^{2,4} and Karim Raza ^{2,4,5}

¹ Department of Public Health Policy and Systems, Institute of Population Health, University of Liverpool, Liverpool, UK.

² Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK.

³ Institute of Applied Health Research, University of Birmingham, Birmingham, UK.

⁴ NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

⁵ Department of Rheumatology, Bronglais Hospital, Hywel Dda University Health Board, Aberystwyth, UK.

*Corresponding author: Alexander d'Elia, ORCID 0000-0001-3245-4634, adelia@liverpool.ac.uk, Department of Public Health, Policy and Systems, The University of Liverpool, Whelan Building, Liverpool, L68 3GB, UK.

Abstract

Objectives

To assess whether prodromal symptoms of rheumatoid arthritis (RA), as recorded in the Clinical Practice Research Datalink Aurum (CPRD) database of English primary care records, differ by ethnicity and socioeconomic status.

Methods

A cross-sectional study to determine the coding of common symptoms ($\geq 0.1\%$ in the sample) in the 24 months preceding RA diagnosis in CPRD Aurum, recorded between January 1st 2004 to May 1st 2022. Eligible cases were adults with a code for RA diagnosis. For each symptom, a logistic regression was performed with the symptom as dependent variable, and ethnicity and socioeconomic status as independent variables. Results were adjusted for sex, age, BMI, and smoking status. White ethnicity and the highest socioeconomic quintile were comparators.

Results

In total, 70115 cases were eligible for inclusion, of which 66.4 % female. Twenty-one symptoms were coded in more than 0.1 % of cases so were included in the analysis. Patients of South Asian ethnicity had higher frequency of codes for several symptoms, with the largest difference by odds ratio being muscle cramps (OR 1.71, 1.44-2.57) and shoulder pain (1.44, 1.25-1.66). Patients of Black ethnicity had higher prevalence of several codes including unintended weight loss (2.02, 1.25-3.28) and ankle pain (1.51, 1.02-2.23). Low socioeconomic status was associated with morning stiffness (1.74, 1.08-2.80) and falls (1.37, 2.03-1.82)

Conclusion

There are significant differences in coded symptoms between demographic groups, which must be considered in clinical practice in diverse populations and to avoid algorithmic bias in prediction tools derived from routinely collected healthcare data.

Key words: Rheumatoid Arthritis, Primary Care, Health Equity, Routine Clinical Data

Key messages:

- There are differences in symptom reporting in new onset rheumatoid arthritis across ethnic groups.
- These differences should be considered in clinical practice in diverse populations.
- The findings are relevant in avoiding bias in prediction tools derived from healthcare data.

Introduction

Rheumatoid arthritis (RA) is a common immune-mediated inflammatory condition with an adult prevalence of 0.8 % in the UK (1). Patients typically present in primary care before being referred to and diagnosed by rheumatologists (2). Treatment within three months of symptom onset is associated with improved clinical outcomes, including higher chances of sustained remission, reduced joint destruction, and reduction of extra-articular disease manifestations (3). Despite this, a recent UK audit found that half of all patients experienced symptoms for longer than six months prior to referral (as reported by secondary care clinicians) (2). Similarly, an older study found that a quarter of patients experience symptoms for more than 66 weeks before seeing a rheumatologist (4) An increase in primary care consultations in the two years preceding a diagnosis of RA has been reported (5) and even after being seen in primary care, 44% of patients are still not referred within

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3 the target of three working days (2), and a Danish study of RA patients found that 25% of RA patients
4 had five or more GP consultations before RA was considered as a cause for their symptoms (6). The
5 above suggest scope for earlier identification and referral of suspect cases to secondary care.
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9 Meanwhile, there are well-documented ethnic and socio-economic disparities in clinical outcomes
10 for RA (7-9), suggesting a lack of health equity along the patient pathway. There is evidence that
11 ethnicity and socio-economic status influence the symptomatic presentation to primary care (8, 10)
12 and patients of non-White ethnicity and low socioeconomic status may be more likely to present
13 with “atypical” musculoskeletal symptoms than their White or more affluent counterparts. Such
14 presentations of prodromal RA may pose a diagnostic challenge, contributing to referral lag (2). This
15 may be further compounded by multimorbidity, which is associated with both ethnicity and
16 socioeconomic status, and makes recognition of early RA more difficult, as new RA-related
17 symptoms may be incorrectly attributed to pre-existing conditions (11).
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20 Improved understanding of how the symptomatology of early RA varies with ethnicity and
21 socioeconomic status is needed to address diagnostic delay, and ultimately reduce health inequities.
22 Development of data-driven clinical prediction models could contribute to earlier referral, diagnosis
23 and treatment (12). However, under-representation of subpopulations within the datasets used to
24 build such prediction models, in combination with demographic differences in presentation, may
25 result in less accurate predictions for some groups. For example, Chen et al. discussed the potential
26 implication of such imbalance in relation to intensive-care-mortality prediction, which was shown to
27 be more accurate for White men compared to women and patients of minority ethnicities (13). This
28 algorithmic bias (14, 15) may further contribute to diagnostic delay and worsen health inequities. As
29 the present study utilises the large Clinical Practice Research Datalink Aurum (CPRD Aurum) dataset
30 (16), our findings offer insight into the risk of algorithmic bias in RA-prediction models built on the
31 same dataset.
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45 46 Aim

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48 To assess whether the prodromal symptoms of rheumatoid arthritis (RA), as recorded in English
49 primary care records in the CPRD Aurum database, differ by ethnicity and socioeconomic status. The
50 analysis aims to offer insight into demographic differences in early RA presentations, and to highlight
51 the risk of algorithmic bias in tools developed from CPRD Aurum data.
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Methods

We conducted a cross-sectional study in the CPRD Aurum database investigating variations in the frequency of common (prevalence $\geq 0.1\%$) symptoms coded in the 24 months preceding a recorded RA diagnosis. Variations were subsequently investigated by ethnicity and socioeconomic status.

CPRD Aurum is an anonymised database of observational clinical routine data (OCRD). It consists of primary care medical records of over 13 million actively registered patients in general practices in England and Northern Ireland that use the EMIS clinical information system. It captures data on patient demographics, diagnoses, symptoms, prescriptions, referrals and laboratory results. Structured data on diagnoses, symptoms and referrals are recorded using SNOMED CT coding terminology. Data are released regularly for research purposes, and this study utilised data from the May 2022 release (16).

Socioeconomic status was defined by the English Indices of Multiple Deprivation (IMD). IMD is a composite measure to quantify socioeconomic deprivation and consists of measures of income, employment, health, crime, barriers to housing and services, and living environment. All in turn are made up of several indicators. IMD data do not represent individuals but rather localities which in this study was a Lower Layer Super Output Area (LSOA) encompassing on average 1500 persons. The IMD data used are provided by CPRD, with IMD quintiles assigned to each individual based on LSOA of residence from the 2019 (latest as of June 2023) release of IMD (17). Quintile 1 represents patients living in the 20% most deprived localities.

The study period covered incident cases of RA registered from 1 January 2004 until 1 May 2022 (from the start of CPRD Aurum data until the working copy was extracted). RA was defined using existing code lists from previous work in CPRD Aurum (5). The following inclusion criteria were applied: adults (≥ 18 years) registered at practices in England with linked IMD data (not available for Northern Ireland), documented ethnicity, incident diagnosis of RA during the study period and at least 24 months registration time at the respective practice before the date of RA diagnosis code. The duration of the prodromal phase was set to 24 months based on consultation with local rheumatology experts and previous research that showed that a large proportion of patients experience symptoms for >12 months prior to diagnosis (18). Note that RA is typically diagnosed in secondary care and subsequently communicated to the patients' GP, who codes it. We only had access to the coded date for this analysis, which is likely to be slightly later than actual diagnosis.

Exposures

The exposures were ethnicity and IMD quintile. Ethnicity categories were defined by the five high-level groups recorded in the CPRD Aurum dataset: White, South Asian, Black, Mixed and Other.

Symptoms and code lists

The symptoms included were initially derived from a CPRD Aurum-based descriptive study by Muller et al (2019) (19) on the prevalence of prodromal symptoms of RA. This was further expanded by an exploratory review of prodromal RA symptoms (Supplementary Data S1, available at *Rheumatology* online). These searches resulted in a list of 36 prodromal symptoms (Supplementary Data S2, available at *Rheumatology* online). The code lists were compiled and developed by two clinical doctors, one GP in training (AD) and one rheumatology fellow (SB), with oversight from a clinically practicing professor in rheumatology (KR). Additionally, code lists were regularly discussed with other senior members of the multidisciplinary author group. Where available, existing CPRD Aurum SNOMED CT code lists generated from prior work by the research team were utilised to capture symptom occurrence. For joint related symptoms, the broad categories used by Muller et al, such as “hand problems”, were subdivided into the cardinal features of rheumatoid arthritis: pain, stiffness and swelling. New code lists were developed for these symptoms according to the following principles:

- Anatomical consideration: e.g., for “hand pain”, all joint areas of hand were included.
- Biological plausibility: e.g. “jaw pain” is a known prodromal symptom, but “jaw swelling” is not and was not included. “Foot swelling” was excluded due to inability to distinguish synovial swelling (which may relate to RA) from the common and unspecific foot oedema.
- Code exclusivity: codes were mutually exclusive in code lists. This was checked when code lists were provisionally completed, and in cases of duplication, a joint decision was made on inclusion, as per the above criteria.

Example code lists can be found in Supplementary Data S3, available at *Rheumatology* online, and the complete set is available on request.

Symptoms coded in more than 0.1 % of cases within the 24 months preceding the diagnosis of RA (equivalent to $n \geq 70$ occurrences) were included in the analysis.

Co-variates

Sex, age, body mass index (BMI) and smoking status were included in the model as co-variates. Sex was treated as binary as per the data in CPRD Aurum. Age was included as four groups (18-30 years, 31-50 years, 51-70 years and >70 years). Sex and, in particular, age bring significant physiological differences which may explain symptom variation. Sex- and age-differences in symptomatology are already well reported (20). BMI was included as it is known to affect musculoskeletal symptoms (21) and varies with ethnicity and socioeconomic status (22). BMI was analysed categorically as per the following groups: <18.5kg/m² (underweight), 18.5-24.9kg/m² (normal weight), 25-29.9kg/m² (overweight), 30-39.9kg/m² (obese) and ≥40kg/m² (morbidly obese). Smoking is also known to correlate with both symptoms and prevalence of RA (23), and was included in the regression models as: current smoker, ex-smoker and never smoked. Smoking status was ascertained from CPRD Aurum data using the method from Subramanian et al (2022) (24).

Statistical methods

Data were extracted from CPRD Aurum using DExtER, an automated epidemiology software platform developed at the University of Birmingham (25). Statistical analysis was then performed in Stata version 14 (26). For each case (i.e. patient), all included symptoms were given a duration variable denoting the time span from the recording of the symptom and the diagnosis date, and only symptoms occurring ≤24 months before diagnosis were included. A binary logistic regression was conducted for each of the 21 included symptoms, including the exposures and covariates as independent variables and the given symptom as the dependent variable.

Results were reported as the odds ratios (OR) of the comparative prevalence of symptoms preceding diagnosis in a subset of the population, grouped by ethnicity and IMD quintile compared to the prevalence in the largest ethnicity (White) and to the least deprived IMD quintile 5. This was adjusted for the confounders of sex, age group, BMI category and smoking status. The risk of type-1 error due to multiple regression models was addressed by incorporating a Bonferroni correction to adjust the *p* value thresholds for statistical significance (21 regression models gave *p*<0.0024 for 95 % confidence), and subsequently results are expressed with 99.76 % confidence interval.

Three supplementary analyses were conducted: a) comparison of the studied symptoms with a matched non-RA population, to assess whether differences in symptomatology reflect differences in RA presentation or other differences between ethnic groups which are unrelated to RA ; b) comparison of adjusted and non-adjusted odds ratios for “any symptom” to assess the impact of the confounders; and c) stratified analyses for “any symptom” by ethnicity and IMD quintile to assess

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3 the interaction between ethnicity and IMD (for further detail see Supplementary Data S4, available
4 at *Rheumatology* online).

5 6 7 8 Missing data

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10 Cases with missing ethnicity and IMD were excluded as these datapoints were central to the aim.
11 Missing data on BMI category and smoking status were replaced by a “missing” value and included.
12 Implausible BMI (<10, >100 kg/m²) was treated as missing.
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15 16 Patient and public involvement

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18 A panel of five patient research partners contributed to the development of the grant application
19 that partially funded this research. Development of the current research objectives and
20 interpretation of findings was supported by monthly project meetings, in which a patient research
21 partner participated. This manuscript was reviewed, proofread, and approved by a patient research
22 partner.
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27 28 Ethics

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30 This study and the use of CPRD Aurum and linked IMD data was approved by the CPRD Research
31 Data Governance board, reference number 22_002367. The study was conducted in accordance with
32 the recommendations for physicians involved in research on human subjects adopted by the 18th
33 World Medical Assembly, Helsinki 1964, and later revisions.
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38 39 Results

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41 The initial dataset included 83660 cases. After excluding cases with missing data on ethnicity
42 (n=12336) and IMD (n=1209), 70115 cases were included in the analysis.
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46 The demographics of the study population are described in Table 1. The majority (66.4 %) of cases
47 were female and the largest age group was 51-70 years (47.3 %), with a mean age of 60.1 years. The
48 most common BMI group was “Overweight” (32.7 %), and the mean BMI was 25.1 (SD 4.1). Current
49 smoking was recorded in 26.9 % of cases. The most common ethnic group was White, with 88.4 %
50 the sample.
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55 Of the initial list of 36 symptoms, 21 symptoms had a prevalence ≥ 0.1 % (equal to ≥ 70 cases) and
56 were included in the analysis (Table 2). Of the sample, 49.6 % (n=34799) of cases had one or more of
57 the 21 eligible symptoms coded. The average number of coded symptoms per case was 0.80 (SD
58 1.03), ranging from 0 to 12 symptoms. After adjusting for confounders the odds ratio (OR) for having
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any symptom coded was higher in cases of Black (OR 1.17, 99.76 % confidence interval 1.04-1.32) and South Asian ethnicity (OR 1.16, 1.07-1.26), compared to White ethnicity. There were no significant differences by IMD quintile for prevalence of “any symptom”.

Statistically significant differences were found for the coding of twelve symptoms (Table 3). Cases of South Asian and Black ethnicity were more likely to have codes for knee pain (OR 1.29, 1.06-1.58 and 1.37, 1.20-1.57 respectively) and shoulder pain (OR 1.33, 1.07-1.65 and 1.44, 1.25-1.66 respectively). South Asian cases more frequently had codes for neck pain (OR 1.28, 1.04-1.57), fatigue (OR 1.28, 1.06-1.55), unspecified muscle cramps (OR 1.71, 1.14-2.57) and hand and finger pain (OR 1.16, 1.00-1.35) than any other ethnic group. However, hip pain was statistically less likely to be coded in cases of South Asian ethnicity (OR 0.66, 0.50-0.89). Ankle pain (OR 1.51, 1.02-2.23) and unintended weight loss (OR 2.02, 1.25-3.28) were more frequently coded in cases of Black ethnicity. Reporting of falls was statistically higher by the “Other” ethnicity and IMD quintile 1 (most deprived) (OR 2.14, 1.02-4.50, and 1.37, 1.03-1.82 respectively). Morning stiffness was also more frequently coded in IMD quintile 1 (OR 1.74, 1.08-2.80). Finally, jaw pain was more frequently coded in cases of Other ethnicity (OR 3.30, 1.02-10.73). See Supplementary Data S5, available at *Rheumatology* online, for full results of the regression models.

The supplementary analyses found that: a) In an age-, sex- and medical-practice-matched control population there were similar differences in coded symptoms between ethnic groups in the non-RA control population. However, the overall symptom prevalence was much lower at 24.1 % (all ethnic groups) in the control group compared to the RA study population at 48.9 %. We interpret this to suggest that, as expected, patients with RA experience musculoskeletal prodromal symptoms as demonstrated by higher prevalence of recorded codes in comparison to the matched non-RA population. The result also suggest that there are baseline differences in musculoskeletal symptom reporting, and possibly recording, between ethnic groups and these differences are maintained within the RA cohort. b) After excluding potential confounders from the analysis, the results were largely unaltered; thus, the included confounders had very limited impact on the results. c) The relationship between ethnic group and IMD quintile and the odds ratios for coding of “any symptom” was preserved after stratification, indicating that the results of the main analysis are unlikely to be affected by interaction between ethnicity and IMD. The results for the supplementary analyses are available in Supplementary Data S4.

Discussion

Significant differences in symptomatology (as coded) were found across twelve prodromal symptoms of RA, with higher prevalence of coded symptoms mainly in cases of South Asian and Black ethnicity. Our findings also suggest that patients of Non-white ethnicity are more likely to report general musculoskeletal symptoms (such muscle cramps and fatigue, or pain in large joints). Such presentations may make symptoms more difficult to attribute to RA, which in turn may delay referral to rheumatology and ultimately delay diagnosis. It has previously been reported that ethnic minorities and socioeconomically disadvantaged subpopulations experience a worse functional status and impact on quality of life from RA (9), and it is possible that delayed diagnosis and treatment is a contributory factor (8). Beyond RA, these groups experience worse overall health outcomes (for example during the COVID-19 pandemic (27)), and reducing these health inequities is a priority and statutory duty for healthcare systems (28), including the English NHS which forms the setting of this analysis (29). Improving diagnostic accuracy and reducing diagnostic delay would help combat these inequities in health.

Socioeconomic deprivation was only found to correlate with increased prevalence of morning stiffness and falls, and only in IMD quintile 1 (most deprived). As such, our data suggest that socioeconomic status impacts the reporting of prodromal symptoms of RA to a lesser degree than ethnicity. However, ethnicity is a static factor whereas patients' socioeconomic status can change throughout lifetime and its impact is more challenging to measure and interpret. There is also a well-known correlation between ethnicity and socioeconomic status, with people of minority ethnicity more likely to be socioeconomically disadvantaged (30). However, IMD quintile was not found to strongly correlate to the prevalence of symptoms in the present study and in further stratified analysis available in Supplementary Data S4, and so it is likely that the majority of the effect can be explained by ethnicity. It must be remembered, however, that IMD quintile is a proxy measure of socioeconomic deprivation as it describes areas, not individuals. The demographics of the study population are in line with preceding literature on the age and sex of incident RA cases (2). White ethnicity was over-represented in comparison to national census data (31) (88.4 % vs. 81.7 %). Finally, we do not seek to establish causality, and it is likely that the observed differences by ethnicity have multifactorial causality; possibly including varied health-seeking behaviours, experiences of the healthcare system, and more.

Beyond informing clinical practice, the results have implications for the usage of CPRD Aurum data (and similar OCRD sources) in creating clinical prediction models. If differences in symptom patterns exist between different ethnic groups (as indicated by this study), prediction models must take this

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3 into account, otherwise the predictive performance will be inferior for the populations which are
4 numerically smaller (e.g., ethnic minorities).
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7 Further research is required on this topic to help effectively mitigate this risk of bias in prediction
8 models. From a clinical perspective, further research would help build on these findings to form
9 more equitable management guidelines to facilitate earlier diagnosis of RA across all ethnic
10 groupings.
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14 15 Strengths and limitations

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17 This analysis presents a pragmatic approach to assess systemic demographic differences in
18 symptomatology as reflected in coding, providing a useful starting point for more targeted research.
19 A strength is the analysis of the CPRD Aurum dataset, enabling inclusion of a large sample size. The
20 analysis does however have limitations. The study relies on the accuracy of symptom data in CPRD
21 Aurum and is dependent on how symptoms and the diagnosis of RA are recorded by individual
22 general practitioners, and recording patterns of general practitioners may vary across ethnic groups.
23 The low frequency of symptoms which are known to be associated with RA suggests under-coding of
24 symptoms in CRPD Aurum. For example, more than half of all RA patients present with painful small
25 joints of hands (2), but in this analysis, only 10.2 % of cases had this symptom coded. The previously
26 mentioned CPRD study by Muller et al (2019) (19) (which draw data from the parallel CPRD system
27 CPRD GOLD) indicate this is to be expected, with a recorded frequency of finger joint pain of 16.2 %
28 using a wider definition, again much lower than would be expected for RA. By design, the study does
29 not differentiate between symptoms directly related to RA and symptoms related to other
30 morbidities. Nonetheless, for the purpose of comparing prodromal symptoms across subpopulations
31 without inferring causality, the current analysis is appropriate: if a certain group has more
32 symptoms, the presence of those symptoms would be likely to introduce bias to a prediction model
33 for RA based on that data. Supplementary analysis A indicated that the baseline prevalence of
34 symptoms was similar across the ethnic groups.
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48 Additionally, it is possible that the dataset was not large enough to test the hypothesis in the
49 smallest groups (e.g., the smallest ethnic group, "Mixed"). Similarly, the five ethnic groups in the
50 CPRD data used within this study encompass vastly varied ethnic subpopulations. Further, through
51 relying on primary care OCRD, subpopulations less likely to be in contact with their general
52 practitioners are likely to have been underrepresented in the analysis, potentially introducing bias
53 from underrepresentation in this study. Frequency of presentation was not included as it was
54 deemed beyond the scope of this study but is relevant for future research. Finally, 14.7 % of the
55 initial sample did not have ethnicity recorded, which may have biased the results. Linking the dataset
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3 to hospital data (i.e. CPRD HES) may have alleviated this but this was not available within the
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5 timeframe of this analysis.
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7 8 Conclusion

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10 In this OCRD-based cross-sectional study, we have assessed the differences in symptoms recorded in
11 the 24 months preceding a diagnosis of RA in primary care in relation to ethnicity and socioeconomic
12 status (defined as IMD quintile). We found significant differences in symptoms coded across ethnic
13 groups, which must be considered in clinical practice in diverse populations as well as in data-based
14 prediction tools derived from OCRD to avoid algorithmic bias. Improved understanding of the
15 differences in symptomatology between groups may enable targeted efforts to reduce inequities in
16 treatment and outcomes of RA. Finally, this study provides guidance for future research into
17 demographic differences in RA symptoms, including the underlying causalities and the clinical
18 implications.
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12
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17 18 Declaration of interests

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20 The authors have declared no conflicts of interest.
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23 24 Data Availability

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26 The data underlying this article will be shared on reasonable request to the corresponding author.
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Tables

Table 1: Demographic characteristics of included and excluded cases

Demographic characteristics of included and excluded cases, and reasons for exclusion. The demographic characteristics of the excluded cases were largely similar to those of the included cases.

| <u>Total number of cases</u> | <u>N</u> | | <u>% of total</u> | |
|---------------------------------|--------------------|----------|--------------------|----------|
| Total n (pre-exclusion) | 83660 | | 100 % | |
| No ethnicity recorded | 12336 | | 14.7 % | |
| No IMD recorded | 1209 | | 1.4 % | |
| Excluded cases | 13545 | | 16.2 % | |
| Included cases | 70115 | | 83.8 % | |
| | | | | |
| <u>Characteristic</u> | <u>Included</u> | | <u>Excluded</u> | |
| Age (years) | mean 60.1, SD 14.8 | | mean 61.6, SD 17.0 | |
| | <u>n</u> | <u>%</u> | <u>n</u> | <u>%</u> |
| 18-30 | 2016 | 2.9 % | 651 | 4.8 % |
| 31-50 | 15842 | 22.6 % | 2798 | 20.7 % |
| 51-70 | 33137 | 47.3 % | 5216 | 38.5 % |
| >70 | 19120 | 27.3 % | 4882 | 36.0 % |
| | | | | |
| Sex | | | | |
| Female | 46563 | 66.4 % | 8828 | 65.2 % |
| | | | | |
| Ethnicity | | | (91.1 % missing*) | |
| White | 62215 | 88.7 % | 1054 | 87.2 % |
| Asian | 4892 | 7.0 % | 85 | 7.0 % |
| Black | 1965 | 2.8 % | 51 | 4.2 % |
| Mixed | 450 | 0.6 % | 7 | 0.6 % |
| Other | 593 | 0.9 % | 12 | 1.0 % |
| | | | | |
| IMD Quintile | | | (11.9 % missing*) | |
| IMD Quintile 5 (least deprived) | 13614 | 19.4 % | 1998 | 16.7 % |
| IMD Quintile 4 | 14412 | 20.6 % | 2264 | 19.0 % |
| IMD Quintile 3 | 13565 | 19.4 % | 2338 | 19.6 % |
| IMD Quintile 2 | 14063 | 20.1 % | 2632 | 22.1 % |
| IMD Quintile 1 (most deprived) | 14461 | 20.6 % | 2702 | 22.6 % |
| | | | | |
| Body Mass Index | mean 25.1, SD 4.1 | | mean 27.2, SD 6.0 | |
| Underweight (10-18.5) | 1221 | 1.7 % | 323 | 2.4 % |
| Normal (18.5-25) | 19931 | 28.4 % | 3914 | 28.9 % |
| Overweight (25-30) | 22948 | 32.7 % | 3714 | 27.4 % |
| Obese (30-40) | 17494 | 25.0 % | 2478 | 18.3 % |
| Morbidly obese (>40) | 2907 | 4.2 % | 373 | 2.8 % |
| (Missing data) | 5614 | 8.0 % | 2743 | 20.3 % |
| | | | | |
| Smoking status | | | | |
| Current | 18888 | 26.9 % | 3692 | 27.3 % |
| Ex-smoker | 28764 | 41.0 % | 4841 | 34.7 % |
| Never | 21171 | 30.2 % | 4173 | 30.8 % |
| (Missing data) | 1292 | 1.8 % | 839 | 6.2 % |

SD = Standard Deviation. IMD = Indices of Multiple Deprivation.

*Out of all of the excluded cases, 91.1 % had no data on ethnicity and 11.9 % had no data on IMD Quintile.

Table 2: List of included symptoms

The 21 symptoms studied and their prevalence in the 24 months preceding a diagnosis of rheumatoid arthritis. Selected from the 36 initial symptoms: Only those coded in >0.1 % of the cases were included.

| Symptom | n | % |
|---------------------------|--------------|---------------|
| Knee pain | 8178 | 11.7% |
| Shoulder pain | 7299 | 10.4% |
| Hand and finger pain | 7184 | 10.2% |
| Foot pain | 4617 | 6.6% |
| Wrist pain | 3988 | 5.7% |
| Joint swelling | 3847 | 5.5% |
| Fatigue | 3569 | 5.1% |
| Neck pain | 3357 | 4.8% |
| Hip pain | 2947 | 4.2% |
| Stress | 1907 | 2.7% |
| Ankle pain | 1629 | 2.3% |
| Hand and finger swelling | 1467 | 2.1% |
| Falls | 1124 | 1.6% |
| Unintended weight loss | 1085 | 1.5% |
| Knee swelling | 905 | 1.3% |
| Elbow pain | 734 | 1.0% |
| Unspecified muscle cramps | 705 | 1.0% |
| Morning stiffness | 632 | 0.9 % |
| Neck stiffness | 412 | 0.6% |
| Jaw pain | 263 | 0.4% |
| Night sweats | 229 | 0.3% |
| <i>Any of the above</i> | <i>34799</i> | <i>49.6 %</i> |

Table 3: Symptoms with significant differences in-between groups

Overview of symptoms where a statistically significant difference was found for ethnicity (compared to White, the largest group) and IMD quintile (compared to quintile 5, least deprived). Statistical significance for $p=0.0024$ ($p=0.05$ divided by the 21 different analyses) gives a confidence interval of 99.76 % for the individual analyses.

| Group | Symptom | OR | 99.76 % CI |
|---|------------------------|-----------|-------------------|
| Black | Unintended weight loss | 2.02 | 1.25-3.28 |
| | Ankle pain | 1.51 | 1.02-2.23 |
| | Shoulder pain | 1.44 | 1.25-1.66 |
| | Knee pain | 1.37 | 1.20-1.57 |
| South Asian | Muscle cramps | 1.71 | 1.14-2.57 |
| | Shoulder pain | 1.33 | 1.07-1.65 |
| | Knee pain | 1.29 | 1.06-1.58 |
| | Fatigue | 1.28 | 1.06-1.55 |
| | Neck pain | 1.28 | 1.04-1.57 |
| | Hand and finger pain | 1.16 | 1.00-1.35 |
| | Hip pain | 0.66 | 0.50-0.89 |
| Other ethnicity | Jaw pain | 3.30 | 1.02-10.73 |
| | Falls | 2.14 | 1.02-4.50 |
| IMD quintile 1 (most deprived) | Morning stiffness | 1.74 | 1.08-2.80 |
| | Falls | 1.37 | 1.03-1.82 |

OR = Odds Ratio. CI = Confidence Interval.

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real-world evidence¹⁻³



8
indications¹⁻³



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Real-world evidence shows a consistent safety profile 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 time⁶

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® (secukinumab) licensed indications in rheumatology: Cosentyx, alone or in combination with methotrexate, is indicated for the treatment of active **psoriatic arthritis** in adult patients 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; 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.^{1,2}

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

*Patients prescribed Cosentyx for any indication since launch.

[†]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; EAIR, exposure-adjusted incidence rate; HCP, healthcare professional; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; 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 February 2024]; **4.** Novartis Data on File. Secukinumab – Sec008. 2023; **5.** Novartis. Novartis Cosentyx® positive 16-week PREVENT results advance potential new indication for patients with axial spondyloarthritis. Available at: <https://www.novartis.com/news/media-releases/novartis-cosentyx-positive-16-week-prevent-results-advance-potential-new-indication-patients-axial-spondyloarthritis> [Accessed February 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.



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-TNF α 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

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-TNF α 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 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

child and benefit of Cosentyx therapy to the woman. **Fertility:** Effect on human fertility not evaluated. **Adverse Reactions:** *Very Common* ($\geq 1/10$): Upper respiratory tract infection. *Common* ($\geq 1/100$ to $< 1/10$): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon* ($\geq 1/1,000$ to $< 1/100$): Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare* ($\geq 1/10,000$ 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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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* ($\geq 1/10$): Upper respiratory tract infection. *Common* ($\geq 1/100$ to $< 1/10$): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon* ($\geq 1/1,000$ to $< 1/100$): Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare* ($\geq 1/10,000$ 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

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child and benefit of Cosentyx therapy to the woman. **Fertility:** Effect on human fertility not evaluated. **Adverse Reactions:** *Very Common* ($\geq 1/10$): Upper respiratory tract infection. *Common* ($\geq 1/100$ to $< 1/10$): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon* ($\geq 1/1,000$ to $< 1/100$): Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare* ($\geq 1/10,000$ 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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