Prognostic factors for colchicine prophylaxis-related adverse events when initiating allopurinol for gout: retrospective cohort study

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Abstract

Objectives: Colchicine is commonly used to prevent flares when starting urate-lowering therapy for gout. Patients with gout are frequently concurrently prescribed other medications (such as statins) that may interact with colchicine, increasing the risk of adverse events. The aim of this study was to describe potential prognostic factors for adverse events in patients prescribed colchicine when initiating allopurinol.

Methods: We conducted a retrospective cohort study in linked UK Clinical Practice Research Datalink and Hospital Episode Statistics datasets. Adults initiating allopurinol for gout with colchicine (01/04/1997 to 30/11/2016) were included. Potential prognostic factors were defined, and the likelihood of adverse events, including diarrhoea, nausea or vomiting, myocardial infarction (MI), neuropathy, myalgia, myopathy, rhabdomyolysis, and bone marrow suppression, were estimated.

Results: From 01/04/1997 to 30/11/2016, 13,945 people with gout initiated allopurinol with colchicine prophylaxis (mean age 63.9 (SD 14.7) years, 78.2% male). One quarter (26%, 95% CI 25% to 27%) were prescribed ≥1 potentially interacting medicines, most commonly statins (21%, 95% CI 20% to 22%). Statins were not associated with increased adverse events, although other drugs were associated with some adverse outcomes. Diarrhoea and MI were associated with more comorbidities and more severe CKD.

Conclusion: People were given colchicine prophylaxis despite commonly having preexisting prescriptions for medications with potential to interact with colchicine. Adverse events were more common in people who had more comorbidities and certain potentially interacting medications. Our findings will provide much-needed information about prognostic factors for colchicine-related adverse events that can inform treatment decisions about prophylaxis when initiating allopurinol.

Keywords: Gout, Colchicine prophylaxis, Adverse events, Urate-lowering therapy, Prognostic factors

Rheumatology key messages

- Colchicine prophylaxis was commonly prescribed in people already taking medications with potential to interact with colchicine.
- Gastrointestinal adverse events were more common in females, older people, and those taking amiodarone and with more comorbidities.
- Overall statin use was not associated with adverse events.

Introduction

Gout is caused by high serum urate levels leading to the formation of monosodium urate (MSU) crystals in and around joints. It is the most prevalent inflammatory arthritis and affects 2.5% of adults in the UK and 3.9% in the USA [1,2]. Gout is characterised by recurrent flares of excruciating joint pain and inflammation, and is associated with substantial comorbidity and impaired health-related quality of life [3,4]. Urate-lowering therapy (ULT) for gout leads to gradual dissolution of MSU crystals and cessation of flares over several months [5-8]. However, initiating or escalating the dose of ULT often precipitates a gout flare, which may lead patients or practitioners to stop ULT, as they believe that it has exacerbated the gout [9]. Anti-inflammatory prophylaxis to prevent such flares, most commonly with colchicine, is therefore recommended for several months when initiating ULT [5-8].

Diarrhoea, nausea and vomiting are common side-effects of colchicine, but rarely, it can cause more serious side-effects such as myopathy, rhabdomyolysis, neuropathy or bone marrow suppression. We recently reported a cohort study which determined the risk of adverse events severe enough to warrant seeking healthcare associated with colchicine prophylaxis when initiating allopurinol in patients with gout in UK primary care [10]. We found that adverse events affected 1 in 15 people taking colchicine. However, serious adverse events were rare.

The risk of side-effects due to colchicine prophylaxis is thought to be influenced by patient characteristics. For example, the risk of serious events including neuromyopathy, rhabdomyolysis and bone marrow suppression, is higher in people with chronic kidney disease (CKD) [11], which affects one in four people with gout [12], and in people taking certain medications. Through its metabolism by CYP3A4, colchicine toxicity is theoretically increased by concomitant treatment with common drugs such as statins, fibrates, macrolide antibiotics, rate-limiting calcium-channel blockers (verapamil, diltiazem), digoxin, amiodarone, and antifungals, as well as protease inhibitors and cyclosporine [13]. Although colchicine is contraindicated in patients taking these medications, in our clinical experience from primary and secondary care, their co-prescription still commonly occurs. However, evidence that these factors are prognostic for adverse events is largely anecdotal or theoretical, and large research studies are lacking [14,15].

In this study, we aimed to assess to what degree co-prescriptions and other potential prognostic factors for adverse events, including age, gender, body mass index, chronic kidney

disease and multimorbidity, affect the risk of adverse events when commencing colchicine prophylaxis for ULT in people with gout.

Methods

Data source

We used data from the Clinical Practice Research Datalink (CPRD, December 2019) GOLD and Aurum datasets, which have more than 3 and 13 million patients, respectively, currently registered and research acceptable. CPRD contains electronic, coded information collected during the course of routine primary healthcare, is representative of the UK population in terms of age, sex and ethnicity, and has been used extensively for primary care research [16-17]. We used the primary care data linked to the Hospital Episode Statistics (HES) Admitted Patient Care dataset, which has coverage from April 1997 to the present. The study was approved by CPRD's in-house Independent Scientific Advisory Committee (ISAC) (protocol number: 19_233).

Study Design and participants

Retrospective cohort studies were assembled in GOLD and Aurum separately. Each consisted of people aged 18 years and over with a clinical code for gout between 01/04/1997 and 30/11/2016 (to allow HES linkage at the time of data access) who received a prescription for colchicine and on the same date received a prescription for allopurinol and did not receive a prescription for NSAID or glucocorticoids in the preceding month. The positive predictive value of a diagnosis of gout in CPRD has been shown to be 90% [18]. The definition of ULT was restricted to allopurinol since this is by far the most commonly prescribed ULT in UK primary care, accounting for 99% of first ULT prescriptions [19-20].

The index date (i.e. start of time at risk) was the date of the concomitant first time prescriptions for allopurinol and colchicine following the diagnostic code for gout. Everyone was followed up for 6 months or until the end of colchicine treatment, whichever was sooner. The end of treatment was defined as 56 days after the last colchicine prescription.

Adverse outcomes

We defined incident adverse events using clinical codes (Read/SNOMED in primary care; ICD in secondary care) during the period of colchicine treatment. Events of interest were diarrhoea, nausea or vomiting, myocardial infarction (MI), neuropathy, myalgia, myopathy, rhabdomyolysis, and bone marrow suppression. Each adverse event was analysed separately. Patients were excluded from the analysis if they had a Read/SNOMED/ICD code for the

outcome in question in the three months preceding the index date. Consistent with the accepted practice for large database research, we assumed that the absence of a recorded adverse event meant that the patient did not consult for that condition or that if they did, the clinician did not think it was of sufficient relevance to record in the coded data. Code lists for all outcomes, exposures and covariates were compiled by a GP and a rheumatologist and are available at https://researchdata.keele.ac.uk/67/.

Potentially interacting prescriptions

Prescriptions for medications that could potentially interact with colchicine (statins, fibrates, verapamil, diltiazem, digoxin, amiodarone, oral ketoconazole, and macrolide antibiotics) in the 30 days before the index date were considered potentially interacting prescriptions.

Potential prognostic factors

We considered the following patient factors that might be associated with the rate of adverse outcomes: age in quartiles, sex, Charlson comorbidity index (scored 0, 1, 2, 3, 4+) [21], body mass index (BMI, categorised as normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (≥30 kg/m^2)), CKD category (1-2 (eGFR ≥60 mL/min), 3 (eGFR 30-59 mL/min), 4-5 (eGFR <30 mL/min) defined by diagnostic codes or a record for eGFR<60 mL/min), and potentially interacting prescriptions (defined above). All were defined before the index date.

Statistical analysis

The proportion (95% confidence interval [CI]) of people receiving one or more and two or more potentially interacting prescription in the period 30 days before the index date was calculated, as was the proportion receiving colchicine in the presence of each named potentially interacting drug separately. These analyses were repeated stratified by age (analysed in quartiles), sex, quartiles of total number of consultations (defined as unique dates with face-to-face contact with the practice) and number of comorbidities (Charlson index [21] categorised 0,1,2,3, ≥4).

We quantified the absolute risk of adverse events for each level of a potential prognostic factor in terms of events per 10,000 person-years with accompanying 95% CIs. We fitted age- and sex-adjusted Cox proportional hazards regression models to examine the association between potential risk factors and adverse events. The assumption of proportional hazards was tested graphically using Schoenfeld residuals for each factor. If necessary, an interaction of the

prognostic factor with time was estimated. Results were presented as hazard ratios with 95% CIs. Statistical analyses were conducted using Stata version 16.1 (StataCorp LLC, College Station, Texas, USA). GOLD and Aurum datasets were analysed separately and combined in a two-stage individual patient data (IPD) meta-analysis. Fixed effects models with an inverse variance approach were used to pool estimates, as clinical and methodological homogeneity was expected between datasets. Meta-analysed results are presented in the manuscript, with results for GOLD and Aurum separately available in the supplementary materials (Supplementary Tables S1 to S3).

Sensitivity analysis

In the main analyses, a missing category approach was used for BMI, as BMI data are unlikely to be missing at random (e.g. BMI is less likely to be recorded in an individual of a healthy weight). In a sensitivity analysis, we generated ten imputed data sets using multiple imputation through chained equations, and the results were compared with non-imputed data. We also examined adverse events associated with individual statins (simvastatin and atorvastatin as others were small in numbers).

Results

There were 13,945 people with gout in the two databases (2,439 in CPRD GOLD and 11,506 in Aurum) (Table 1). Their mean age was 63.9 (SD 14.7) years, and more than two-thirds (78.2%) were male. Background characteristics were fairly similar between both databases. The median time from colchicine initiation to adverse event varied from 21 days (IQR 21 to 35) for bone marrow suppression to 61 days (IQR 38 to 92) for myalgia in CPRD GOLD, and from 63 days (IQR 28 to 84) for diarrhoea to 70 days (IQR 53 to 98) for myalgia in CPRD Aurum (Supplementary Table 4).

Prescription of potentially interacting drugs

Proportions of people with potentially interacting prescriptions issued in the 30-day period prior to the index date are presented in Table 2. One quarter (0.26, 95% CI 0.25 to 0.27) of people were prescribed one or more potentially adverse prescriptions. Statins were the most common prescription (0.21, 95% CI 0.20 to 0.22), followed by digoxin (0.05, 95% CI 0.05 to 0.05), diltiazem (0.02, 95% CI 0.02 to 0.02), and macrolide antibiotics (0.01, 95% CI 0.01 to 0.01). Of 2943 people prescribed a statin, 1677 (57.0%) were prescribed simvastatin, 972 (33.0%) atorvastatin, 180 (6.1%) pravastatin, 105 (3.5%) rosuvastatin, and 14 (0.4%) fluvastatin. Older age (>75 years), female sex, frequently (≥10) consulting in the last year, and

Charlson comorbidity index ≥4, were associated with potentially interacting prescriptions (Supplementary Tables S5-S8).

The highest rates (per 10,000 person-years) of adverse event reporting were seen for diarrhoea with the prescriptions of fibrates (4322.8, 95% CI 2161.8 to 8644.0), myalgia with prescriptions of verapamil (2873.7, 95% CI 404.8, 20000.0), and diarrhoea with macrolide antibiotics (2855.3, 95% CI 1361.2, 5989.3) (Table 3). There was no overall significantly increased risk of any of the adverse outcomes with the prescription of statins or digoxin (Table 4). The additional sensitivity analysis by individual statins revealed no association of either atorvastatin or simvastatin with any adverse outcome except for atorvastatin with MI (HR 2.21, 95% CI 1.14, 4.27) (Supplementary Table S9). However, adverse outcomes could have some potential interaction with medicines, but no obvious patterns of increased risk were observed, and confidence intervals were often very wide.

Patient-related prognostic factors

Further, the incidence of diarrhoea, nausea and vomiting were generally higher with older age and in females (Table 3). Rates of MI were also higher at older ages. Less clear patterns with age were seen with other adverse outcomes. After adjusting for age and sex, the only significant associations between patient-related prognostic factors and adverse outcomes were Charlson comorbidity index 2 (HR 1.97, 95% CI 1.25, 3.09) and ≥4 (HR 2.70, 95% CI 1.77, 4.11) for diarrhoea; Charlson comorbidity index ≥4 (HR 4.01, 95% CI 1.18, 13.59) for MI (all compared to Charlson index of 0) and CKD stage 4-5 (HR 3.47, 95% CI 1.60, 7.50) compared to stage 1-2 (Table 4). BMI category was not associated with any adverse outcomes in either main or sensitivity analysis (Supplementary Table S10). Myopathy and rhabdomyolysis outcomes were not analysed as there were too few incident occurrences of these outcomes.

Discussion

This is the first large observational study to investigate prognostic factors for adverse events related to colchicine prophylaxis when initiating allopurinol for gout. Using UK primary care data linked to hospital admission records, we were able to capture rare but potentially serious side-effects. We found that females were more likely to develop diarrhoea and nausea/vomiting. Older age was linked to a greater risk of diarrhoea, nausea and vomiting, and myocardial infarction. A quarter of people with gout taking colchicine prophylaxis were already prescribed a medication with the potential to interact with colchicine. In the majority

of cases, this was a statin (mainly simvastatin or atorvastatin). Whilst there were some associations of medicines and some adverse outcomes, there were no associations between statins and any adverse outcomes except for atorvastatin with MI. Significant increases in the risk of diarrhoea were seen with amiodarone, fibrates and macrolide antibiotics, neuropathy with diltiazem, bone marrow suppression with fibrates and ketoconazole, myalgia with amiodarone, fibrates and verapamil, and MI with diltiazem and macrolides. A higher comorbidity index was associated with a significantly increased risk of diarrhoea and MI. CKD was significantly associated with an increased risk of MI.

Previous studies have demonstrated the clinical and cost-effectiveness of colchicine prophylaxis when initiating ULT [22-23]. The risk of adverse events, such as diarrhoea, bone marrow suppression, vomiting or myopathy, from concomitant prescription of colchicine with other medications, including macrolide antibiotics and statins has been highlighted [24-28]. Until now, these observations have been based on case reports, case series, reviews of adverse event reporting systems, or adverse event reporting in individual clinical trials.

We found that concomitant prescriptions of some of these medications are associated with an increased risk of some outcomes, but with no consistent pattern to this association. For example, in our study, fibrates were associated with an increased risk of diarrhoea, bone marrow suppression, myalgia and MI. Anecdotally, the potential interaction of colchicine best recognised by clinicians is that with statins. However, we found no statistically significant increase in adverse events in patients prescribed statins (except for atorvastatin with MI). Statins are used more frequently than fibrates to reduce cholesterol levels and cardiovascular risk. Macrolides are most commonly prescribed as short courses of a few days and hence arguably it would have been more appropriate to ascertain only macrolide prescriptions closer in time to colchicine initiation than the 30-day window employed. However, numbers of macrolide prescriptions in the 10 days preceding colchicine initiation were very small (7 in CPRD GOLD and 36 in Aurum for 1-10 days, 6 in CPRD GOLD and 38 in Aurum for 11-20 days, and 19 in CPRD GOLD and 42 in Aurum for 21-30 days).

Several large RCTs have shown cardiovascular benefits of colchicine in people with coronary heart disease or post-MI [24,25,29,30]. In these studies, the dose of colchicine used was 0.5mg daily, which is consistent with that recommended for prophylaxis in gout management guidelines and commonly used in clinical practice [5,6]. In our study, the risk of MI when commencing colchicine was significantly higher in patients with a history of severe CKD (stage 4 or above), a greater burden of comorbidity, or concomitant prescription of macrolide antibiotics or diltiazem. The increased risk observed in patients with severe CKD is

likely to be due to CKD being both a cardiovascular risk factor and associated with traditional cardiovascular risk factors. However, colchicine is relatively contraindicated in people with severe CKD and should be prescribed with caution and at lower doses in that patient group. Furthermore, it is reassuring that no statistically significant increase in MI was seen in those patients with CKD stage 3. It is likely that patients prescribed diltiazem receive it due to underlying hypertension or cardiovascular disease, likely explaining the association seen between its co-prescription with colchicine and risk of MI. However, the increased risk of MI in patients prescribed macrolide antibiotics cannot be explained by these mechanisms, and this has not been observed in previous studies.

Females experienced higher incidence of diarrhoea and nausea/vomiting. The reason for this is not known but it could arise from sex differences in consulting behaviour, symptom reporting, pharmacogenetics, or females with gout being older than males. We didn't calculate the risk associated with age and sex as it was a type 2 prognostic study and we decided *a priori* to consider age and sex independent prognostic factors.

The main strengths of our study are the large sample size and the ability to investigate the use of different medicines in clinical practice. Linking primary care consultation and prescription data to hospital records over a period of 20 years allowed us to derive a comprehensive, high-quality dataset. Several limitations are worthy of acknowledgement. First, gout was ascertained according to a clinical diagnosis in primary care rather than classification criteria or synovial fluid microscopy following joint aspiration. However, a coded gout diagnosis in CPRD has a positive predictive value of 90% [18] and these patients were being managed by their GP as though they did have gout, through the prescription of allopurinol. Second, the use of CPRD/HES data permitted us to consider only adverse events severe enough to warrant consultation or result in hospitalisation and hence, milder adverse events, such as gastrointestinal symptoms may have been missed. The COLCHICORT trial [31] suggested that co-treatment with a statin could increase the occurrence of mild diarrhoea in people with acute calcium pyrophosphate crystal arthritis. Third, despite the size of our sample and linkage to hospital admissions data, coded occurrences of myopathy and rhabdomyolysis remained rare. This rarity was compounded when stratifying the data, particularly when considering rarely prescribed medications such as oral ketoconazole. Although it was important to interrogate the data and include this medication, there were insufficient numbers of patients even in this large observational cohort to provide clear answers around its risk profile. Fourth, we aimed to study drugs that are commonly prescribed in primary care and did not have access to secondary care prescription data, meaning we were

unable to study certain specialist drugs such as targeted anti-cancer therapies and anti-retrovirals. Fifth, analysable data on colchicine dosage were not available as it is most commonly recorded as 'as directed' and therefore, no dose-related analyses could be performed. A further caveat is a consequence of the desire of this study to look at a range of medications and outcomes leading to a risk of type I statistical errors due to multiple testing. However, the aim of this study was to provide an overview of the risk of different potential prognostic factors when prescribing colchicine to people with gout rather than to prove causation.

Conclusion

We found that people were given colchicine prophylaxis despite commonly having preexisting prescriptions for medications with potential to interact with colchicine. Adverse events were more common in people who were older, had more comorbidities and were prescribed certain potentially interacting medications. Reassuringly, the rate of serious adverse events was low, providing reassurance for people with gout and for clinicians. We also found no evidence that the prescription of statins significantly increased the risk of adverse events except atorvastatin being associated with MI.

Future research is needed to determine which patients are at greatest risk of adverse events from prophylaxis and whether the cardiovascular benefits of colchicine reported in RCTs of people at high risk of cardiovascular events because of a prior history of coronary heart disease also apply to people with gout. Our findings will provide much-needed information about the safety of flare prophylaxis that can inform treatment decisions when initiating allopurinol, directly benefitting people with gout and their clinicians.

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Conflicts of interests

The authors declare no conflicts of interest.

Data availability statement

Data may be obtained from a third party and are not publicly available. The data were obtained from the Clinical Practice Research Datalink (CPRD). CPRD data governance does not allow us to distribute patient data to other parties. Researchers may apply for data access at http://www.CPRD.com.

Author contribution

All authors contributed to interpretation of data, writing and review of the manuscript, and approval of the final version. E.R., C.D.M., and S.M. conceived the study. E.R., R.B., H.F., R.P., C.D.M., L.C., R.W., and S.M. designed the study. R.B., R.P., and S.M. acquired and analysed data. E.R., R.B., R.P., and S.M. co-wrote the first draft of the manuscript. N.P. and all authors critically revised the manuscript. E.R. is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Table 1: Background characteristics of included patients in analysis

Sample characteristics	Combined (%)	CPRD GOLD (%)	CPRD Aurum (%)
Total	**13945**	**2439**	**11506**
Mean age at index date (SD)	63.9 (14.7)	63.98 (14.6)	63.73 (14.9)
Age quartiles (years)			
Q1 (19-53)	3670 (26.3)	626 (25.7)	3044 (26.5)
Q2 (54-65)	3447 (24.7)	606 (24.8)	2841 (24.7)
Q3 (66-75)	3367 (24.1)	581 (23.8)	2786 24.2)
Q4 (>75)	3461 (24.8)	626 (24.7)	2835 (24.6)
Sex			
Female	3040 (21.8)	545 (22.3)	2495 (21.7)
Male	10905 (78.2)	1894 (77.7)	9011 (78.3)
BMI			
Normal (18.5–24.9 kg/m^2)	1958 (14.0)	342 (14.0)	1616 (14.0)
Overweight (25–29.9 kg/m^2)	4907 (35.2)	904 (37.1)	4003 (34.8)
Obese (≥30 kg/m^2)	5601 (40.2)	1018 (41.7)	4583 (39.8)
Missing	1479 (10.6)	175 (7.2)	1304 (11.4)
CKD stage			
1-2 (eGFR ≥60 mL/min)	10154 (72.8)	1701 (69.9)	8453 (73.5)
3 (eGFR 30-45 mL/min)	3179 (22.8)	627 (25.7)	2552 (22.2)
4-5 (eGFR <30 mL/min)	609 (4.4)	108 (4.4)	501 (4.3)
Number of consultations quartiles			
Q1 (0-3)	3312 (23.8)	523 (21.5)	2789 (24.2)
Q2 (4-5)	3430 (24.6)	561 (23.0)	2869 (24.9)
Q3 (6-9)	3538 (25.4)	608 (24.9)	2930 (25.5)
Q4 (≥10)	3665 (26.3)	747 (30.6)	2918 (25.4)
Charlson comorbidity score			
0	4425 (31.7)	750 (30.8)	3675 (31.9)
1	2403 (17.2)	445 (18.2)	1958 (17.0)
2	2324 (16.7)	401 (16.4)	1923 (16.7)
3	1685 (12.1)	293 (12.0)	1392 (12.1)
≥4	3108 (22.3)	550 (22.6)	2558 (22.2)

CPRD: Clinical Practice Research Datalink; SD: standard deviation; BMI body mass index; CKD: chronic kidney disease.

Table 2: Proportion of people prescribed colchicine who were also prescribed a potentially interacting medication in the 30-day period prior to the index date by combining CPRD GOLD and Aurum data using two-stage IPD meta-analysis

Frequency and prescriptions of drugs (N = 13945)	Total	Proportion (95% CI)
No. of drugs		
≥1	3625	0.26 (0.253, 0.267)
≥2	590	0.042 (0.039, 0.046)
Specific drugs		
Statins	2943	0.211 (0.204, 0.218)
Fibrates	78	0.006 (0.004, 0.007)
Verapamil	65	0.005 (0.004, 0.006)
Diltiazem	239	0.017 (0.015, 0.019)
Digoxin	697	0.050 (0.046, 0.054)
Amiodarone	93	0.007 (0.005, 0.008)
Oral ketoconazole	21	0.001 (0.001, 0.002)
Macrolide antibiotics	136	0.010 (0.008, 0.011)

CPRD: Clinical Practice Research Datalink; CI: confidence interval; IPD: individual participant data.

Table 3: Incidence rates of adverse outcomes (per 10,000 person years) by patient characteristics and potentially interacting prescriptions by combining CPRD GOLD and Aurum data using two-stage IPD meta-analysis

Covariates	Diarrhoea	Nausea/vomiting	Neuropathy	Bone marrow suppression	Myalgia	Myocardial infarction
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
Age quartiles (years)						
Q1 (19-53)	336.1 (235.0, 480.6)	84.5 (40.3, 177.2)	88.8 (12.5, 630.7)	48.2 (18.1, 128.4)	37.2 (12.0, 115.5)	64.4 (28.9, 143.3)
Q2 (54-65)	575.1 (428.0, 772.8)	176.2 (107.9, 287.6)	84.8 (11.9, 602.1)	45.8 (17.2, 121.9)	239.6 (119.8, 479.1)	195.4 (119.7, 318.9)
Q3 (66-75)	820.4 (639.7, 1052.3)	144.3 (83.8, 248.4)	323.5 (121.4, 862.0)	38.4 (12.4, 119)	128.6 (64.3, 257.1)	169.5 (102.2, 281.2)
Q4 (>75)	1492.5 (1250.7, 1780.9)	452.1 (330.4, 618.8)	92.3 (13, 655.1)	97.7 (48.8, 195.3)	88.3 (42.1, 185.3)	397.1 (283.8, 555.8)
Sex						
Male	600.7 (514.0, 702.1)	128.9 (93.4, 178.0)	164.9 (74.1, 367.0)	56.5 (34.6, 92.2)	115.8 (74.7, 179.5)	200.2 (154.4, 259.5)
Female	1467.4 (1207.4, 1783.4)	502.3 (365.5, 690.3)	101.5 (14.3, 720.8)	45.1 (14.6, 139.9)	90.2 (40.5, 200.9)	189.1 (112, 319.3)
Charlson comorbidity index						
0	377.3 (270.9, 525.5)	104.3 (57.8, 188.4)	144.4 (36.1, 577.5)	19.8 (5.0, 79.3)	141.7 (70.9, 283.3)	147.5 (61.4, 354.3)
1	487.3 (334.2, 710.6)	111.1 (53.0, 233.1)	116.1 (16.4, 824.0)	73.4 (27.6, 195.7)	99.6 (32.1, 308.9)	143.9 (74.9, 276.6)
2	896.4 (681.2, 1179.5)	218.1 (126.7, 375.7)	135.7 (19.1, 963.6)	18.8 (2.7, 133.8)	127.5 (60.8, 267.5)	85.2 (35.5, 204.8)
3	689.4 (479.1, 992.1)	206.2 (103.1, 412.4)	--	142.3 (59.3, 342)	135.8 (51.0, 361.8)	231.5 (120.4, 444.8)
4+	1573.5 (1312.7, 1886.1)	447.3 (322.7, 620.1)	277 (89.3, 858.9)	86.4 (41.2, 181.3)	72.4 (27.2, 193)	537.2 (398.4, 724.3)
BMI						
Normal (18.5–24.9 kg/m^2)	962.2 (720.7, 1284.6)	291.6 (172.7, 492.3)	--	86.2 (32.4, 229.3)	60.9 (15.2, 243.4)	210.1 (113.0, 390.4)
Overweight (25–29.9 kg/m^2)	790.5 (642.9, 971.9)	227.9 (158.4, 328.0)	175.7 (56.7, 544.9)	39.8 (16.6, 95.7)	80.3 (41.8, 154.3)	214.8 (147.3, 313.2)
Obese (≥30 kg/m^2)	749.5 (616.7, 911.0)	163.2 (109.4, 243.5)	203.1 (76.2, 541.1)	61.2 (31.9, 117.7)	165.3 (96.0, 284.8)	218.6 (154.6, 309.1)
Missing	710.2 (467.6, 1078.6)	203.7 (101.9, 407.3)	--	27.3 (3.8, 193.6)	92.8 (23.2, 371)	54.6 (13.7, 218.3)
CKD stage						
1-2 (eGFR ≥60 mL/min)	626 (532.5, 735.8)	162 (120.1, 218.4)	122.9 (46.1, 327.3)	49.3 (28.6, 85)	126.4 (82.4, 193.8)	134.5 (96.1, 188.3)
3 (eGFR 30-45 mL/min)	1189.3 (970.5, 1457.3)	311.2 (210.3, 460.5)	254.8 (82.2, 789.9)	81.8 (36.7, 182)	73.9 (30.8, 177.7)	344.9 (238.1, 499.5)
4-5 (eGFR <30 mL/min)	1355.7 (864.7, 2125.4)	460.8 (219.7, 966.5)	--	--	--	598.4 (311.4, 1150.2)
Adverse prescriptions						
Amiodarone	2134.7 (801.2, 5687.8)	536 (75.5, 3804.7)	--	--	2225.8 (313.5, 16000.0)	--
Digoxin	1437.6 (971.4, 2127.5)	466.8 (222.6, 979.2)	343 (48.3, 2434.9)	343 (48.3, 2434.9)	345 (48.6, 2448.9)	66.7 (9.4, 473.6)
Diltiazem	1127.8 (506.7, 2510.4)	536.6 (173, 1663.6)	1323.8 (186.5, 9398.1)	--	--	830 (345.5, 1994).0
Fibrates	4322.8 (2161.8, 8644)	--	--	576.5 (81.2, 4092.4)	572 (80.6, 4061)	588.7 (82.9, 4179.5)
Macrolide antibiotics	2855.3 (1361.2, 5989.3)	729.2 (182.4, 2915.6)	--	--	--	1293.7 (485.6, 3447.0)
Oral ketoconazole	--	--	--	1730.2 (246.6, 12000)	--	--

Statins	1034.8 (821.4, 1303.7)	341.7 (232.7, 501.9)	196 (49.0, 783.9)	81.3 (33.8, 195.4)	280 (140.0, 559.9)	305.7 (203.1, 460)
Verapamil	1535.7 (384.1, 6140.5)	--	--	--	2873.7 (404.8, 20000.0)	--

CPRD: Clinical Practice Research Datalink; -- not enough events to calculate estimates; CI: confidence interval; IPD: individual participant data.

Table 4: Association of prognostic factors with adverse outcomes, over and above effect of age and sex by combining CPRD GOLD and Aurum data using two-stage IPD meta-analysis

Covariates	Diarrhoea	Nausea/vomiting	Neuropathy	Bone marrow suppression	Myalgia	Myocardial infarction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Charlson index						
0	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
1	1.15 (0.69, 1.91)	0.9 (0.34, 2.37)	0.75 (0.07, 8.39)	3.76 (0.68, 20.87)	0.56 (0.15, 2.15)	2.35 (0.52, 10.69)
2	1.97 (1.25, 3.09)	1.34 (0.57, 3.18)	0.93 (0.08, 10.9)	1 (0.09, 11.47)	1.33 (0.43, 4.08)	1.49 (0.31, 7.2)
3	1.32 (0.79, 2.23)	1.32 (0.47, 3.68)	--	4.15 (0.63, 27.46)	0.99 (0.27, 3.61)	16.46 (2.03, 133.76)
4+	2.7 (1.77, 4.11)	1.94 (0.91, 4.14)	1.59 (0.2, 12.9)	4.67 (0.79, 27.74)	0.48 (0.13, 1.78)	4.01 (1.18, 13.59)
BMI						
Normal (18.5–24.9 kg/m^2)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Overweight (25–29.9 kg/m^2)	0.87 (0.61, 1.25)	1 (0.53, 1.91)	--	0.52 (0.12, 2.35)	1.74 (0.37, 8.2)	1.2 (0.58, 2.49)
Obese (≥30 kg/m^2)	0.86 (0.61, 1.23)	0.7 (0.36, 1.37)	1.25 (0.27, 5.72)	0.96 (0.25, 3.7)	2.27 (0.5, 10.2)	1.49 (0.72, 3.08)
Missing	0.86 (0.51, 1.43)	0.97 (0.4, 2.33)	--	0.43 (0.04, 4.19)	1.76 (0.25, 12.63)	0.44 (0.09, 2.09)
CKD stage						
1-2 (eGFR ≥60 mL/min)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
3 (eGFR 30-45 mL/min)	1.21 (0.91, 1.61)	0.97 (0.57, 1.65)	2.07 (0.39, 11.13)	0.9 (0.26, 3.08)	0.54 (0.19, 1.53)	1.68 (0.97, 2.92)
4-5 (eGFR <30 mL/min)	1.39 (0.85, 2.28)	1.41 (0.62, 3.22)	--	--	--	3.47 (1.6, 7.5)
Interacting prescriptions						
Amiodarone	3.16 (1.17, 8.54)	2.4 (0.33, 17.35)	--	--	8.27 (1.03, 66.2)	--
Digoxin	1.3 (0.85, 1.97)	1.41 (0.64, 3.13)	2.29 (0.25, 21.11)	--	1.28 (0.16, 10.5)	0.21 (0.03, 1.55)
Diltiazem	1.13 (0.5, 2.53)	2.13 (0.67, 6.8)	8.7 (1.03, 73.38)	--	--	3.8 (1.53, 9.45)
Fibrates	4.58 (2.26, 9.28)	--	--	11.78 (1.55, 89.64)	13.1 (1.7, 101.15)	2.78 (0.39, 20.07)
Macrolide antibiotics	2.4 (1.13, 5.13)	2.35 (0.57, 9.65)	--	--	--	5.37 (1.94, 14.88)
Oral ketoconazole	--	--	--	37.37 (4.91, 284.65)	--	--
Statins	1.1 (0.84, 1.45)	1.49 (0.92, 2.41)	1.27 (0.23, 6.91)	0.78 (0.22, 2.8)	1.77 (0.7, 4.48)	1.35 (0.82, 2.23)
Verapamil	1.05 (0.26, 4.23)	--	--	--	10.88 (1.37, 86.45)	--

CPRD: Clinical Practice Research Datalink; Each model was adjusted for age and gender for a given exposure; -- not enough events to calculate estimates; HR hazard ratio; CI confidence interval; Ref reference category; IPD: individual participant data.

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

Cosentyx® secukinumab

1,000,000 patients treated globally, and counting*[4]

100+ clinical trials*[5]

8+ years of real-world evidence[1–3]

8 indications[1–3]

Click here to visit our HCP portal and learn more

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 time[6]

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

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

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

Cosentyx® (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; EIAR, 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.

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UK | February 2024 | 407722

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

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

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

UK | 284832 | May 2023

Adverse Event Reporting:

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

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

Cosentyx® (secukinumab) Great Britain Prescribing Information.

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

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

UK | 290802 | June 2023

Adverse Event Reporting:

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

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