The association between drugs and vaccines commonly prescribed to older people and bullous pemphigoid: a case-control study

Running head: Association between drugs for older people and bullous pemphigoid

Mikolaj Swiderski,[1] Yana Vinogradova,[1] Roger D. Knaggs,[2] Karen Harman,[3] Rowan H. Harwood,[4] Vibhore Prasad,[1,5,6] Monica S.M. Persson,[7] Grazziela Figueredo,[8] Carron Layfield[1] and Sonia Gran[1]

[1]School of Medicine, University of Nottingham, Nottingham, UK
[2]School of Pharmacy, University of Nottingham, Nottingham, UK
[3]Department of Dermatology, University Hospitals of Leicester NHS Trust, Leicester, UK
[4]School of Health Sciences, University of Nottingham, Nottingham, UK
[5]King's College London, London, UK
[6]NHS Nottinghamshire, Nottingham, UK
[7]Swedish Rheumatism Association, Sweden
[8]School of Computer Science, University of Nottingham, Nottingham, UK

Corresponding author: Dr Sonia Gran
Email: sonia.gran@nottingham.ac.uk

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Data availability: CPRD provided the data supporting this study's findings under a licence that does not permit sharing. The data is available by applying to CPRD directly via www.cprd.com.

Ethics statement: This study does not raise any ethical issues. Data in the CPRD are anonymised and provided to the researchers by the Medicines and Healthcare Regulatory Authority after external peer review and approval by their Independent Scientific Advisory Committee.

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What's already known about this topic?

- Bullous pemphigoid (BP) is predominantly a disease of older people.
- Numerous drugs have been reported to be associated with BP. However, the majority of previous findings are from case series or small hospital-based studies.

What does this study add?

- Reliable and precise estimates of the association between BP and several therapeutic groups, drug classes, subclasses, and substances based on a large UK population-based study of over 16,800 people with BP.
- The need to raise awareness among healthcare professionals of increased BP risk following the use of certain drugs such as: penicillins, penicillinase-resistant penicillins (flucloxacillin), gliptins, second-generation antipsychotics (olanzapine).

Abstract

Background: Bullous pemphigoid (BP) is an autoimmune skin disease that affects mainly older people. Numerous drugs have been previously associated with BP based on case series and small hospital-based studies. More reliable and precise estimates of associations between a broad selection of drugs/vaccines and BP will enable greater awareness of potential increased risk of BP following certain medicines and help identify clinical, histological and genomic characteristics of drug-induced BP for different types of culprit drugs. Greater awareness could lead to earlier recognition or suspicion of BP and referral to a dermatologist for diagnosis. Earlier diagnosis may lead to less aggressive treatment and improved well-being.

Objectives: To determine the association between drugs/vaccines commonly prescribed to older people and BP risk.

Methods: We conducted a population-based nested case-control study between 1998-2021 using electronic primary care records from the Clinical Practice Research Datalink. We matched BP cases with up to 5 controls. Exposures were drugs/vaccines commonly prescribed to older people. We used multivariable conditional logistic regression adjusting for multiple drug use. For antibiotics, we considered prescriptions may be prescribed for undiagnosed symptoms of BP which resemble skin infection (protopathic bias) in a sensitivity analysis.

Results: Antibiotics were the therapeutic group associated with the highest risk of BP (OR: 4.60; 95%CI 4.40-4.80). However, after adjusting for protopathic bias, the OR reduced to 2.08 (95%CI 1.99-2.17). After adjusting for protopathic bias, of all antibiotic classes and subclasses, penicillins and penicillinase-resistant penicillins had the strongest associations with BP risk (OR: 3.44; 95%CI 3.29-3.60; sensitivity analysis OR; 1.74; 1.66-1.84 and OR: 7.56; 95%CI 7.15-8.00; sensitivity analysis OR: 2.64; 95%CI 2.45-

2.85, respectively). Other drugs strongly associated with increased risk were gliptins (OR: 2.77; 95% CI 2.37-3.23), and second-generation antipsychotics (OR: 2.58; 95%CI 2.20-3.03).

Conclusions: Healthcare professionals need to be aware of BP risk in older people particularly when prescribing penicillinase-resistant penicillins, gliptins, and second-generation antipsychotic drugs to recognise and manage BP early. Due to the low prevalence of disease, we do not suggest avoidance of drugs/vaccines to prevent BP. Further research should consider recency, dosage, and duration of antibiotic treatments.

Introduction

Bullous Pemphigoid (BP), characterised by pruritus and blisters, is the most common autoimmune blistering skin disease. [1-3] BP is a rare disease, predominant in older people (prevalence: 141 per 100 000 people for >60 year-olds). [3] BP can take years to resolve and has a threefold increased mortality risk than the general population. [2,3] BP is typically treated with oral prednisolone[4,5], which has known side effects such as osteoporosis and diabetes. [4,5] Despite being associated with high morbidity, mortality, and healthcare costs[6,7], BP aetiology is unknown. [2,3,8]

The pathogenesis of BP may be immune-mediated. [9] The pathomechanism initiates with the binding of autoantibodies to hemidesmosome proteins BP180 and BP230 and ends with the release of enzymes inducing the cell-matrix adhesion loss and the creation of subepidermal blisters. [10] Previously, reported BP triggers include drugs, vaccines, neurological conditions (e.g., dementia) and genetic predisposition. [1,11-15] Previous studies have described drug-induced BP[9,11,16,17], and withdrawal of the culprit drug leading to remission of BP. [18] Unlike the idiopathic type, drug-induced BP has diverse clinical characteristics, varying between culprit drugs [11], making it difficult to diagnose and initiate earlier treatment. [11,19,20] Systematic reviews and case-control studies report various drugs associated with BP, including gliptins, anticholinergics, aldosterone antagonists, antibiotics, and loop diuretics. [9,11,16,17,21] Most evidence relies on case series or small hospital-based studies (likely reflecting severe presentations of BP).

Reliable and precise information on drugs/vaccines associated with BP risk is important in helping earlier recognition in primary care and referral to a dermatologist for diagnosis. Earlier diagnosis may mean less severe, more manageable symptoms and less aggressive treatment. Furthermore, associations for a broad selection of drugs could help clinicians and researchers identify clinical, histological and genomic characteristics of drug-induced BP, improve its recognition, understand its trigger mechanisms and compare differences between culprit drugs. To address this important knowledge gap, we conducted a

large population-based nested case-control study using routinely collected electronic primary care records in the United Kingdom (UK). This study design has allowed us to identify cases of BP, a rare disease, and account for multiple drug prescriptions (reflecting age-dependent polypharmacy). [22] Using electronic healthcare records from the Clinical Practice Research Datalink (CPRD), we could match cases to controls from the general population and conduct a study representative of the UK population. [23,24] We aimed to examine whether drugs and vaccines prescribed for common conditions in older people are associated with increased BP risk at population-level, accounting for other drug use. Our objective comprised obtaining more reliable and precise estimates for previously associated drugs/vaccines and drugs that have not been investigated.

Methods

Study design

We used a nested case-control study, a recommended design for rare diseases like BP and when multiple exposures are evaluated. [25,26] This study followed the RECORD-PE reporting guidelines. [27] We published the protocol containing full details of this study. [28]

Data Source

The CPRD was used to draw cases and controls for our study. The CPRD is a longitudinal database containing anonymised, routinely collected healthcare records from over 2000 GP practices, comprising 60 million patients, 18 million currently registered at a practice, representing 26% of the UK population. [24,29] The data come from Vision and EMIS general practice systems, stored in GOLD and Aurum datasets. [23,30] These datasets cover UK and English only practices, respectively, [23,30]

Cases and controls selection

We identified incident BP cases (≥18 years) between 1st January 1998 and 22nd December 2021 using Read codes from patients' electronic clinical records (Appendix S1). We cannot specify exactly how the diagnoses were made but assume that for most patients, GPs received confirmation from dermatologists who would have diagnosed BP from a skin biopsy and/or direct or indirect immunofluorescence. The GP would then add a BP Read code to the patient's electronic records. Our previous validation study using inpatient data (Hospital Episode Statistics), identified BP codes with high positive predictive value (>85%).[31]

The index date was the earliest assigned BP code. At least one year of follow-up was required to minimise the inclusion of prevalent cases. [32,33]

We matched up to five controls (without BP diagnosis at index date) by birth year, sex, and GP practice using incidence density sampling. [34] We matched by GP practice to account for differences in the diagnoses recording and prescribing. [33] Controls were registered at least one year before the index date of their matched case. This step ensured controls had records in the same observation period and, if they became a BP case later, no retrospective BP record was added after their registration. We verified if we had sufficient BP cases for our analysis by comparing the number of BP cases with the power calculation described in Appendix S2.[28]

Exposures

We selected drugs used commonly by older people. [35] We included latest prescriptions of antibiotics, antidiabetic, antihypertensive, antithrombotic, lipid-modifying, analgesics, anti-dementia, antiepileptic, antipsychotic, and antidepressant drugs issued within one year before the index date. We included the latest influenza vaccine immunisations within three months before the index date. The cut-off points were based on previously reported lengths of immune responses to drugs and vaccines. [11,36,37] The drugs were divided into therapeutic groups, defining the pathology they treat. Each group contained drug

classes which describe their mode or mechanism of action. When applicable, a class comprised subclasses from the British National Formulary. [38] Clinicians (RH, RK) helped develop product lists for all groups.

Confounding variables

We tested dementia, stroke, Parkinson's disease, Index of Multiple Deprivation (IMD), and ethnicity as confounders. All but IMD are potential BP risk factors. [39-41] If the adjusted odds ratio (OR) changed by >10% compared to the unadjusted OR, the condition was considered a confounder and included in the multivariable models.

We classified people with dementia, stroke, or Parkinson's disease if they had a clinical diagnosis at least one year before BP.

Statistical analysis

We used unadjusted, partially adjusted, and multivariable conditional logistic regression models to determine the association between drugs and BP risk.

Partially adjusted models checked whether drug groups were confounded by stroke, dementia, or Parkinson's disease (Table S1). [39,40,42-44]

Multivariable models were then developed to account for (i) therapeutic groups, (ii) classes, and (iii) subclasses of drugs (with classes that couldn't be subdivided).

We conducted analyses separately for GOLD and AURUM and then combined the datasets, adjusting for data source, if the results were similar. We used Bonferroni correction to adjust for multiple testing and considered p-value<0.001 as statistically significant, and OR>2 a strong association. [45,46]

For ethnicity, we conducted multiple imputation using gender, age at diagnosis, deprivation, and BP status.

Data management and analyses were conducted in R programming language version 4.2.2. [47]

Sensitivity analyses

For antibiotics, we investigated protopathic bias potentially arising from treating symptoms of undiagnosed BP. [48] This analysis excluded six months of antibiotics prescriptions before the index date based on a mean diagnostic delay for BP[36,49] We adjusted for the number of consultations (categorical variable) six months before the index date to account for health-seeking behaviour. To adjust for a possible increase in GP visits for people with BP (surveillance bias), we excluded people with any drug prescription within three months before BP.

Other sensitivity analyses explored biases, like accounting for ethnicity and IMD (data from Hospital Episode Statistics linked practices only), diagnostic delay by extending the exposure window, preceding skin infection diagnosis as BP can be misdiagnosed as such, and a higher comorbidity burden in BP patients by adjusting for Cambridge Multimorbidity Score comorbidities (further details in Appendices S3-S4). [50]

Additional analysis

For classes and subclasses associated with BP, we identified the top five most prescribed drug substances with OR>2 BP risk.

Results

Results for GOLD and AURUM were similar (Tables S2a-b, S3a-b). Therefore, we report results from the datasets combined.

Study population

The study population comprises 16 844 cases and 79 493 controls (Figure S1). Table 1 presents the characteristics of the cases and controls. The median age was 80 (IQR: 71-86) years (Table 1). Most cases were female (55.5%) and white (75.1%). Dementia, stroke, and Parkinson's disease were 2 to 3 times more prevalent in cases than in controls.

Main analysis

More cases were exposed to each drug/vaccine than controls (Figure 1, Table S4a). Stroke was not a confounder for any drug. Dementia was a confounder for mirtazapine, and Parkinson's disease was a confounder for monoamine oxidase inhibitors (Table S4b). Both were accounted for in the multivariable analysis.

Antibiotics

Antibiotic exposure was associated with increased BP risk (OR: 4.60; 95%CI 4.40-4.80Penicillinase-resistant penicillins had the highest BP risk (OR: 7.56; 95%CI 7.15-8.00).

Antidiabetic drugs and insulins

Antidiabetic drugs and insulins were associated with increased BP risk (OR: 1.35; 95%CI 1.26-1.44). Gliptins were the only class with significant results (OR: 2.77; 95%CI 2.37-3.23).

Antihypertensive drugs

Antihypertensive drugs were associated with increased BP risk (OR: 1.48; 95%CI 1.41-1.56). The highest OR for antihypertensive drug classes was reported for diuretics (OR: 1.42; 95%CI 1.35-1.49). Thiazides and related diuretics (OR: 1.36; 95%CI 1.28-1.44) and loop diuretics (OR: 1.32; 95%CI 1.24-1.41) were the only diuretic subclasses with increased BP risk.

Antithrombotic drugs

Antithrombotics were associated with increased BP risk (OR: 1.33; 95%CI 1.26-1.39), and the only class with a significant association were antiplatelet drugs (OR: 1.36; 95%CI 1.29-1.44).

Lipid-modifying drugs

Lipid-modifying drugs were not associated with BP.

Analgesics

Analgesics were associated with increased BP risk (OR: 1.17; 95%CI 1.12-1.22), likely attributed to the non-opioid analgesics class (OR: 1.39; 95%CI 1.32-1.48). Two classes were associated with reduced BP risk: non-steroidal anti-inflammatory drugs (NSAIDs; OR, 0.86; 95%CI 0.81-0.93) and opioids (OR: 0.82; 95% CI 0.77-0.87).

Antidementia drugs

Antidementia drugs were associated with increased BP risk (OR: 2.22; 95%CI 1.93-2.56), including specific classes like centrally-acting anticholinesterases (OR: 2.16; 95%CI 1.84-2.54) and N-methyl-D-aspartate (NMDA) receptor antagonists (OR: 2.10; 95%CI 1.58-2.80).

Antiepileptic drugs

Antiepileptic drugs were associated with increased BP risk (OR: 1.58; 95%CI 1.45-1.72).

Antipsychotic drugs

Antipsychotics were associated with increased BP risk (OR: 1.61; 95%CI 1.47-1.77). The second-generation antipsychotic drugs had the strongest association with BP (OR: 2.58; 95%CI 2.20-3.03).

Antidepressants

Antidepressants were associated with increased BP risk (OR: 1.31; 95%CI 1.24-1.38). The classes associated with BP were selective serotonin reuptake inhibitors (OR: 1.43; 95%CI 1.33-1.53) and tricyclic antidepressants (OR: 1.16; 95%CI 1.08-1.25).

Influenza vaccine

Influenza vaccine was associated with increased BP risk (OR: 1.51; 95%CI 1.42-1.61).

For univariate and partially adjusted results, see Tables S4a-b.

Sensitivity analyses

Protopathic bias

After excluding antibiotic prescriptions six months before BP diagnosis, the OR for antibiotics changed from 4.60 to 2.08 (Figure 2). The OR for penicillins also dropped (3.44 to 1.74), with the highest

reduction reported for penicillinase-resistant penicillins (7.56 to 2.64). Table S5 shows all results for this sensitivity analysis.

Impact of adjusting for the number of consultations Antibiotics remained the most strongly associated group with BP (OR: 3.63; 95%CI 3.47-3.79). Penicillins (OR: 2.86; 95%CI 2.73-2.99) and penicillinase-resistant penicillins remained associated with increased BP risk (OR: 6.57; 95%CI 6.20-6.95). Nearly all other drugs hadlower OR than in the main analysis. Almost 86% of BP patients attended at least one consultation within six months before BP compared to 59% of controls (full results: Table S6).

Surveillance bias

After excluding patients with drug prescriptions within three months before BP, antibiotics remained strongly associated with BP (OR: 3.46; 95%CI 2.94-4.08). Penicillins (OR: 3.26; 95%CI 2.69-3.95) and the penicillinase-resistant subclass were also associated with increased BP risk (OR: 4.71; 95%CI 3.50-6.33). The influenza vaccine was no longer associated with BP (full results: Table S7).

Appendix S5 contains results of other sensitivity analyses: the effect of ethnicity and IMD (Table S8), a longer exposure window (Table S9), a preceding skin infection diagnosis (Table S10), and comorbidity burden (Table S11).

Additional analysis

Flucloxacillin had the highest adjusted OR (Figure 3, OR: 7.74; 95%CI 7.31-8.19; adjusted for protopathic bias: OR, 3.10; 95%CI 2.68-3.59) followed by linagliptin (OR: 5.05; 95%CI 3.99-6.40). Other strong associations with BP were estimated for second-generation antipsychotics risperidone (OR: 2.63; 95%CI

2.04-3.38), olanzapine (OR: 2.26; 95%CI 1.64-3.12), and antidementia drug memantine (OR: 2.30; 95%CI 1.70-3.12). See Table S12 for full results.

Discussion

This large population-based study has shown that several therapeutic groups, classes, subclasses, and substances are associated with BP risk after adjusting for multiple drug use. Antibiotics were associated with a high risk, particularly flucloxacillin. Both had over a 2-fold increase in BP risk following protopathic bias analysis. Gliptins were the only antidiabetic drug associated with increased BP risk (3-fold increase), and linagliptin had the strongest association (5-fold increase). We also estimated an increased BP risk following antidementia drugs, particularly centrally-acting anticholinesterases and NMDA receptor antagonists. Furthermore, we report the first-ever estimates of BP risk following a second-generation antipsychotic drug, olanzapine (2.3-fold increased risk), and influenza vaccine (1.5-fold increased risk). The latter is no longer statistically significant after accounting for surveillance bias.

We compared our findings with previous studies investigating associations between drugs and BP (Table S13: complete comparison). To our knowledge, we have conducted the largest population-based case-control study to date (>16 000 cases).

Our results were similar to those of Verheyden et al.'s systematic review, which reported strong associations with gliptins, loop diuretics, penicillins, and thiazides. [11] Regarding drugs for neurological disorders, our results confirm the associations between fluoxetine (Table S12), risperidone (Table S12), and BP reported by Verheyden et al. [11] However, unlike the review, we found no association between galantamine, gabapentin, and BP (Table S12). [11] Furthermore, we report results for olanzapine, a second-generation antipsychotic drug that was not investigated previously.

Compared to our study, Liu et al.'s meta-analysis showed an increased BP risk following gliptins (pooled OR: 1.92; 95%CI 1.55-2.38). [16] Our estimate (OR: 2.77; 95%CI 2.3-3.23 was based on fewer cases, but the studies included in the meta-analysis were mostly hospital-based. [16] Our gliptins estimate was also confirmed by a large CPRD cohort study by Douros et al. (adj. HR, 2.21; 95%CI 1.45-3.38). [51]

In a UK-based, single hospital case-control study by Lloyd-Lavery et al., loop diuretics (OR: 3.8; 95%CI 1.5-9.7) and antibiotics (OR: 3.4; 95%CI 1.1-11.2) were associated with a high BP risk but with higher estimates than ours (OR: 1.32; 95%CI 1.24-1.41 and OR 2.08; 95%CI 1.99-2.17 respectively). [17] These differences may be attributed to different settings and not adjusting for multiple drug use. Furthermore, we adjusted for protopathic bias in antibiotic prescribing, which the authors did not address.

The increased BP risk following penicillins could relate to metabolism, which exposes a thiol group possibly involved in the drug reaction pathogenesis. [9] After diagnosing BP, clinicians may need to avoid prescribing penicillins, particularly the penicillinase-resistant subclass. Gliptin treatment, while having an overall lower hypoglycaemia risk compared to other antidiabetic drugs[52], may also need to be replaced if a person develops BP to prevent prolonged disease progression. However, we do not suggest avoiding drugs with reported associations with BP due to the low absolute number of BP cases compared to the number of people who are treated with these drugs without developing BP. Instead, early biopsy and direct immunofluorescence should be performed in cases of acute pruritus onset and skin changes to determine if a patient has BP and then drug-induced factors should be evaluated.

Previous studies report varying times of BP onset after drug exposures[11], between 24 hours and 16.5 months[53,54 55,56] Therefore, prompt withdrawal of the offending agent and the initiation of treatment for BP before symptoms become severe may be required.

Strengths and Limitations

The combined CPRD GOLD and Aurum datasets represent >2000 UK GP practices. [23] These features allowed for a study design with sufficient power and generalisable results. The detailed electronic prescriptions from CPRD allowed for accounting for multiple exposures of many groups of drugs. We explored various biases by sensitivity analyses. The study's main limitation is possible confounding by indication. The estimates for antidementia drugs are likely affected by this bias because dementia has been previously associated with BP.[13,57-58] Therefore, we cannot infer if the association is between antidementia drugs or dementia per se and BP. Schizophrenia, bipolar disorder, epilepsy, and stroke have also been reported to be associated with BP.[14,44,57-63] We therefore advise cautious interpretation of the associations between the drugs indicated for these conditions and BP. Due to the nature of routinely collected data, unmeasured confounding might also affect our results. BP patients have poorer outcomes than controls, evidenced by a higher 2-year mortality rate. [3] Our comorbidity data also indicated that 51% of BP patients had at least one comorbidity compared to only 39% of controls (Table S14), which could explain why some drugs were associated with BP. Hence, we cannot always imply a drug-induced mechanism. We tried to minimise unmeasured confounding by conducting sensitivity analyses, like adjusting for comorbidity, health-seeking behaviour, and skin infection before diagnosis, which showed similar results to the main analysis.

Public health policies, like free influenza immunisation for people over 65 or with long-term conditions[64], could also increase vaccine exposure in sicker patient populations like BP patients. Our surveillance bias analysis supports this interpretation because it reported no association between the influenza vaccine and BP. Given an OR <2, and that BP is generally rare, we argue that the benefits of influenza vaccines outweigh the low BP risk in the general population.

Some drugs were licensed after our study started in 1998, which may explain the low number of cases and controls exposed to said drugs. For example, linagliptin was approved for prescribing in the UK in 2011[65-66], which means there was no prescription data for this drug for 13 years of our study. Finally, the BP risk following antibiotics could be overestimated in our analysis, but a strong association remains after adjusting for protopathic bias and skin infections.

Conclusions

Clinicians need to be aware of BP risk in older people following administration of penicillinase-resistant penicillins, gliptins, and second-generation antipsychotic drugs to recognise BP early and consider withdrawal or administration of alternative drugs, which confer a lower BP risk. We do not suggest avoiding drugs/vaccines with the reported associations, as most people use them without developing BP and the absolute number of BP cases is low. Further research should consider recency, dosage, and duration of antibiotic treatments and whether neurological conditions or drugs indicated for them are associated with BP.

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Figure legends

Figure 1. BP risk estimates (OR) following latest drug prescriptions issued within one year before BP diagnosis accounting for multiple drug exposures: using combined GOLD and AURUM datasets.

Figure 2. BP risk estimates (OR) following latest drug prescriptions within 6-12 months before BP diagnosis after excluding six months of antibiotics prescription before BP diagnosis and accounting for multiple drug exposures: using combined GOLD and AURUM datasets.

Figure 3. BP risk estimates (OR) of drug substances following latest prescriptions issued within one year before BP diagnosis accounting for multiple drug exposures: using combined GOLD and AURUM datasets.

1 Table 1 Study population characteristics.

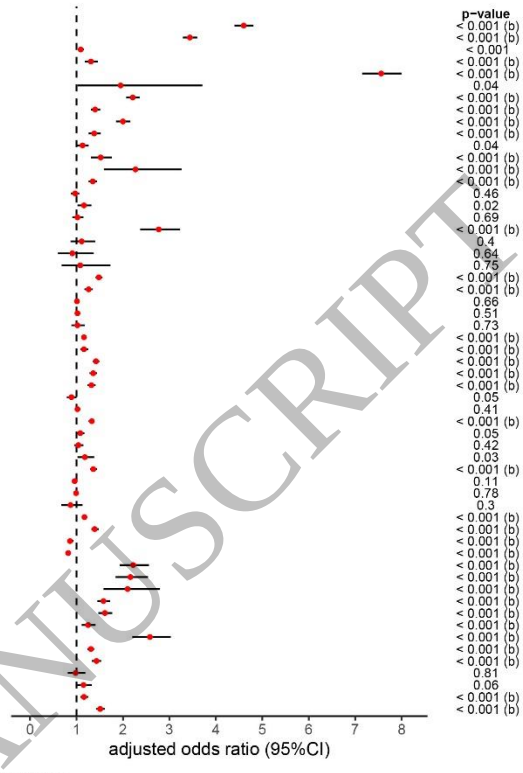
Total study population: n=96 337	Cases: n=16 844	Controls: n=79 493
Characteristic	**N (%)**	**N (%)**
Age at index date (mean±SD) (years)	76.6±14.1	76±14.1
Age group (years)		
< 60	1868 (11.1)	9183 (11.6)
60 - 69	1876 (11.1)	9223 (11.6)
70 - 79	4510 (26.8)	22 039 (27.7)
80 - 89	6301 (37.4)	29 871 (37.6)
>= 90	2289 (13.6)	9177 (11.5)
Sex		
Female	9350 (55.5)	44 363 (55.8)
Male	7494 (44.5)	35 130 (44.2)
Ethnicity[a]		
Asian	502 (2.9)	1344 (1.7)
Black	234 (1.3)	770 (0.9)
White	12 646 (75.1)	55 805 (70.2)
Other	157 (0.9)	608 (0.8)
Unknown	3331 (19.7)	16 403 (20.7)
Index of Multiple Deprivation		
1 (most affluent)	3100 (18.4)	14 997 (18.9)
2	2908 (17.3)	13 797 (17.4)
3	2897 (17.2)	13 147 (16.5)
4	2465 (14.6)	11 455 (14.4)
5 (most deprived)	2143 (12.7)	9694 (12.2)
Unknown	3331 (19.8)	16 403 (20.6)
Comorbidities diagnosed at least 1 year before the index date		
Dementia	1502 (8.9)	2679 (3.4)
Stroke	2675 (15.9)	8358 (10.5)
Parkinson's disease	416 (2.5)	850 (1.1)

Percentages are rounded and might not total 100.
a Modified ethnicity groups based on the CPRD Aurum/GOLD higher-level classification derived from the official 2011 UK Census ethnicity categories[67]. The 'mixed' group was merged with the 'other' group.

2

3

Therapeutic Group/Class/SubClass	Cases N(%)	Controls N(%)	Adjusted OR (a)	p-value
Antibiotics	9381 (55.69)	18 358 (23.09)	4.60 (4.40 – 4.81)	< 0.001 (b)
Penicillins	7098 (42.14)	12 176 (15.32)	3.44 (3.29 – 3.60)	< 0.001 (b)
Broad spectrum penicillins	3801 (22.57)	9508 (11.96)	1.09 (1.03 – 1.16)	< 0.001
Broad spectrum penicillin w. beta lactamase inh.	1177 (6.99)	1867 (2.35)	1.31 (1.18 – 1.46)	< 0.001 (b)
Penicillinase resistant penicillins	5106 (30.31)	3919 (4.93)	7.56 (7.15 – 8.00)	< 0.001 (b)
Mecillinams	24 (0.14)	35 (0.04)	1.95 (1.02 – 3.71)	0.04
Macrolides	2227 (13.22)	3309 (4.16)	2.21 (2.07 – 2.36)	< 0.001 (b)
Sulphonamides and trimethoprim	1770 (10.51)	3905 (4.91)	1.40 (1.31 – 1.51)	< 0.001 (b)
Tetracyclines	1705 (10.12)	2557 (3.22)	2.00 (1.85 – 2.16)	< 0.001 (b)
Cephalosporins	1080 (6.41)	2039 (2.57)	1.38 (1.26 – 1.52)	< 0.001 (b)
Quinolones	643 (3.82)	1232 (1.55)	1.13 (1.01 – 1.26)	0.04
Metronidazole and tinidazole	403 (2.39)	596 (0.75)	1.52 (1.31 – 1.76)	< 0.001 (b)
Lincosamides	85 (0.50)	75 (0.09)	2.27 (1.59 – 3.26)	< 0.001 (b)
Antidiabetic drugs and insulins	1908 (11.33)	4942 (6.22)	1.35 (1.26 – 1.44)	< 0.001 (b)
Biguanides	1251 (7.43)	3594 (4.52)	0.97 (0.88 – 1.06)	0.46
Insulins	553 (3.28)	1089 (1.37)	1.16 (1.02 – 1.32)	0.02
Sulphonylureas	728 (4.32)	1940 (2.44)	1.02 (0.91 – 1.15)	0.69
Gliptins	480 (2.85)	611 (0.77)	2.77 (2.37 – 3.23)	< 0.001 (b)
Thiazolidinediones	131 (0.78)	354 (0.45)	1.11 (0.87 – 1.40)	0.4
Gliflozins	45 (0.27)	113 (0.14)	0.91 (0.60 – 1.37)	0.64
Glp 1 receptor agonists	35 (0.21)	73 (0.09)	1.08 (0.68 – 1.73)	0.75
Antihypertensive drugs	9197 (54.60)	31 488 (39.61)	1.48 (1.41 – 1.56)	< 0.001 (b)
Alpha adrenoceptor blocking drugs	1595 (9.47)	4635 (5.83)	1.26 (1.17 – 1.35)	< 0.001 (b)
Beta adrenoceptor blocking drugs	3226 (19.15)	11 583 (14.57)	1.01 (0.96 – 1.07)	0.66
Selective beta adrenoceptor blocking drugs	2905 (17.25)	10 345 (13.01)	1.02 (0.96 – 1.08)	0.51
Non selective beta adrenoceptor blocking drugs	357 (2.12)	1318 (1.66)	1.02 (0.89 – 1.18)	0.73
Angiotensin converting enzyme inhibitors	3842 (22.81)	12 865 (16.18)	1.16 (1.10 – 1.22)	< 0.001 (b)
Angiotensin II receptor antagonists	1569 (9.31)	5193 (6.53)	1.16 (1.08 – 1.25)	< 0.001 (b)
Diuretics	5681 (33.73)	16 540 (20.81)	1.42 (1.35 – 1.49)	< 0.001 (b)
Thiazides and related diuretics	2913 (17.29)	9907 (12.46)	1.36 (1.28 – 1.44)	< 0.001 (b)
Loop diuretics	3328 (19.76)	7580 (9.54)	1.32 (1.24 – 1.41)	< 0.001 (b)
Potassium sparing diuretics with other diuretics	679 (4.03)	1673 (2.10)	0.89 (0.79 – 1.00)	0.05
Calcium channel blockers	3387 (20.11)	12 714 (15.99)	1.02 (0.97 – 1.08)	0.41
Antithrombotic drugs	6143 (36.47)	18 693 (23.52)	1.33 (1.26 – 1.39)	< 0.001 (b)
Anticoagulants	1307 (7.76)	4036 (5.08)	1.08 (1.00 – 1.17)	0.05
Warfarin	942 (5.59)	3068 (3.86)	1.04 (0.95 – 1.15)	0.42
Direct oral anticoagulants	413 (2.45)	1063 (1.34)	1.18 (1.02 – 1.38)	0.03
Antiplatelet drugs	5070 (30.10)	15 304 (19.25)	1.36 (1.29 – 1.44)	< 0.001 (b)
Lipid modifying drugs	5125 (30.43)	17 916 (22.54)	0.96 (0.91 – 1.01)	0.11
Statins	5064 (30.06)	17 679 (22.24)	0.99 (0.94 – 1.05)	0.78
Fibrates	97 (0.58)	320 (0.40)	0.87 (0.67 – 1.13)	0.3
Analgesics	6849 (40.66)	21 515 (27.07)	1.17 (1.12 – 1.22)	< 0.001 (b)
Non opioid analgesics	5938 (35.25)	17 529 (22.05)	1.39 (1.32 – 1.48)	< 0.001 (b)
Non steroidal anti inflammatory drugs	1437 (8.53)	6209 (7.81)	0.86 (0.81 – 0.93)	< 0.001 (b)
Opioid analgesics	3616 (21.47)	11 778 (14.82)	0.82 (0.77 – 0.87)	< 0.001 (b)
Antidementia drugs	429 (2.55)	685 (0.86)	2.22 (1.93 – 2.56)	< 0.001 (b)
Centrally acting anticholinesterases	331 (1.97)	561 (0.71)	2.16 (1.84 – 2.54)	< 0.001 (b)
NMDA receptor antagonists	119 (0.71)	156 (0.20)	2.10 (1.58 – 2.80)	< 0.001 (b)
Control of epilepsy	1240 (7.36)	2364 (2.97)	1.58 (1.45 – 1.72)	< 0.001 (b)
Antipsychotic drugs	892 (5.30)	1715 (2.16)	1.61 (1.47 – 1.77)	< 0.001 (b)
First generation antipsychotic drugs	513 (3.05)	1284 (1.62)	1.25 (1.11 – 1.41)	< 0.001 (b)
Second generation antipsychotic drugs	413 (2.45)	459 (0.58)	2.58 (2.20 – 3.03)	< 0.001 (b)
Antidepressants	3306 (19.63)	8316 (10.46)	1.31 (1.24 – 1.38)	< 0.001 (b)
Selective serotonin reuptake inhibitors	1729 (10.26)	3922 (4.93)	1.43 (1.33 – 1.53)	< 0.001 (b)
Serotonin and noradrenaline reuptake inhibitors	209 (1.24)	489 (0.62)	0.98 (0.81 – 1.19)	0.81
Mirtazapine (c)	388 (2.30)	853 (1.07)	1.15 (0.99 – 1.33)	0.06
Tricyclic and related antidepressant drugs	1413 (8.39)	3924 (4.94)	1.16 (1.08 – 1.25)	< 0.001 (b)
Influenza vaccine	4757 (28.24)	17 031 (21.42)	1.51 (1.42 – 1.61)	< 0.001 (b)



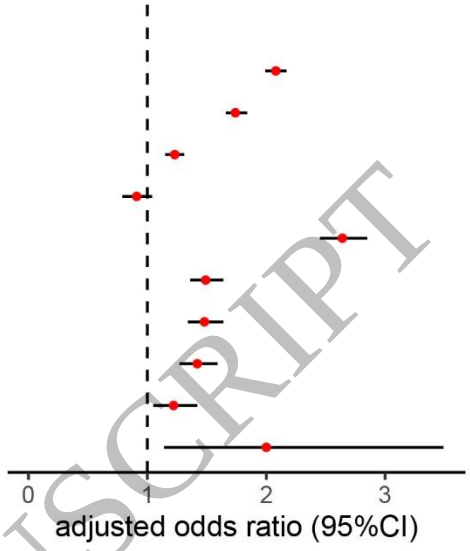
(a) The group model mutually adjusted for all drug groups, and the class model mutually model adjusted for all drug classes. The subclass model adjusts for all subclasses and classes of drugs which could not be further divided into subclasses.

(b) Statistically significant results after Bonferroni correction.

Figure 1

271x184 mm (x DPI)

Therapeutic Group/Class/SubClass	Cases N(%)	Controls N(%)	Adjusted OR (a,b)	p−value
Antibiotics	5111 (30.34)	11 726 (14.75)	2.08 (1.99 − 2.17)	< 0.001 (c)
Penicillins	3253 (19.31)	7281 (9.16)	1.74 (1.66 − 1.84)	< 0.001 (c)
Broad spectrum penicillins	2101 (12.47)	5607 (7.05)	1.23 (1.15 − 1.31)	< 0.001 (c)
Broad spectrum penicillin w. beta lactamase inh.	448 (2.66)	1064 (1.34)	0.91 (0.79 − 1.04)	0.17
Penicillinase resistant penicillins	1520 (9.02)	2160 (2.72)	2.64 (2.45 − 2.85)	< 0.001 (c)
Macrolides	902 (5.36)	1901 (2.39)	1.49 (1.36 − 1.64)	< 0.001 (c)
Tetracyclines	701 (4.16)	1469 (1.85)	1.48 (1.34 − 1.64)	< 0.001 (c)
Cephalosporins	590 (3.50)	1198 (1.51)	1.42 (1.27 − 1.59)	< 0.001 (c)
Quinolones	319 (1.89)	672 (0.85)	1.22 (1.05 − 1.42)	0.01
Lincosamides	28 (0.17)	34 (0.04)	2.00 (1.14 − 3.49)	0.01

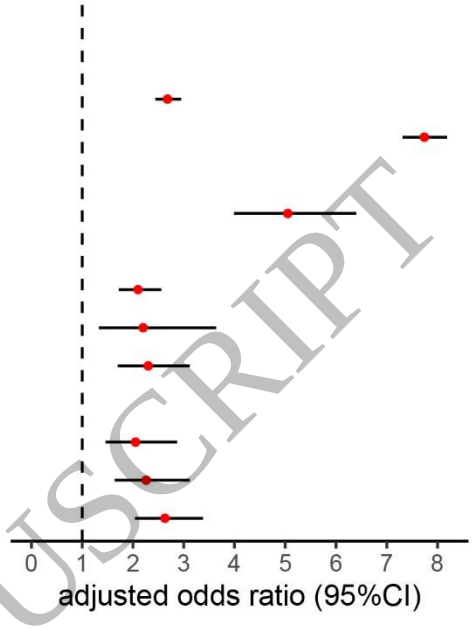


(a) BP risk estimates (odds ratios) following latest drug prescriptions within 6−12 months before BP diagnosis, after excluding six months of antibiotics prescription data before BP diagnosis.
(b) The group model mutually adjusted for all drug groups, and the class model mutually model adjusted for all drug classes. The subclass model adjusts for all subclasses and classes of drugs which could not be further divided into subclasses.

(c) Statistically significant results after Bonferroni correction.

Figure 2
184x100 mm (x DPI)

Therapeutic Group/Substance	Cases N(%)	Controls N(%)	Adjusted OR (a)	p−value
Antibiotics				
Erythromycin	1183 (7.02)	1481 (1.86)	2.68 (2.44 − 2.95)	< 0.001 (b)
Flucloxacillin	5010 (29.74)	3811 (4.79)	7.74 (7.31 − 8.19)	< 0.001 (b)
Antidiabetic drugs and insulins				
Linagliptin	284 (1.69)	188 (0.24)	5.05 (3.99 − 6.40)	< 0.001 (b)
Antidementia drugs				
Donepezil	237 (1.41)	416 (0.52)	2.10 (1.72 − 2.56)	< 0.001 (b)
Galantamine	39 (0.23)	63 (0.08)	2.20 (1.33 − 3.64)	< 0.001
Memantine	119 (0.71)	156 (0.20)	2.30 (1.70 − 3.12)	< 0.001 (b)
Antipsychotic drugs				
Haloperidol	99 (0.59)	113 (0.14)	2.05 (1.46 − 2.87)	< 0.001 (b)
Olanzapine	100 (0.59)	130 (0.16)	2.26 (1.64 − 3.12)	< 0.001 (b)
Risperidone	200 (1.19)	190 (0.24)	2.63 (2.04 − 3.38)	< 0.001 (b)



(a) Mutually adjusted for the top five most prescribed drug substances belonging to classes/subclasses of drugs associated with BP and therapeutic groups containing drugs which did not make the top list.

(b) Statistically significant results after Bonferroni correction

Figure 3
184x100 mm (x DPI)

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

Cosentyx® secukinumab

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

150+ clinical trials across indications[5]

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

8 indications[1–3]

Click here to visit our HCP portal and learn more

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

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

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

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

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

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

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

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

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

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

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

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

NOVARTIS

UK | August 2024 | FA-11239622

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

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

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

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Adverse Event Reporting:

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

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

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