Mortality, bone density and grip strength: lessons from the past and hope for the future?

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Abstract

Objectives. Therapeutic advances in management of osteoporosis and sarcopenia have occurred at different rates over the last two decades; here we examined associations between grip strength and bone mineral density (BMD) with subsequent all-cause and cause-specific mortality in a UK community-dwelling cohort.

Methods. Data from 495 men and 414 women from the Hertfordshire Cohort Study were analysed. Grip strength was assessed by grip dynamometry; femoral neck BMD was ascertained using DXA; deaths were recorded from baseline (1998-2004) until 31st December 2018. Grip strength and BMD in relation to mortality outcomes (all-cause, cardiovascular-related, cancer-related, and mortality due to other causes) were examined using Cox regression with adjustment for age and sex.

Results. Mean (SD) baseline age of participants was 64.3 (2.5) and 65.9 (2.6) years in men and women respectively. Lower grip strength was associated with increased risk of all-cause mortality (hazard ratio (95% CI): 1.30 (1.06,1.58), p=0.010) and cardiovascular-related mortality (1.75 (1.20,2.55), p=0.004). In contrast, BMD was not associated with any of the mortality outcomes (p>0.1) for all associations.

Conclusion. We report strong relationships between grip strength and mortality in comparison with BMD. We hypothesize that this may reflect better recognition and treatment of low BMD in this cohort.

Keywords: Mortality, Sarcopenia, Osteoporosis, Epidemiology

Key messages:

1. Grip strength was related to subsequent mortality in a community-based cohort.
2. By contrast, there was no relationship between baseline bone mineral density and subsequent mortality.
3. We hypothesize that this may reflect better diagnosis and management of osteoporosis.

Lay summary

What does this mean for patients?

Low grip strength is important in the diagnosis of sarcopenia (loss of muscle mass and strength with age); low bone density is used to define osteoporosis. Both sarcopenia and osteoporosis are common conditions among older people and are related to increased risk of poor health. In this study, we examined grip strength and bone density in relation to risk of death using data from older UK men and women from the Hertfordshire Cohort Study (aged 59-73 years at the start of the study). Lower grip strength was related to increased risk of death (any cause) and death due to cardiovascular causes. In contrast, the relationships between bone density and risk of death (any cause) and death due to cardiovascular causes were weak. Relationships between muscle strength and risk of death were much stronger than relationships between bone density and risk of death. This may reflect better treatment of low bone density, compared to low muscle strength, in this group of older people. This suggests that advances in the treatment of low muscle strength are required.

Introduction

Musculoskeletal health disorders including osteoporosis and sarcopenia are highly prevalent in older adults [1]. Osteoporosis, a disease characterised by low bone mass and structural deterioration of bone tissue, is the most common chronic metabolic bone disease and is associated with fragility fractures – including fractures at the hip or spine, which have been associated in several studies with excess mortality [2]. Sarcopenia is characterised by progressive and generalised decline in muscle strength, function and muscle mass with increasing age or secondary to disease [3] and is also associated with a range of adverse physical and metabolic outcomes including excess mortality [4].

Although historically, several studies have reported associations between either low bone mineral density (BMD) or low grip strength and mortality risk, therapeutic advances in management of osteoporosis and sarcopenia have occurred at different rates over the last two decades, with many more therapeutic modalities available for osteoporosis. Recent recognition of a high prevalence of coexistence of both osteoporosis and sarcopenia in individuals has led to the existence of the term ‘osteosarcopenia’, the so-called hazardous duet where adverse consequences are commonly recognised in individuals with the condition [5], with higher mortality risk recognised among individuals with the condition who have sustained a hip fracture [6]. In this study, we examined relationships between BMD and grip strength and subsequent all-cause and cause-specific mortality

in a real world setting in a UK community-dwelling cohort of participants aged 59-73 years at baseline, and followed up for approximately 20 years.

Methods

The Hertfordshire Cohort Study

The Hertfordshire Cohort Study (HCS) is a study of 2,997 women and men born in Hertfordshire (UK) between 1931 and 1939. The participants were all living in Hertfordshire in 1998-2004, when they completed a home interview and clinic visit for a detailed characterization of their health. The HCS received ethical approval from the Hertfordshire and Bedfordshire Local Research Ethics Committee, and all participants gave informed consent for the investigations they underwent during the home interview and clinic visit and for researchers to access their medical records in the future [7, 8]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ascertainment of participant information at the baseline clinic (1998-2004)

At the baseline clinic, grip strength was measured three times on each side using a Jamar hand-held dynamometer (Promedics, Blackburn, UK); the highest of the six measurements was used for analysis. A subgroup of 498 men and 468 women had their femoral neck bone mineral density assessed at the lumbar spine and proximal femur using a Hologic QDR 4500 dual energy x-ray absorptiometer. Current use of bisphosphonates was part of the exclusion criteria for the baseline DXA scan (though approximately 15% of women who had a baseline DXA scan were on hormone replacement therapy). Results from the baseline DXA scan were fed back to participants and their GPs, and osteoporosis therapy was recommended if clinically indicated. Among the subgroup who underwent baseline DXA scans, follow-up studies that also involved DXA were conducted in 2011-2012 (n=443) and 2017 (n=224) [8]; at each of these time-points, around 10% of participants reported taking bisphosphonates.

Probable sarcopenia (low grip strength of < 27kg (men), <16kg (women)) was defined according to the 2019 European Working Group on Sarcopenia in Older People (EWGSOP2) [4]. Osteoporosis was defined according to the World Health Organization criteria as a femoral neck BMD T-score of < -2.5. Probable osteosarcopenia was defined as the combination of both low grip strength and osteoporosis.

Ascertainment of mortality outcomes

The Ethics and Confidentiality Committee of the National Information Governance Board and NHS Digital provided permission to obtain mortality data from HCS participants from baseline until 31/12/2018. Mortality outcomes included all-cause mortality, cancer-related mortality (ICD-10 codes for underlying cause: C00-C97), cardiovascular-related mortality (ICD-10 codes: I10-I79) and mortality not due to cancer or cardiovascular causes. (REC reference: 16/EE/0374 01 April 2020 IRAS project ID: 208811).

Statistical methods

Summary statistics, such as means and standard deviations, medians and interquartile ranges, and percentages, were used to describe participant characteristics. Grip strength and femoral neck BMD were normally distributed within each sex; this was confirmed through visual examination of histograms. Cox regression was used to examine grip strength and femoral neck BMD in relation to the following mortality outcomes (all-cause mortality, cardiovascular-related mortality, cancer-related mortality and mortality not due to cancer or cardiovascular causes). Hazard ratios, along with their 95% confidence intervals, were derived using these models. Models were adjusted for age and sex; evidence of sex-interaction effects was weak ($p>0.2$ for all interactions). Analyses were performed using Stata (STATA Corp, College Station, Texas, USA), version 17.0; $p<0.05$ was regarded as statistically significant. The sample size was the largest possible, given the data available; the analysis sample comprised participants who underwent the baseline DXA scan (none of these participants were taking bisphosphonates) who were also not on hormone replacement therapy (n=909); all these participants had values for grip strength and femoral neck BMD.

Results

Table 1 presents the participant characteristics of the analysis sample. Mean (SD) age at baseline was 64.3 (2.5) and 65.9 (2.6) years among men and women respectively. Mean grip strength was higher among men compared to women (44.1 vs 27.5 kg); this was also the case for femoral neck BMD (0.85 vs 0.75 g/cm^2). The prevalence of EWGSOP2 probable sarcopenia (low grip strength of < 27kg (men), <16kg (women)) was 1% in both men and women, while the prevalence of osteoporosis (femoral neck BMD T-score of < -2.5) was 1% in men and 5% in women. No participants had probable

osteosarcopenia, defined as the combination of low grip strength and osteoporosis. Approximately 35% of men and 25% of women died during follow-up.

Age- and sex-adjusted hazard ratios for mortality outcomes per SD lower grip strength and femoral neck BMD are presented in Table 2. Lower grip strength was associated with increased risk of all-cause mortality (hazard ratio (95% CI): 1.30 (1.06,1.58), p=0.010) and cardiovascular-related mortality (1.75 (1.20,2.55), p=0.004). In contrast, femoral neck BMD was not associated with any of the mortality outcomes (p>0.1) for all associations. Mutually-adjusted associations were similar when grip strength and femoral neck BMD were included in the same model with age and sex as adjustments (data not shown).

Discussion

In this study, we report strong relationships between grip strength and mortality after adjustment for age and sex in comparison with BMD. We hypothesize that this may reflect better recognition and treatment of low bone density, as evidenced by the proportion of our participants reporting bisphosphonate use in follow up studies. Our study might be considered to represent a natural experiment, as we fed back DXA results from scans performed at baseline as part of this study to participants and their GPs, representing a form of case-finding. In support of this, we found that among participants who were seen in clinic in subsequent studies, about 10% reported current bisphosphonate use. Although we might expect the prevalence of osteoporosis to be slightly higher (25% in women and 6% in men aged over 65 years) [9], it is possible that some participants may have been taking a holiday from therapy. Furthermore, we know that drug adherence is typically only 30% at one year and lower still in subsequent years. For example, approximately 75% of women who used oral bisphosphonates revealed a non-adherence within 1 year and 50% discontinued therapy by this time [10]. Our figure of 10% represents participants who have been prescribed bisphosphonates and were currently taking them at the time of our research clinic. At the time of these clinics (2011-2012 and 2017), this was the usual therapy for osteoporosis. Fewer than 7 women were on HRT in 2011-2012 (n=433) and in 2017 (n=224), and less than 6 women were on strontium therapy in 2017. Denosumab use was not ascertained in this cohort.

The first full publications on the biological effects of bisphosphonates appeared in 1969 [11], but did not become common in osteoporosis management until the 1990s when etidronate was used, to be followed by more potent bisphosphonates such as alendronate, with the advent of large randomised trials. The management of osteoporosis was facilitated by international consensus regarding a

definitional approach by the World Health Organisation [12]. By contrast, agreement regarding a definitional approach to sarcopenia has been slower [13] and to date fewer therapeutic targets have been identified [14].

It has long been recognised that hip and vertebral osteoporotic fractures are associated with considerable immediate and long-term increased mortality risk which is associated with immediate complications relating to the fracture and surgical repair in the case of hip fractures, and comorbidity in the case of vertebral fractures [15]. Treatment with bisphosphonates has been associated with a decreased risk of mortality in patients with osteoporotic fractures in some observational studies and in randomized controlled trials of zoledronate therapy following hip fracture, with acute phase response identified as important [16].

We have speculated that relationships between BMD and mortality risk were weaker than between grip strength and mortality risk because there is a recognised diagnosis pathway and commonly used treatment for the condition that might reduce mortality risk. Previous studies have considered whether bisphosphonate use reduces mortality. For example, a recent Taiwanese study, using the Taiwan National Health Insurance Research Database (NHIRD) linked to national death registration data in 59,926 patients with osteoporotic vertebral fractures, found that after excluding patients with short-term mortality, patients who had previously received anti-osteoporotic medications had a lower mortality risk (hazard ratio (HR): 0.84, 95% confidence interval (CI): 0.81–0.88). Patients receiving treatment for more than 3 years had a much lower mortality risk (HR: 0.53, 95% CI: 0.50–0.57) regardless of which therapy was used [17]. This followed a previous study using the same database that suggested that bisphosphonate use was associated with reduced risk of mortality [18].

Grip strength has likewise been associated with excess risk of all-cause mortality in several studies [19]. Furthermore, there is evidence that the combination of low strength and low BMD confers greater risk of adverse health outcomes compared to either condition in isolation. For example, in a study comprising 1044 women, aged 75 at baseline from the OPRA Cohort, probable osteosarcopenia (low knee muscle strength of < 175 Nms and low femoral neck BMD T-score of < -1.0) was associated with higher risk of hip and major osteoporotic fracture and mortality compared to low femoral neck BMD alone [20]. This suggests that additional treatments and interventions to those aimed at addressing low BMD may be required to reduce risk of adverse health outcomes among individuals with probable osteosarcopenia.

This study has some limitations and strengths. A significant strength of our analysis is the standardised method of assessment of both grip strength and BMD measurement in a large single community-

based cohort who have been followed up through linked registries. This assures almost 100% follow-up. As explained above, our classification of sarcopenia is probable rather than confirmed, as specified according to the EWGSOP2 definition, and this, together with the low prevalence of low muscle strength and bone density in this population, meant that we could not explore the coexistence of both conditions in relation to health outcomes in this study. While participants of the HCS have been shown to be generally representative of the UK population, they are all Caucasian, limiting the generalisability of our results. Regarding therapy for osteoporosis, we do not have information on intermittent annual treatments such as zoledronate. However, our observation that BMD was not associated with mortality over 20 years of follow up where linked data assure no healthy cohort bias is of interest. Further studies of comparable cohorts are now required.

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Data availability: Data relating to this study cannot be shared due to consent restrictions.

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References

1. Curtis E, Litwic A, Cooper C, Dennison E. Determinants of Muscle and Bone Aging. *J Cell Physiol.* 2015;230(11):2618-25.
2. Sattui SE, Saag KG. Fracture mortality: associations with epidemiology and osteoporosis treatment. *Nat Rev Endocrinol.* 2014;10(10):592-602.
3. Rosenberg IH. Sarcopenia: origins and clinical relevance. *Clin Geriatr Med.* 2011;27(3):337-9.
4. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;48(1):16-31.
5. Hamad B, Basaran S, Coskun Benlidayi I. Osteosarcopenia among postmenopausal women and handgrip strength as a practical method for predicting the risk. *Aging Clin Exp Res* 2020;32(10):1923-30.
6. Yoo J-I, Kim H, Ha Y-C, Kwon H-B, Koo K-H. Osteosarcopenia in patients with hip fracture is related with high mortality. *J Korean Med Sci.* 2018;33(4):e27.
7. Syddall HE, Sayer AA, Dennison EM, Martin HJ, Barker DJP, Cooper C. Cohort Profile: The Hertfordshire Cohort Study. *Int J Epidemiol.* 2005;34(6):1234-42.
8. Syddall HE, Simmonds SJ, Carter SA, Robinson SM, Dennison EM, Cooper C, et al. The Hertfordshire Cohort Study: an overview. *F1000Res.* 2019;8(82):10.12688/f1000research.7457.1.
9. Clynes MA, Harvey NC, Curtis EM, Fuggle NR, Dennison EM, Cooper C. The epidemiology of osteoporosis. *Br Med Bull.* 2020;133(1):105-17.
10. Hesari E, Sanjari M, Mansourzadeh MJ, Fahimfar N, Khalagi K, Ghazbani A, et al. Osteoporosis medication adherence tools: a systematic review. *Osteoporos Int.* 2023;34(9):1535-48.
11. Russell G. Bisphosphonates: from bench to bedside. *Ann N Y Acad Sci.* 2006;1068(1):367-401.
12. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med.* 1993;94(6):646-50.
13. Westbury LD, Beaudart C, Bruyère O, Cauley JA, Cawthon P, Cruz-Jentoft AJ, et al. Recent sarcopenia definitions-prevalence, agreement and mortality associations among men: Findings from population-based cohorts. *J Cachexia Sarcopenia Muscle.* 2023;14(1):565-75.
14. Reginster J-Y, Beaudart C, Al-Daghri N, Avouac B, Bauer J, Bere N, et al. Update on the ESCEO recommendation for the conduct of clinical trials for drugs aiming at the treatment of sarcopenia in older adults. *Aging Clin Exp Res.* 2021;33(1):3-17.
15. Toro G, Braile A, Liguori S, Moretti A, Landi G, Cecere AB, et al. The role of the fracture liaison service in the prevention of atypical femoral fractures. *Ther Adv Musculoskelet Dis.* 2023;15:1759720X231212747.
16. Lu K, Wu Y-M, Shi Q, Gong Y-Q, Zhang T, Li C. The impact of acute-phase reaction on mortality and re-fracture after zoledronic acid in hospitalized elderly osteoporotic fracture patients. *Osteoporos Int* 2023;34(9):1613-23.
17. Tai T-W, Tsai Y-L, Shih C-A, Li C-C, Chang Y-F, Huang C-F, et al. Refracture risk and all-cause mortality after vertebral fragility fractures: Anti-osteoporotic medications matter. *J Formos Med Assoc.* 2023;122(Suppl 1):S65-S73.
18. Hsu YH, Li CC, Liang FW, Peng ZY, Chang YF, Hsu JC, et al. Reduced All-Cause Mortality With Bisphosphonates Among Post-Fracture Osteoporosis Patients: A Nationwide Study and Systematic Review. *Clin Pharmacol Ther.* 2022;112(3):711-9.
19. López-Bueno R, Andersen LL, Koyanagi A, Núñez-Cortés R, Calatayud J, Casaña J, et al. Thresholds of handgrip strength for all-cause, cancer, and cardiovascular mortality: A systematic review with dose-response meta-analysis. *Ageing Res Rev.* 2022;82:101778.
20. Paulin TK, Malmgren L, McGuigan FE, Akesson KE. Osteosarcopenia: Prevalence and 10-Year Fracture and Mortality Risk - A Longitudinal, Population-Based Study of 75-Year-Old Women. *Calcif Tissue Int* 2024:doi: 10.1007/s00223-023-1181-1.
21.

Table 1: Participant characteristics of the analysis sample (n=909)

Participant characteristic	Mean (SD), median (lower quartile, upper quartile) or %	
	Men (n=495)	Women (n=414)
Age (years)	64.3 (2.5)	65.9 (2.6)
Grip strength (kg)	44.1 (7.3)	27.5 (5.0)
EWGSOP2 probable sarcopenia	1%	1%
Femoral neck BMD (g/cm^2)	0.85 (0.12)	0.75 (0.12)
Osteoporosis	1%	5%
Mortality outcomes		
All-cause mortality	35%	25%
Cancer-related	15%	10%
Cardiovascular-related	10%	5%
Other (not cancer or cardiovascular-related)	10%	10%
Follow-up time (years)	18.8 (16.5, 19.3)	17.3 (16.3, 17.8)

Percentages for mortality outcomes were rounded to the nearest 5%
Follow-up time until death or until participants were censored is presented
EWGSOP2 probable sarcopenia: low grip strength of < 27kg (men), <16kg (women)
Osteoporosis: femoral neck BMD T-score of < -2.5

Table 2: Risk of mortality outcomes per SD lower grip strength and femoral neck BMD (adjusted for age and sex)

Mortality outcome (underlying cause)	Grip strength (z-score)		Femoral neck BMD (z-score)	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
All-cause	1.30 (1.06,1.58)	0.010	1.05 (0.93,1.20)	0.422
Cancer	1.01 (0.74,1.39)	0.932	1.19 (0.97,1.46)	0.104
Cardiovascular	1.75 (1.20,2.55)	0.004	1.12 (0.87,1.44)	0.389
Other (not cancer or cardiovascular)	1.30 (0.92,1.83)	0.136	0.89 (0.72,1.10)	0.280

Grip strength and femoral neck BMD were included in separate models; each model was adjusted for age and sex

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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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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. 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. 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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