TITLE PAGE

Title: Definitions of and Instruments for Disease Activity, Remission, and Relapse in Polymyalgia Rheumatica: A Systematic Literature Review

Running head: PMR relapse remission

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- A definition-based model for polymyalgia rheumatica remission and relapse as disease state (transitions) was developed
- Instruments for a variety of domains are used, but need a clearer description and validation
- Qualitative research is needed regarding the concepts of, and instruments for, remission and relapse.

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ABSTRACT

OBJECTIVE. To perform a systematic literature review on definitions and instruments used to measure remission, relapse, and disease activity in polymyalgia rheumatica (PMR), to inform an OMERACT project to endorse instruments for these outcomes.

METHODS. A search of Pubmed/MEDLINE, EMBASE, CINAHL, Cochrane, and Epistemonikos was performed May 2021 and updated August 2023. Qualitative and quantitative studies published in English were included if they recruited people with isolated PMR regardless of treatment. Study selection and data extraction was performed independently by two investigators and disagreement was resolved through discussion. Data extracted encompassed definitions of disease activity, remission and relapse, and details regarding the instruments used to measure these outcomes.

RESULTS. From the 5,718 records, we included 26 articles on disease activity, 36 on remission, and 53 on relapse; 64 studies were observational and 15interventional, and none used qualitative methods. Some heterogeneity was found regarding definitions and instruments encompassing the domains pain, stiffness, fatigue, laboratory markers (mainly acute phase reactants), and patient and physician global assessment of disease activity. However, instruments for clinical signs were often poorly described. Whilst measurement properties of the polymyalgia rheumatica activity score (PMR-AS) have been assessed, data to support its use for measurement of remission and relapse is limited.

CONCLUSION. Remission, relapse, and disease activity have been defined heterogeneously in clinical studies. Instruments to measure these disease states still need to be validated. Qualitative research is needed to better understand the concepts of remission and relapse in PMR.

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Introduction

In polymyalgia rheumatica (PMR), glucocorticoids (GC) are the mainstay of treatment (1, 2). After achieving remission, GC are tapered to reduce the risk of GC-related adverse events. However, this can only continue provided a patient remains in remission. When a relapse occurs, GC dose is usually increased to the last effective dose. Relapses occur in up to 55% of PMR patients (3-5).

Measuring remission and relapse in PMR can be particularly challenging as concomitant disorders such as osteoarthritis or rotator cuff disease may mimic PMR disease activity. Acute phase reactants, which often form an integral part of disease activity assessment, may be increased for other reasons such as infection (6). The identification of parameters that can be used to assess 'disease activity' as well as 'remission' and 'relapse' are important, since these are typical (primary) outcomes in clinical trials and routine practice.

In 2011, Dejaco et al performed a systematic literature review (SLR) and Delphi study on remission and relapse criteria in PMR, and identified several important domains used to define these states (7). Moreover, a multi-outcome score, called the PMR activity-score (PMR-AS), has been developed and partly validated as a multi-item outcome instrument for disease activity (8, 9). Nevertheless, many studies have used different instruments to measure disease activity, remission, and relapse. This likely reflects that no measurement instrument has yet been thoroughly validated and no consensus established. Consequently, the definition and validation of outcomes for (in-)active disease, along with international endorsement for outcomes of remission and relapse in PMR remains both an unmet research and clinical need.

The present work is part of a project of the PMR Working Group of Outcome Measures in Rheumatology (OMERACT), which is a global, volunteer-driven, non-profit research group aiming to improve outcome measures in rheumatic diseases. The 'COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) criteria are used to define and validate outcomes for remission and relapse. Accordingly, this first step consists of a SLR summarizing current evidence for definitions of, and instruments for evaluating, these outcomes (10). This evidence may then be used together with qualitative research to generate conceptual descriptions and items or instruments for evaluating these outcomes, as broadly outlined in **supplementary figure 1**.

The objectives of this SLR were to 1) identify textual definitions (or descriptions) of disease activity, remission, and relapse; 2) identify items and instruments used to evaluate these outcomes; 3) describe how these instruments are combined; 4) assess which measurement properties were explicitly studied.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) were used; a PRISMA checklist is depicted in **supplementary table 1** (11). The SLR protocol was registered in PROSPERO (CRD42021255925).

All authors helped to draft the research questions which were eventually transformed into the respective Patient (P), Instrument (I), Outcome (O), and Measurement properties of Interest (MI) questions based on the OMERACT handbook and the strategy employed by Terwee et al (12, 13). A total of nine PICO questions were specified, as detailed in **supplementary table 2.**

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Information Sources and Search

PubMed/MEDLINE, EMBASE, CINAHL, Cochrane, and Epistemonikos were searched from inception to May 2021 and August 2023 using a search strategy developed in collaboration with an expert librarian (LF) with terms for PMR (*patients*), as well as for disease activity/remission/relapse (*outcome*). In order to increase the sensitivity of the search we did not apply any restrictions based on treatment or design. To test the search strategy, we checked if all articles included in the paper by Dejaco et al and Bolhuis et al were identified; sensitivity was increased until all pilot articles were found (7, 9). The final search strategy is shown in **supplementary text 1**.

Selection Process

Records were exported to Endnote and duplicate records removed. Study selection was performed by two independent investigators (TB, PB). Records were first screened based on title and abstract using the Rayyan online platform (https://www.rayyan.ai/) and thereafter, articles were assessed as full-texts (14). Disagreement between investigators was resolved through discussion. Both quantitative and qualitative studies were included if they were available in English as full text, included participants with isolated PMR discernible from giant cell arteritis (GCA) with at least 20 participants for quantitative studies (no limitations for qualitative studies), and presented original data that could be assigned to one of our research questions. For multiple papers concerning the same sample (e.g., studies on the same cohort) and using an identical instrument only one paper was included.

Data Extraction

A-priori standardized data extraction sheets that were tested with five articles, iteratively refined, and approved by all authors, were used (see **supplementary text 2**)**.** Two investigators (TB, PB) separately extracted study characteristics and definitions of remission, relapse, and disease-activity. The same investigators extracted individual items (e.g., VAS pain) from the definitions. These items were subsequently grouped into the categories: 'medical (treatment) history' (A), 'clinical signs' (B), 'laboratory markers' (C), 'current or planned treatment' (D), and PMR-AS. These categories were based on the previous SLR by Dejaco et al and the OMERACT domains for PMR (7, 15). Combination of items, in either composite outcome instruments or multi-outcome instruments, was then based on Wells *et al* as described in **supplementary text 2** (8). Finally, we extracted whether the measurement properties (structural and construct) validity, reliability, and interpretability were explicitly studied (16). As our objective was to collect definitions and instruments used in studies as comprehensively as possible, the risk of bias of the individual studies did not impact the conduct and conclusions of this SLR. Consequently, the risk of bias of the individual studies was not assessed. Venn-diagrams of the combination of categories were made using the R package ggVenn (version 0.19).

Results

Studies included

The (updated) search resulted in 5,718 records and ultimately 79 articles were included in this review, as depicted in **supplementary figure 2.** From the articles included we used 26, 36, and 53 articles for our research questions on disease activity, remission, and relapse, respectively.

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Study characteristics are shown in **table 1**. Overall, 64 observational, 15 interventional, and no qualitative studies were included. Interventional studies were more often multi-centre (32 vs. 85%), had smaller sample sizes (median (IQR) 60 (50-72) vs 177 (89-378)), and used disease-modifying anti-rheumatic drugs more frequently than observational studies. Studies from at least 3 continents were included, fulfilling the recommended minimum number of continents described in the OMERACT handbook and by Francis *et al* Characteristics of individual studies are summarized in **supplementary table 3** (17)**.**

Disease activity

Definitions

Full textual definitions of disease activity (PICO 7) are detailed in **supplementary table 4;** in general, disease activity was used for monitoring purposes, particularly to evaluate the change of disease activity at one visit compared to a preceding visit. Instruments for disease activity generally included laboratory markers. After 2007, the PMR-AS was the most common, and only multi-outcome, instrument used to measure disease activity with 89% [12/14] studies.

Individual Categories and Instruments

The categories and instruments used to measure disease activity are shown in detail in **table 2**. The category most frequently used was 'laboratory markers' [11/26 (42%)], followed by 'clinical signs' [6/26 (24%)], whereas none used 'medical history' or 'treatment-based instruments' to measure disease activity. For 'clinical signs', scales were either not described or inconsistently applied: in 4/9 (44%) studies at least one scale was not described (e.g. there was a description of a VAS for pain and disease activity, but no scale given regarding morning stiffness). Regarding the PMR-AS, three alternatives for calculating the PMR-AS without CRP were provided for patients treated with interleukin-6 inhibitors (18). Moreover, the PMR-impact scale (PMR-IS) described a multi-dimensional outcome with a subscale for symptoms (19)

Combinations and Weighting of Instruments

A combination of 'laboratory markers' and 'clinical signs' was used almost as frequently as 'laboratory markers' alone, as depicted in **figure 1.** In contrast, there were just two articles that only used 'clinical signs'(20, 24, 35). Apart from the PMR-AS, no multi-item instruments nor weighting of individual items was performed.

Measurement properties

Six articles studied measurement properties of the PMR-AS for monitoring disease activity: construct validity was examined in each study (6, 18, 31, 32, 34, 43) and both structural validity (6) and criterion validity (18) were assessed in one article each. More specifically, variants of the PMR-AS without CRP were assessed for patients treated with interleukin-6 inhibitors. One article studied multiple aspects, including reliability, validity and responsiveness, of both the PMR-IS as a whole and its subscales (19).

Remission

Definitions

Full textual definitions of remission are shown in **supplementary table 5;** there were some differences between the definition of remission among the included studies. Firstly, a distinction was

made based on current treatment, with some articles explicitly requiring absence of (GC-) treatment (25, 43-57) while others explicitly allowed treatment (31, 35, 58-60). Three studies specified differences between remission and GC-free remission, indicating that active treatment may be an independent additional parameter (39, 61, 62). Secondly, some articles drew a parallel between remission and patient response. Three articles required a response (of at least 70%) that permitted continued GC tapering (63-65). A third article mentioned that successful weaning and cessation was incorporated into the definition of remission without further elaboration on the precise methodology (46).

Individual Categories and Instruments

The categories and instruments used to measure remission are depicted in **table 3;** the categories 'clinical signs' and 'laboratory markers' were used most often (69% [25/36] and 67% [24/36] respectively). A small proportion of articles used instruments based on 'medical (treatment) history' [5/36 (14%)] or the PMR-AS [7/36 (19%)]. The most frequently used instruments were based on PMR symptoms [23/36 (64%)], followed by GC treatment [14/36 (43%)], erythrocyte sedimentation rate (ESR) and CRP [11/36 (31%) and 12/28 (33%) respectively]. Some articles provided an exact description of the type of PMR symptoms (e.g., pain or stiffness) [7/23 (30%)], the location of symptoms [3/23 (13%)], or the recall period [5/23 (22%)]. For VAS scales, no articles [0/3] indicated whether the minimum, maximum or average of symptom intensity was reported. It should be noted that most criteria (except for laboratory values) applied binary variables (e.g., symptoms present or absent [18/23 (78%)]), while continuous variables were rarely used (e.g., VAS pain ≥ 70% improvement). In addition, for some continuous instruments, different cut-offs were used in different articles (e.g., CRP < 3 mg/L, CRP ≤ 5 mg/L, or normal CRP for remission).

When assessing the definitions and instruments used to measure remission by year of publication, newer studies seemed to be more accepting of residual symptoms and newer studies seemed to use PMR-AS based remission criteria more often. Moreover, some differences were noted when comparing the definitions and instruments of the 10 interventional and 26 observational studies. From the 10 interventional studies, none incorporated medical history, 50% [5/10] incorporated clinical parameters, 40% [4/10] ESR and/or CRP, and 20% [2/10] treatment-based instruments. Of the 26 observational studies, 19% [5/26] incorporated medical history, 77% [20/26] clinical parameters, 46% [12/26] ESR and/or CRP, and 76% [18/26] treatment-based instruments. The PMR-AS was applied more often in interventional than observational studies ([4/26] 15% and [3/10] 30% respectively) . Additionally, a larger proportion of interventional studies seemed to accept residual PMR symptoms, with 60% [6/10] accepting either 50 or 70% improvement (27, 39, 41, 64, 65, 71) , compared to observational studies which all required the complete absence of PMR symptoms.

Combinations and Weighting of Instruments

The categories of instruments that were combined most frequently to measure remission were clinical signs and laboratory markers, as shown in **figure 1.** All composite instruments weighted individual items equally and all composite outcome instruments used an 'and' to connect the criteria, thus requiring fulfilment of all items (see **table 3)**. The PMR-AS, which was the only multi-outcome instrument, weighted individual items differently (31). Morning stiffness, for example, was measured in minutes and multiplied by 0.1.

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Measurement properties

Construct validity of the PMR-AS based remission criteria were studied in one article (31). More specifically, both a patient satisfaction of 1 (from a range 0-5) and a VAS patient global < 10 (from a range 0-100) corresponded to a PMR-AS average of 0.7 (range 0–3.3).

Relapse

Definitions

Full textual definitions of relapse are shown in **supplementary table 6;** significant heterogeneity in relapse definition was apparent. The most prominent heterogeneity between studies was in the distinguishment between relapse and recurrence in 25% [13/53] of the studies (32, 44, 49, 54, 55, 67, 72-78). Relapse, contrary to recurrence, most often required cases to (have recently) be(en) on treatment, although there was one article that defined a relapse based on the absence of (GC) treatment (71). In five articles, no distinction was made between relapse and recurrence; a relapse could occur both during treatment and after its discontinuation (53, 66, 79-81). Another particularity is the divergent use of the term flare to describe either: a worsening of symptoms (38, 50, 75, 82) sufficient enough to warrant an increase in treatment (45, 51, 60, 83), the transition from inactive to active disease (84), or relapse (34). Lastly, a previous (partial or complete) response to therapy was never mentioned explicitly, although it may be inferred from 87% [40/46] of the studies by using the terms 'reappearance' or 'worsening' of clinical signs (32, 44, 45, 47-54, 57, 60-62, 65-67, 69-77, 79, 80, 83, 85-93).

Individual Categories and Instruments

The categories and instruments used to measure a relapse are detailed in **table 4.** 'Clinical signs' were mentioned most often with 92% [49/53] of studies, while 'laboratory markers' and 'current/planned treatment' were used in 45% [24/53] and 40% [21/53] of studies, respectively. By contrast, 'medical (treatment) history' and the PMR-AS were rarely included in relapse criteria (8% [4/53] and 4% [2/53] respectively). The instruments that were most frequently used to measure a relapse were PMR symptoms [45/53 (85%)], ESR [21/53 (40%)], CRP [23/53 (43%)], and GC dose escalation [17/53 (32%)]. A minority of articles provided an explicit description of the type of PMR symptoms (e.g., pain or stiffness) [10/45 (22%)] the location of symptoms [9/45 (20%)] or the recall period [2/45 (4%)]. Binary variables for clinical signs were used most frequently (44/45 [98%]), rather than continuous variables with cut-offs (e.g., VAS pain ≥ 70% improvement). Similar to remission, exact criteria for instruments differed across studies e.g., five different cut-off values were used for CRP ranging from > 3 mg/L to > 30 mg/L.

When assessing the definitions and instruments for relapse according to the year of publication, we observed no particular differences. However, there were some notable findings when comparing the 8 interventional and the 45 observational studies. None of the 8 interventional studies utilised medical history to measure relapse, while 88% [7/8] used clinical signs, 63% [5/8] ESR and CRP, and 13% [1/8] of studies utilised an increase in (GC). Of the 45 observational studies, medical history was incorporated by 16% [7/45], clinical signs by 93% [42/45], ESR and/or CRP by 44% [20/45], and an increase in treatment by 40% [18/45] of studies. The PMR-AS was used in a one observational (PMR ≥ 9.35 and PMR-AS change ≥ 6.6) and one interventional study (PMR-AS score ≥ 10).

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Combinations and Weighting of Instruments

The most common combinations of categories used to measure a relapse was that of 'clinical signs' and 'laboratory markers', as shown in **figure 1.** All composite instruments weighted items equally. However, an article by Weyand *et al* required fulfilment of at least three out of five items, thereby combining items in a composite outcome instrument through 'or' criteria (95). The PMR-AS remained the only multi-outcome instrument utilizing weighed items (e.g., morning stiffness in minutes is multiplied by 0.1).

Measurement properties

PMR-AS based relapse criteria were explicitly studied in two articles (34, 84). These articles studied PMR-AS based cut-offs for relapse as well as the linkage of these criteria with the physician judgement and GC dose (escalation).

Discussion

This SLR on definitions, items, and instruments used to determine remission, relapse and disease activity in patients with PMR demonstrates that there is heterogeneity with the conceptual definitions, although there seems to be consensus concerning some aspects. Instruments used to measure these outcomes often involve multiple domains but are frequently poorly described. Finally, although the PMR-AS is increasingly used for disease activity, its criteria for remission and relapse still necessitate further study.

Based on the various definitions spanning initial presentation until either (sustained) treatment-free remission or relapse, and recurrence, we propose a disease state transition model, shown in **figure 2.** Disease activity was mainly used for measuring (longitudinal) change during follow-up, remission for indicating a (cross-sectional) disease state with absent or sufficiently low disease activity (to taper GC), and relapse to either express as a disease state or dynamic change therein for patients who previously achieved (either complete or partial) remission. A complex conceptual relationship between relapse and remission was found; remission could only occur in the absence of relapse/recurrence and relapse could only occur after a previous period of remission. However, the absence of relapse did not necessarily mean presence of remission i.e. implying there may be an in-between state of disease activity. Moreover, in some instances, similarly as in diseases such as RA, remission could be on or off-therapy, suggesting treatment may be considered complimentary for higher order outcomes (e.g., remission with GC, without GC, and without GC-sparing agent) (96).

Clinical signs of interest in PMR studies are frequently mapped to the "inner" OMERACT core domains of pain and stiffness, and to a lesser extent to the "outer" domains of patient global and fatigue (15). Although instruments for physical function are frequently evaluated as a secondary outcome, physical function itself was typically neglected in the context of remission and relapse measurement, except for the elevation of the upper limbs in the PMR-AS. This may be due to limited information on its measurement properties in PMR e.g., for the HAQ-DI and mHAQ (6, 97). Unlike physical function, physician assessment is not included as a core OMERACT domain for PMR yet, even though it was commonly used to assess disease activity. In rheumatoid arthritis and spondyloarthropathies, physician global assessment of disease activity has been incorporated in some (e.g., CDAI and SDAI) but not all disease activity scores (e.g., the DAS28 and BASDAI/ASDAS) (98). However, there may be a discrepancy between physician and patient perspectives when evaluating disease activity (e.g., inclusion of non-specific pain and depression by patients but not by doctors), which in turn may limit measurement properties of patient and physician assessment of

disease activity (states). This may also explain why this item did not reach consensus in a previous Delphi study on instruments for remission and relapse in PMR (7).

When choosing specific scales and cut-offs, or binary requirements for instruments in the context of remission and relapse, several aspects need to be considered. Firstly, a complete absence of clinical signs may not be an achievable goal in many patients, as discussed previously (99). Therefore, scales in which some residual symptoms are acceptable (e.g., VAS/NRS for pain or morning stiffness) may result in more feasible treatment targets (8). Secondly, it is questionable whether dichotomizing components of a composite instrument, without weighting, is best practice from a measurement perspective, unless each item is agreed to be of exactly equal importance. Another option would be multi/composite outcome instruments in which residual symptoms of one item may be compensated by another item (8). However, such a composite outcome instrument was only identified once in this literature review and concerned the PMR-AS, which was mostly used to measure disease activity (9). The PMR-AS was also the only instrument for which measurement properties were assessed in the context of disease activity (states). However, its criteria for remission and relapse have been used scarcely and, consequently, information on their psychometric properties is limited.

Different (cut-off) criteria were also used for the inflammatory markers CRP and ESR. An advantage of using "(ab)normal" as criteria for remission and relapse as outcome instead of consistent specific cut-offs, is the minimization of differences in laboratory procedures and reference values based on sex and age. Nonetheless, a criterion requiring an "abnormal" CRP/ESR may have some disadvantages. Firstly, up to 20% of PMR patients may have a normal CRP/ESR at diagnosis and up to 27% of patients with raised acute phase reactants at diagnosis may not have abnormal values during relapse (7). Secondly, IL-6 inhibiting agents may normalize CRP and ESR independent of disease activity, thereby either fulfilling remission criteria or not fulfilling relapse criteria when the opposite may be true (100). Thirdly, a patient's personal "normal" CRP/ESR values are determined by comorbidity burden and laboratory "normal" (reference) values are in turn determined by local comorbidity patterns.

Some strengths and limitations of this study should be discussed. Strengths include the various goals, designs and populations, thereby supporting the generalizability of results. Limitations are that no qualitative studies – exploring, for example, patient-centered views - were found. Such studies could have helped to provide a more comprehensive view of remission and relapse. Furthermore, research in PMR utilizing the COSMIN methodology on composite criteria like remission and relapse is still limited and, therefore, some aspects of added value may have been missed.

In conclusion, a conceptual model of remission and relapse as a PMR disease state (transition) and measurement domains and instruments for these outcomes are under development. Qualitative research is required and should include aspects like the conceptual definitions, the multiple outcome domains involved, the choice of instruments for these domains, and how instruments should be combined (8). A broad project outline of future steps for the OMERACT PMR project to establish outcomes for remission and relapse in PMR is displayed in **supplementary figure 1.** Items and instruments need to be selected and both the (sub)-instruments for individual domains (e.g., for pain) and the global instruments (for disease activity, remission, and relapse) need to be validated.

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Statements

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Transparency declaration. The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained

Data availability. The data underlying this article are available in the article and in its online supplementary material.

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Figures

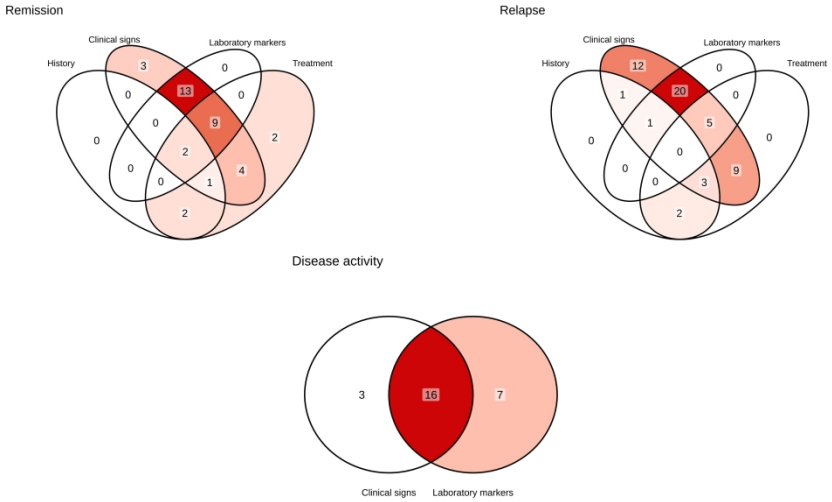
Figure 1. Venn-diagram(s) regarding Combination of Instruments From Categories Used to Measure Remission, Relapse, and Disease Activity**.**

Figure 2. Graphical representation of our proposals for remission, relapse, and recurrence based on this review.

Note. In red are the conceptual definitions of relapse and recurrence, indicating both the dynamic disease state transition (through an arrow) from inactive to active disease and the final (active) disease state through a square at the end. In green are the conceptual definitions of remission, indicating a static inactive disease (through a circle). Dotted arrows indicate transitions through treatment change. *Abbreviations*. PMR, polymyalgia rheumatica; T-, no active treatment; T+ with active treatment.

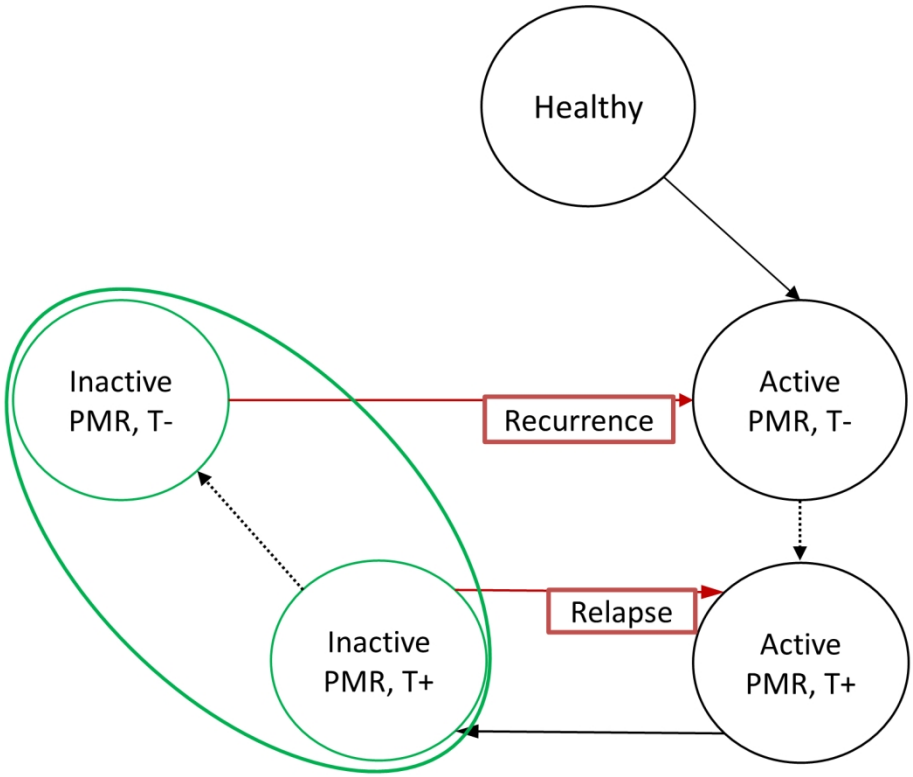
Tables

Supplements



Venn-diagram(s) regarding Combination of Instruments From Categories Used to Measure Remission, Relapse, and Disease Activity.

1291x726mm (118 x 118 DPI)



Graphical representation of our proposals for remission, relapse, and recurrence based on this review.

150x120mm (300 x 300 DPI)

Characteristics	Total No. studies = 79
Study design, observational	64 (81%)
• Observational design, cohort	56 (88%)
○ cohort, retrospective	26 (47%)
○ cohort, prospective	22 (40%)
○ cohort, not specified	7 (13%)
• Observational design, cross-sectional	8 (13%)
Study design, interventional	15 (19%)
• Interventional, comparison	11 (73%)
• Interventional, without control	4 (27%)
Monocentre, no. (%)[a]	45 (58%)
Year(s) study patients where included (start), median (range)[b]	2007 (1970-2022)
Sample size, median (range)	72 (20-1420)
Sex, median % female (IQR)[c]	66% (58-72)
Age, median age in years (IQR)[d]	72 (69-74)

Table 1. Study Characteristics.

Notes. [a] No. studies = 77. [b] No. studies = 47. [c] No. studies = 67. [d] No. studies = 69. *Abbreviations*. IQR, interquartile range; No., number of.

Article	Clinical Signs	Laboratory markers	PMR-AS
Eghtedari, 1976 (20)		ESR	
Esselinckx, 1977 (21)	proximal girdle muscle pain; morning stiffness; general wellbeing	ESR; Plasma viscosity	
Jones, 1981 (22)		ESR	
Benlahrache, 1983 (23)		ESR; haptoglobin; orosomucoid	
Kyle, 1989 (24)	scale 0-2 for proximal girdle muscle; morning stiffness; GCA symptoms; other illness		
Corrigall, 1997 (25)	proximal girdle muscle pain VAS; morning stiffness; Synovitis	ESR; Complete blood count; L6; lymphocytes	
Dolan, 1997 (26)	proximal girdle muscle pain VAS; morning stiffness	ESR; Complete blood count	
Dasgupta, 1998 (27)	morning stiffness; disease activity VAS	ESR; Complete blood count	
Cutolo, 2002 (28)		ESR; CRP; IL-6	
Leeb, 2003 (6)			PMR-AS
Barnes, 2004 (29)		ESR; CRP	
Brun, 2005 (30)		ESR	
Leeb, 2007 (31)			PMR-AS

Macchioni, 2009 (32)			PMR-AS
Kreiner, 2010 (33)			PMR-AS
Cleuziou, 2012 (34)			PMR-AS
McCarthy, 2013			PMR-AS
Albrecht, 2018 (35)	Rheumatologist NRS		
Devauchelle-Pensec, 2018 (18)			PMR-AS; clin-PMR-AS; ESR-PMR-AS; CRP-imp PMR-AS
Nakajima, 2020 (36)			PMR-AS
Owen, 2020 (37)			PMR-AS
Marsman, 2021			PMR-AS
Sattui, 2022(40)			PMR-AS
Devauchelle-Pensec, 2022(41)			PMR-AS
Horai, 2023(42)		CRP, ESR, Matrix Metalloproteinase	
Twohig, 2023(19)	Pain, stiffness, weakness and fatigue NRS and duration		

Table 2. Instruments Used to Measure Disease Activity in PMR.

Notes. ESR-PMRAS was calculated in the same way as the PMR-AS, but used ESR (in millimetres per hour * 0.1) instead of CRP. Clin-PMR-AS was the sum of morning stiffness, elevation of the upper limbs, physician VAS and pain VAS. CRP-imp PMR-AS was calculated as 1.12* (clin-PMR-AS) + 0.26.

Abbreviations. GCA, giant cell arteritis; VAS, visual analogue scale; NRS, numerical rating scale; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; IL-6, interleukin-6; PMR-AS, Polymyalgia Rheumatica Activity Score.

Article	History (A)	Clinical signs (B)[a]	Laboratory (C)[b]	Treatment (D)	PMR-AS (E)	Combination and Weighting [c]
Chuang, 1982 (55)	Previously treated with GC/NSAIDS	PMRS absent		Currently no treatment		A+B+D
Van der Veen, 1996 (44)				Currently no GC and trial medication		D
Corrigall, 1997 (25)		Clinical judgement				B
Dasgupta, 1998 (27)		VAS pain ≥ 50% improvement and duration of morning stiffness < 30 min	ESR < 20 and Hb > 12 g/dl			B+C
Cantini, 2000 (54)	No relapse or recurrence			Currently no GC treatment		A+D
Martinez-taboda, 2004 (66)		PMRS absent	APR normal			B+C
Kremers, 2005 (56)	No relapse in 5 years	PMRS absent	ESR normal	GC ≤ 5 mg/day		A+B+C+D
Salvarani, 2007 (67)		PMRS absent	ESR normal			B+D
Leeb, 2007 (31)					PMR-AS < 1.5	E

Cimmino, 2011 (63)	PMRS ≥ 70% improvement [d]	ESR normal and CRP normal			B+C
Kim, 2012 (45)	PMRS absent > 2 months		No treatment > 2 months		B+D
Lee, 2013 (47)	PMRS absent	ESR normal and CRP normal	No current treatment		B+C+D
Mccarthy, 2013 (43)	PMRS absent > 6 weeks		Stable GC treatment > 6 weeks		B+D
Do-nguyen, 2013 (46)			No current GC treatment	PMR-AS (no cut-off specified)	D+E
Yurdakul, 2015 (53)	PMRS absent	APR normal	No current treatment		B+C+D
Devauchelle-pensec, 2016 (68)				PMR-as ≤ 10	E
Cutolo, 2017 (64)	PMRS VAS ≥ 70% improvement and duration of morning stiffness ≥ 70% improvement	CRP > 70% improvement and/or < 2× ULN			B+C
Miceli, 2017 (59)	No girdle pain	ESR ≤ 40 and/or CRP ≤ 5	Current GC treatment < 5 mg/day		B+C+D

Shbeeb, 2018 (52)	No relapse			No current GC treatment		A+D
Albrecht, 2018 (35)		Clinical judgement				B
Do, 2018 (69)		PMRS absent 1 year after GC initiation	CRP < 3 at 1 year after start GC			B+C
Jung, 2019 (51)		PMRS absent > 2 months		No current treatment > 2 months		B+D
Birra, 2019 (58)		No girdle pain	ESR ≤ 40 and CRP ≤ 5	Current GC treatment ≤ 5 mg/day		B+C+D
Hattori, 2020 (50)	No relapse in 30 months	PMRS absent	ESR ≤ 30 and CRP ≤ 3	No current GC treatment		A+B+C+D
Owen, 2020 (37)					PMR-AS < 9.35	E
Van Sleen, 2020 (61)		PMRS absent ≥ 6 months		No current GC treatment ≥ 6 months		B+D
Aoki, 2020 (48)		PMRS absent	CRP normal	No current GC treatment		B+C+D
De la Torre, 2020 (49)				No current GC treatment		D
Emamifar, 2021(65)		PMR VAS ≥ 70% improvement and duration morning	ESR < 20 mm/h and CRP < 6			B+C

	stiffness ≥ 70% improvement				
Marsman, 2021(39)				PMR-AS ≤ 10	F
Sattui, 2022(40)				PMR-AS < 1.5	F
Bonelli, 2022(57)	PMRS absent	ESR normal and/or CRP normal	No current treatment		B+C+D
Devauchelle-Pensec, 2022(41)				PMR-AS ≤10	F
Perricone, 2022(60)	PMRS absent for 3 months	ESR < 40 mm/h and CRP < 5 for 3 months	Current GC treatment ≤ 7.5 mg/day for 3 months		B+C+D
Yamaguchi, 2023(62)	PMRS absent	CRP normal	No current treatment		B+C+D
Ishiguro, 2023(70)	No girdle pain/stiffness				B

Table 3. Instruments Used to Measure Remission in PMR.

Notes. Within columns for categories, items are separated by 'and' when both are required and by 'and/or' if either is required. [a] PMRS are PMR symptoms not otherwise specified unless explicitly stated. [b] ESR is displayed in mm/hour and CRP in mg/L. [c] Combination of items by + indicates an AND requirement. *Abbreviations*. PMR, polymyalgia rheumatica; GC, glucocorticoids; NSAIDS, Non-steroid anti-inflammatory drugs; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; Hb,

haemoglobin; CRP, c-reactive protein; ULN, upper limit of normal; APR, acute phase reactants; mg, milligram; PMR-AS, Polymyalgia Rheumatica Activity Score;

Article	History (A)	Clinical signs (B)[a]	Laboratory (C)[b]	Treatment (D)	PMR-AS (E)	Combination and Weighting [c]
Chuang, 1982 (55)	After previous clinical improvement on treatment	PMRS reappearance		Increase in GC dose		A+B+D
Behn, 1983 (85)		PMRS reappearance				B
Ayoub, 1985 (72)		PMRS reappearance		Increase in GC dose		B+D
Kyle, 1989 (24)		Proximal girdle (muscle) pain, GCA symptoms and other illness				B
Cimmino, 1994 (71)		PMRS reappearance		Increase in GC dose		B+D
Van der Veen, 1996 (44)		PMRS reappearance	Increase of ESR and/or CRP by 100%			B+C
Caplanne, 1996 (94)		Proximal girdle (muscle) pain reappearance and (morning) stiffness reappearance				B

Gonzalez-Gay, 1997 (82)	After previously asymptomatic phase	PMRS reappearance		Increase in GC dose	A+B+D
Salvarani, 1998 (73)		Articular signs or symptoms reappearance			B
Weyand, 1999 (95)		1) patient global assessment ≥ 2 on 0-5 scale; 2) physician global assessment ≥ 2 on 0-5 scale; 3) patient pain assessment ≥ 3 on VAS; 4) morning stiffness ≥ 60 minutes	ESR abnormal		(B1+B2+B3+B4+C) ≥ 3 [d]
Cantini, 2000 (54)		Articular signs or symptoms reappearance		Increase in, or reinstitution of, GC dose	B+D
Gonzalez-Gay, 2002 (74)	After previous clinical	PMRS flare up			A+B

	improvement on treatment				
Martinez-Taboda, 2004 (66)		PMRS reappearance		Increase in GC dose	B+D
Caporali, 2004 (75)		PMRS flare up	ESR and/or CRP abnormal		B+C
Kremers 2005 (56)	occurence ≥ 30 days after diagnosis	PMRS worsening		Increase in GC dose (≥ 5 mg/day)	A+B+D
Boiardi, 2006 (76)		PMRS reappearance	ESR > 30 and/or CRP > 5		B+C
Cimmino, 2006 (77)		Proximal girdle (muscle) pain and (morning) stiffness flare up	ESR > 30 and/or CRP > 5		B+C
Hutchings, 2007 (86)		PMRS reappearance		Increase in dose, or maintenance beyond schedule of, GC	B+D

Salvarani, 2007 (67)	Proximal girdle (muscle) pain reappearance and (morning) stiffness reappearance	ESR > 30 and/or CRP > 5	During GC tapering	B+C+D
Blockmans, 2008 (87)	Proximal girdle (muscle) pain reappearance and (morning) stiffness reappearance ≥ 4 week	ESR > 40 and/or CRP > 30		B+C
Binard 2008 (84)	Clinician judgement			B
Pulsatelli, 2008 (79)	PMRS reappearance	ESR > 30 and CRP > 5		B+C
Macchioni, 2009 (32)	PMRS reappearance	ESR > 30 and/or CRP > 5		B+C
Mackie, 2010 (88)	PMRS worsening		Increase in GC dose	B+D
Cleuziou, 2012 (34)	Clinician judgement			B

Kim, 2012 (45)	PMRS worsening		Increase in GC dose	B+D
Lee, 2013 (47)	PMRS reappearance or worsening	ESR > 30 and/or CRP > 5		B+C
Yurdakul, 2015 (53)	PMRS reappearance	ESR abnormal and/or CRP abnormal		B+C
Fukui, 2016 (80)	PMRS reappearance or worsening	ESR > 30 and/or CRP > 5		B+C
Shbeeb, 2018 (52)	PMRS reappearance	ESR abnormal and/or CRP abnormal	Increase in GC dose	B+C+D
Do, 2018 (69)	PMRS reappearance or worsening	ESR > 40 and/or CRP > 3	During GC tapering	B+C+D
Jung, 2019 (51)	PMRS worsening		Increase in GC dose	B+D
Hattori, 2020 (50)	PMRS flare up			B
Okazaki, 2020 (90)	Proximal girdle (muscle) pain worsening	CRP abnormal		B+C

Owen, 2020 (37)	Previous PMR-AS < 9.35				PMR-AS score ≥ 9.35 and/or PMR-AS change ≥ 6.6	A+F
Van Hemelen, 2020 (81)	Previous clinical improvement on treatment			Increase in GC dose and/or addition of a GC-sparing agent		A+D
Van Sleen, 2020 (61)		PMRS reappearance				B
Aoki, 2020 (48)		PMRS reappearance	CRP abnormal	Increase in GC dose		B+C+D
Ayano, 2020 (89)		PMRS reappearance	ESR and/or CRP abnormal	Increase in GC dose and/or addition of a GC-sparing agent		B+C+D
De la Torre, 2020 (49)		Proximal girdle (muscle) pain	ESR and/or CRP abnormal			B+C

	reappearance and/or (morning) stiffness reappearance			
Marsman, 2021 (38)	Clinician judgement			B
Mork, 2021 (91)	PMRS reappearance	CRP abnormal		B+C
Aoki, 2021(92)	PMRS worsening		Increase in, or reinstitution of, GC dose	B+D
Emamifar, 2021(65)	Proximal girdle (muscle) pain reappearance and/or (morning) stiffness reappearance and/or GCA symptoms	ESR and/or CRP abnormal		B+C
Marsman, 2021(39)	Clinician judgement and PMRS reappearance	ESR and/or CRP abnormal		B+C

Bonelli, 2022(57)		Proximal girdle (muscle) pain reappearance				B
Devauchelle-Pensec, 2022(41)					PMR-AS score ≥ 10	F
Perricone, 2022(60)		PMRS reappearance or worsening	ESR > 40 and/or CRP > 5			B+C
Bolhuis, 2022(78)	occurence ≥ 30 days after diagnosis			Increase in GC dose and/or addition of a GC-sparing agent		A+D
Yamaguchi, 2023(62)		PMRS reappearance or worsening	CRP abnormal			B+C
Ishiguro, 2023(70)		PMRS reappearance				B
Vinicki, 2023(93)		PMRS reappearance				B
Conticini, 2023(83)		PMRS reappearance	ESR and/or CRP abnormal			B+C

Table 4. Instruments Used to Measure Relapse in PMR.

Notes. Within columns for categories, items are separated by 'and' when both are required and by 'and/or' if either is required. [a] PMRS are PMR symptoms not otherwise specified unless explicitly stated. [b] ESR is displayed in mm/hour and CRP in mg/L. [c] Combination of instruments from different categories by + indicates an AND requirement. [d] Requirements for at least 3 out of 5 items had to be met for relapse. *Abbreviations*. PMR-AS, Polymyalgia Rheumatica Activity Score; GCA, giant cell arteritis; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; GC, glucocorticoids; mg, milligram.

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

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

Joint relief in PsA:

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

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

Click here to visit our HCP portal and learn more

Skin clearance in PsO:

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

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

Axial joint relief in PsA:

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

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

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

8 years

A **consistent safety profile** with **over 8 years** of real-world experience[5,6,11]

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

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

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

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

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

NOVARTIS

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

UK | May 2024 | 425034

Cosentyx® (secukinumab) Great Britain Prescribing Information.

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

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

UK | 290802 | June 2023

Adverse Event Reporting:

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

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

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

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

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

UK | 284832 | May 2023

Adverse Event Reporting:

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

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