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**P10 HAEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS IN THE RETURNING TRAVELLER WITH FEVER... ESPECIALLY IF SLOW TO DEFERVESCE ON TREATMENT!**

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**Introduction:** Haemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening hyperinflammatory disorder characterised by dys-regulated immune activity resulting in malignant inflammation and multi-organ failure. Early recognition and treatment reduces mortality. HLH associated with rickettsial infection is described, and we present two cases of HLH secondary to severe rickettsial infection. We

compare clinical and biochemical responses to IV methylprednisolone versus anakinra after HLH was suspected, identified and treated early in both presentations. We recommend a low index of suspicion for HLH for the returning traveller with fever where rickettsial infection is considered possible, especially if patients are slow to defervesce on treatment with doxycycline.

**Case description:** Case 1 was of a 63-year old-male with no past medical history of note, who presented to hospital with fevers, rigors, loose stool and jaundice one week after returning from Ethiopia. He had stayed exclusively in Addis, had not visited any rural locations and did not recall any insect bites during his trip but had contact with one dog. On review, he denied any symptoms of systemic upset prior to his presentation and had no symptoms suggestive of an underlying rheumatological disease other than myalgia and arthralgia. On examination, he had no evidence of synovitis or rash, but had hepatosplenomegaly. He was diaphoretic with daily temperature spikes of up to > 39 degrees Celsius. He was investigated extensively as an inpatient, but no clear infectious trigger was identified. He was treated empirically on admission with IV ceftriaxone, but continued to deteriorate and a state of hyperinflammation was suspected. By day two of his admission, his HScore was 166 and he improved rapidly after treatment with oral doxycycline and two doses of IV methylprednisolone.

Case 2 was a 44-year-old male with no past medical history of note, who presented to hospital with fever, myalgia and arthralgia two weeks after returning from Cameroon. Again, he denied any rural travel and did not recall having sustained any insect bites or animal exposure. On review, he denied systemic upset prior to this presentation or other symptoms suggestive of an underlying rheumatological disease. Clinically, he had no rash, synovitis or organomegaly. He was also treated empirically with IV ceftriaxone. Two days later, initial infection screening was negative but fever persisted, and doxycycline was added. Fever persisted still, and by day four, HScore was 167. Anakinra was initiated, resulting in marked clinical improvement.

**Discussion:** Fever in the returning traveller is often associated with serious illness and the initial focus of evaluation should be trying to identify infections that are potentially life-threatening, treatable or transmissible. In both cases, this was done and patients were investigated thoroughly and extensively, but no clear infectious trigger had been identified at the time of deterioration. Treatment was therefore empirical as both people were at risk of rickettsial infection. In both cases, systemic symptoms progressed and, despite a lack of immediate identification of a causal agent, there was recognition of a hyperinflammatory response to a likely infectious trigger. Hyperinflammation and HLH have a high mortality, prompting discussion in respective HLH MDTs for initiation of immunomodulation in parallel to anti-microbial treatment. Interestingly, in case one, doxycycline was started at the same time as IV methylprednisolone, which raises the question of whether the clinical and biochemical improvement was due to the antimicrobial treatment rather than corticosteroids. However in case two, there was no immediate improvement with introduction of oral doxycycline, and it was after anakinra was introduced at least two days later that there was a dramatic clinical and biochemical response.

Both cases raise the question of how much inflammation is acceptable in the context of acute inflammation when the body is trying to respond to, and tackle, an infectious agent. At what point does the inflammatory response become harmful, and is consideration and introduction of an immunomodulatory or immunosuppressive agent in the context of unidentified infection dangerous? What is the local pathway for urgent discussion of patients with hyperinflammation? These cases highlight that while the cause or trigger for HLH is unknown, the patient still needs immunomodulation promptly to prevent the potentially life-threatening manifestations of hyperinflammatory syndromes. Joint working between infectious disease and rheumatology is imperative.

**Key learning points:**

- It is recognised that systemic hyperinflammation and HLH can occur in nearly any inflammatory state, but certain predisposing conditions and/or triggers warrant a high index of suspicion. These cases suggest that rickettsial infection, when considered, should prompt the clinician to have a low index of suspicion for associated HLH, and that early recognition using the HScore and treatment can lead to a good outcome. Although the exact mechanisms that trigger HLH are not fully understood, it is interesting to consider why certain infections are more likely to cause it than others. In rickettsial disease, the fourth most common infectious group of diseases associated with HLH, it is likely that the cytokine storm associated with the immune response to rickettsial infection may be involved in the pathogenesis of complicated typhus that can lead to life-threatening complications such as ARDS, DIC and HLH. It is possible that early identification of HLH in our two cases with early control of the cytokine storm with immunosuppressive and immunomodulatory treatment halted progression of further life-threatening

complications associated with rickettsial disease. Although treatment in our cases with doxycycline was started early, it is interesting to think what would have happened if treatment for identified HLH was started promptly, but specific anti-rickettsial treatment delayed. Would we have allowed the host more time to mount an appropriate level of response to infection pending decision about correct and definitive treatment, or would ongoing manifestations of life-threatening complications have ensued regardless? It is also interesting to note that in both cases, only a short course of immunosuppression was required to treat HLH which is not always the case with infectious triggers of HLH. This raises the question of whether early treatment can also lead to shorter duration of disease, and highlights the role of the MDT approach to HLH.

# Biologics may be **less effective** in patients who are **overweight**<sup>1,2</sup>



**Eligible patients, weighing  $\geq 90$ kg with PsA and concomitant moderate to severe PsO, may need an individualised treatment approach<sup>4,5</sup>**



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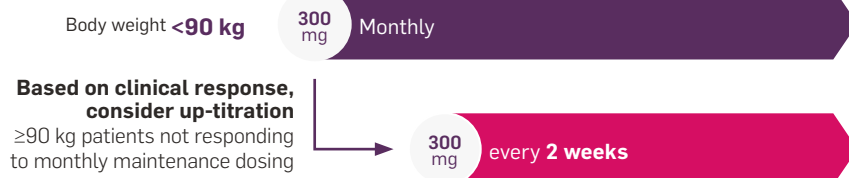
**>6 in 10** adults over the age of 18 years in England are estimated to be overweight or living with obesity<sup>3</sup>

Cosentyx<sup>®</sup> (secukinumab) provides **flexible dosing** based on your eligible patients' needs<sup>\*4,5</sup>

#### Loading dose



#### Maintenance dosing



Adapted from Cosentyx<sup>®</sup> (secukinumab) SmPC.<sup>4,5</sup>

\*For adult patients with PsA and concomitant moderate to severe PsO, the recommended dose of Cosentyx is 300 mg with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by **monthly maintenance dosing**. Based on clinical response, a maintenance dose of 300 mg **Q2W** may provide additional benefit for patients with a body weight of **90 kg or higher**.<sup>4,5</sup>

Cosentyx is indicated for the 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 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; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional 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 and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.<sup>4,5</sup>

PsA, psoriatic arthritis; PsO, plaque psoriasis; Q2W, every 2 weeks.

**References:** **1.** Warren RB, et al. *J Invest Dermatol* 2015;135:2632–2640; **2.** Warren RB, et al. *Br J Dermatol* 2019;180(5):1069–1076; **3.** Office for Health Improvement and Disparities. Obesity profile: short statistical commentary May 2024. Available at: <https://www.gov.uk/government/statistics/update-to-the-obesity-profile-on-fingertips/obesity-profile-short-statistical-commentary-may-2024> [Accessed August 2024]; **4.** Cosentyx<sup>®</sup> (secukinumab) GB Summary of Product Characteristics; **5.** Cosentyx<sup>®</sup> (secukinumab) NI Summary of Product Characteristics.

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## **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  $\geq$  50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. **Psoriatic Arthritis:** For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNF $\alpha$  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  $\geq$  50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. **Hidradenitis suppurativa:**

## **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  $\geq$  50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. **Psoriatic Arthritis:** For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNF $\alpha$  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  $\geq$  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. **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 ( $\geq$ 1/10):** Upper respiratory tract infection. **Common ( $\geq$ 1/100 to <1/10):** Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. **Uncommon ( $\geq$ 1/1,000 to <1/100):** Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. **Rare ( $\geq$ 1/10,000 to <1/1,000):** anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. **Not known:** Mucosal and cutaneous candidiasis (including oesophageal candidiasis). **Infections:** Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). **Neutropenia:** Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. **Hypersensitivity reactions:** Urticaria and rare cases of anaphylactic reactions were seen. **Immunogenicity:** Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. **Other Adverse Effects:** The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 – £304.70; PLGB 00101/1029 – 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 – 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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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 ( $\geq$ 1/10):** Upper respiratory tract infection. **Common ( $\geq$ 1/100 to <1/10):** Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. **Uncommon ( $\geq$ 1/1,000 to <1/100):** Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. **Rare ( $\geq$ 1/10,000 to <1/1,000):** anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. **Not known:** Mucosal and cutaneous candidiasis (including oesophageal candidiasis). **Infections:** Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). **Neutropenia:** Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. **Hypersensitivity reactions:** Urticaria and rare cases of anaphylactic reactions were seen. **Immunogenicity:** Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. **Other Adverse Effects:** The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 – 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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