Mapping oSCORAD and SCORAD to EASI to facilitate large-scale meta-analyses of molecular data

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Dear Editor, atopic dermatitis (AD) represents the most common chronic inflammatory skin disorder, affecting people of all ages and ethnicities and having a substantial impact on quality of life. [1] Over recent years, molecular studies of genome [2], methylome [3] and transcriptome [4] have identified disease mechanisms and therapeutic targets. More recently, international research initiatives, such as BIOMAP (IMI2 grant agreement No 821511, https://biomap-imi.eu), have facilitated integrative analyses of unprecedented scale, furthering our understanding of AD and related diseases.

To monitor disease course and response to treatment, multiple severity scores have been developed, including the Eczema Area and Severity Index (EASI) and (objective) SCORing of Atopic Dermatitis ((o)SCORAD). [5] An international harmonization process (HOME, http://www.homeforeczema.org/) has recommended core outcome measures for clinical research, but historic datasets are not harmonized. The resulting lack of homogeneous phenotype information is a limiting factor in clinically-important large-scale analyses, such as transcriptomic meta-analyses of disease severity.

Previous studies have shown moderate-to-strong correlation between severity scores, e.g. between EASI and oSCORAD (R^2=0.87) as well as EASI and SCORAD (R^2=0.85). [6] However, to date no direct mathematical or clinically representative relationship has been derived. We therefore developed methods for non-linear mapping between the three most widely used scoring systems.

We used 7485 paired measurements of oSCORAD, SCORAD and EASI taken from 1501 adolescent and adult participants (44% female, 56% male, median [lower quartile (LQ), upper quartile (UQ)] age (in years) 39 [29, 53], median oSCORAD 39 [28, 51], median SCORAD 51 [36, 65] and median EASI 12 [6, 22] at study inclusion) of the TREATgermany registry. [7] Implementations of all models are available at https://github.com/huebenthal-cau/mapSeverityScores.

We tested a linear model (LM, lm(y~x)), a non-linear model (NLM, nls(y~b0+b1·x+b2·x2)) and locally estimated scatterplot smoothing (LOESS, loess(y~x)). Quality of fit was assessed using mean absolute error (MAE). Based on repeated cross-validation (10 repeats, 50 folds) we estimated the median [LQ, UQ] MAE for predicting EASI from oSCORAD as 3.60 [3.39, 3.83] using the LM, 2.79 [2.60, 3.01] using NLM and 2.78 [2.59, 3.00] using LOESS (Fig. 1A). Similarly, prediction of EASI from SCORAD showed MAE 3.70 [3.49, 3.93] (LM), 2.99 [2.79, 3.21] (NLM) and 2.98 [2.78, 3.20] (LOESS) (Fig. 1C). The NLM therefore provided the best approximation of EASI score from oSCORAD and SCORAD, with oSCORAD outperforming SCORAD as a predictor.

Next, we used the generated models to predict severity groups. To evaluate classifier performance, we used balanced accuracy (BACC=(sensitivity+specificity)/2) and repeated cross-validation (10 repeats, 50 folds). We estimated the median [LQ, UQ] BACC for classifying EASI based on oSCORAD as 0.79 [0.74, 0.83] with LM, 0.78 [0.75, 0.82] with NLM and 0.78 [0.75, 0.82] with LOESS, for classifying EASI based on SCORAD as 0.79 [0.74, 0.83] with LM, 0.77 [0.74, 0.80] with NLM and 0.77 [0.74, 0.81] with LOESS. The quality of EASI score prediction varies considerably (Fig. 1A, Fig. 1C), however, the predicted values appear to give reasonably good classification results across all AD severity groups (Fig. 1B, Fig. 1D).

The presented models allow robust prediction of EASI from oSCORAD or SCORAD, and classification into severity sub-groups. The tools we have generated will facilitate progress in harmonizing AD severity data across studies, enabling comparative analyses at scale. Importantly, this will allow the pooling of clinically relevant disease severity assessments from different studies, to increase statistical power and move further towards the goal of personalised medicine.

Acknowledgments

The authors gratefully acknowledge the substantial contributions made to this work by the participating patients, physicians and clinical staff, the documentation team and last but not least the TREATgermany Study Group. We thank Dr. Eva Haufe for her substantial contribution to this project.

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Conflicts of interest: MH has performed consulting work for Sanofi. JS has received institutional grants from Novartis and Pfizer for scientifically initiated research; and has received honoraria for consulting from Sanofi, Lilly, Novartis and ALK. TW has received honoraria for lectures or scientific advice on atopic dermatitis from AbbVie, Almirall, Galderma, Janssen/JNJ, LEO Pharma, Leti, Lilly, Novartis, Pfizer and Regeneron/Sanofi. SW has received institutional research grants from LEO, Pfizer and Sanofi; and has performed consulting work and lectures for AbbVie, Almirall, Eli Lilly, Galderma, Kymab, LEO Pharma, Pfizer, Sanofi, and Regeneron. SJB holds a Wellcome Trust Senior Research Fellowship (ref 220875/Z/20/Z) and she has previously received research funding (but no personal financial benefits) from the Rosetrees Trust, Stoneygates Trust, British Skin Foundation, Charles Wolfson Charitable Trust, anonymous donations from people with eczema, Pfizer, Abbvie, Sosei-Heptares, Janssen, European Lead Factory (multiple industry partners) and the BIOMAP consortium (EU H2020 project ref No 821511). All of the other authors declare they have no conflicts of interest.

Data availability: The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement: The study was approved by the ethics committee of the Medical Faculty of the Carl Gustav Carus University, Dresden, Germany (No. EK 118032016) and the local committees of the participating recruitment centres.

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Figure legends

Fig 1. "Mapping oSCORAD and SCORAD to EASI." For each model (A, oSCORAD) and (C, SCORAD) depict the MAE's distribution as estimated by repeated cross-validation for the entire range of the severity score (total) as well as stratified by severity groups (mild, moderate, severe). (B, oSCORAD) and (D, SCORAD) depict the distribution of the balanced accuracy (BACC) when classifying predicted EASI scores into EASI severity groups.

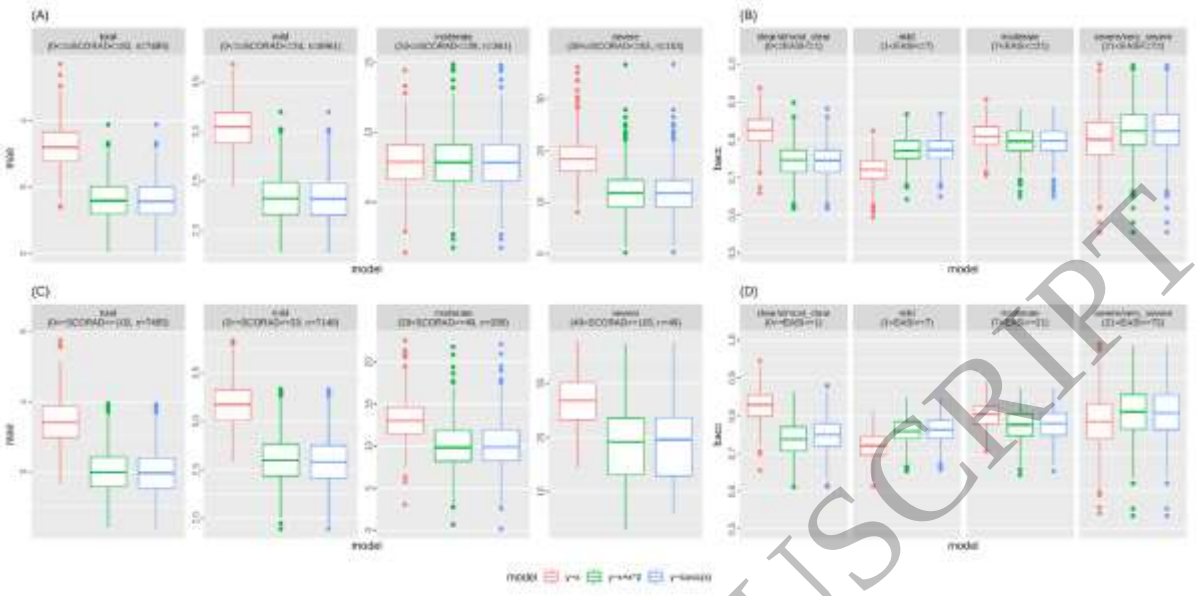

Figure 1
159x80 mm (x DPI)

Cosentyx® secukinumab

Cosentyx® (secukinumab) is available for eligible patients with moderate to severe hidradenitis suppurativa (HS)*[1,2]

Cosentyx can help to provide **fast relief and lasting control** for your eligible patients with HS[3]

FAST: Improved outcomes in HiSCR50 vs placebo by Week 16[1,2]

LASTING: Improved outcomes lasted through Week 52 (observed data with no statistical testing)[3–5]

HiSCR50 (primary endpoint)

>40%

of patients achieved **HiSCR50 at Week 16 in both trials**†[1,2]

Pain (observational, pooled data)

>65%

of patients who started with moderate or severe pain had only **mild or no pain at Week 52**‡[4]

Flares (observational, pooled data)

>70%

of patients **were flare free at Week 52**§[3]

Draining tunnels (observational, pooled data)

>80%

of patients **had no increase in draining tunnels at Week 52**¶[5]

The primary endpoint was met for Cosentyx 300 mg Q2W in both SUNRISE and SUNSHINE (p=0.015 and p=0.007, respectively) and was met for Cosentyx 300 mg Q4W in SUNRISE (p=0.002), but not in SUNSHINE.[4]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[1,2]

No new safety signals observed in HS trials[3]

The most frequently reported adverse events in SUNSHINE and SUNRISE were headache, nasopharyngitis and worsening of hidradenitis up to Week 16.[3]

Please consult the SmPC before prescribing.

Cosentyx is recommended by NICE as an option for the treatment of moderate to severe HS in adults who have not responded to conventional systemic treatment (subject to eligibility criteria)[6]

Cosentyx is approved for use in eligible patients with HS[1,2]

Click here to find out more

Cosentyx licensed indications in dermatology: 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 moderate to severe **HS** (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. For full indications, please see the SmPC.[1,2]

SUNSHINE AND SUNRISE: Two randomised, double-blind, multicentre, Phase III trials: SUNSHINE and SUNRISE (Cosentyx 300 mg Q4W, n=360 or Cosentyx 300 mg Q2W, n=361). The primary endpoint for both SUNSHINE and SUNRISE studies in adult patients with moderate to severe HS was the clinical response (as measured by HiSCR), defined as a decrease in abscess and inflammatory nodule count by 50% or more with no increase in the number of abscesses or draining fistulae compared with baseline, of Cosentyx versus placebo at Week 16, assessed in the overall population. Clinical response was sustained to Week 52 in both trials.[4]

*Cosentyx is indicated in adult patients with moderate to severe HS (acne inversa) with an inadequate response to conventional HS therapy.[1,2] Please see above for the licensed dermatology indications.

†HiSCR50: ≥50% decrease in abscesses and inflammatory nodules count with no increase in the number of abscesses and/or in the number of draining fistulae relative to baseline at Week 16. In HS study 1 HiSCR50 was 41.8% and 45.0% in the Q4W arm (n=180) and Q2W arm (n=181), respectively. In HS study 2 HiSCR50 was 46.1% and 42.3% in the Q4W arm (n=180) and Q2W arm (n=180), respectively.[1,2]

‡The percentage of patients who started with moderate or severe pain and had mild or no pain was 65.3% in the Cosentyx group and 80.9% in the placebo group for the Q2W dosing regimen. The percentage of patients who started with moderate or severe pain and had mild or no pain at Week 52 was 70.1% in the Cosentyx group and 64.8% in the placebo group for the Q4W dosing regimen.[3]

§Flare, a prespecified exploratory endpoint, is defined as at least a 25% increase in AN count with a minimum increase of 2 in absolute AN count relative to baseline. In the Q4W arm, 360 patients were evaluable at Week 16 and 278 patients were evaluable at Week 52, 27.3% of patients experienced flares at Week 52. In the Q2W arm, 361 and 289 were evaluable at Week 16 and Week 52, respectively with 20.4% of patients experiencing flares at Week 52.[4]

¶Observed data from full analysis set. Number of patients with no increase from baseline from Week 16 to Week 52 in patients with at least one draining fistulae at baseline. 82.6% in Q4W arm (n=218), 80.7% in Q2W arm (n=239).[5]

Abbreviations: AN, abscess and inflammatory nodule; HiSCR, hidradenitis suppurativa clinical response; HS, hidradenitis suppurativa; Q2W, every 2 weeks; Q4W, every 4 weeks; SmPC, summary of product characteristics.

References: 1. Cosentyx® (secukinumab) GB Summary of Product Characteristics; **2.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **3.** Kimball AB, et al. *Lancet* 2023;401(10378):747–761 and supplementary appendix; **4.** Novartis Data on File. SUNNY clinical programme post-hoc analysis of skin pain severity. March 2023; **5.** Novartis Data on File. Draining fistulas; **6.** National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe hidradenitis suppurativa. Available at: https://www.nice.org.uk/guidance/ta935 [Accessed April 2024].

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

UK | April 2024 | 421564

NOVARTIS

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

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

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

UK | 284832 | May 2023

Adverse Event Reporting:

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

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

Cosentyx® (secukinumab) Great Britain Prescribing Information.

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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. 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Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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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