
Article:
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British Journal of Dermatology
Research Letter

The effects of ciclosporin and methotrexate on kidney function in the treatment of severe atopic dermatitis in children: results from the TREAT trial

Dear Editor, The TREatment of severe ATopic eczema (TREAT) trial evaluated the impact of ciclosporin (CyA) vs. methotrexate (MTX) on severe atopic dermatitis in children and young people, with 103 participants randomized between May 2016 and February 2019, 52 to CyA and 51 to MTX.[1,2] Primary outcomes were changes in the Objective Severity Scoring of Atopic Dermatitis (o-SCORAD) at 12 weeks and the time to first significant flare following treatment cessation at 36 weeks. The trial reported that CyA at a dose of 4 mg kg^{-1} daily demonstrated a greater improvement in severity scoring at 12 weeks, but this was reversed in favour of MTX at a dose of 0.4 mg kg^{-1} weekly by weeks 48 and 60.

While MTX is not regarded as being nephrotoxic in low doses, CyA and MTX can both affect kidney function and frequent renal profile measurements are routinely undertaken as part of safety monitoring.[3,4] However, such standard tests are not very sensitive, as serum creatinine may change late in the evolution of acute kidney injury (AKI).

Cystatin C (CysC) may identify AKI earlier in children,[5] and a combination strategy incorporating serum creatinine, CysC and urinary N-acetyl-β-D-glucosaminidase (uNAG) measurement has also been shown to identify AKI earlier.[6] uNAG is an enzyme found in the lysosomes of proximal tubule epithelial cells, and therefore a raised level is likely to reflect proximal tubular damage.[7] Symmetric dimethylarginine (SDMA) has also been identified as a clinically useful biomarker for chronic kidney disease (CKD) and can be raised in CKD irrespective of the creatinine level.[8]

To comprehensively assess the impact of CyA vs. MTX on renal function, our initial study protocol included an evaluation of both functional (serum creatinine, SDMA, CysC) and kidney injury (uNAG) markers at baseline, and at weeks 2, 12, 36 (9 months on treatment from baseline) and 60 (6 months off treatment). Two outcomes were newly defined. The first was the change in markers across timepoints and between treatment arms, using linear mixed models, including a random intercept to allow for within-participant correlations at different visits. The covariates in the models were the baseline value and an interaction between treatment group and visit in order to estimate the treatment effect at each timepoint. The second was the total number and percentage of potentially clinically relevant treatment-emergent decreases in estimated glomerular filtration rate (eGFR). This was defined in the study protocol as a drop in eGFR > 20% from baseline, with eGFR calculated using the formula eGFR = height (in cm) × 40/plasma creatinine.

At baseline, demographics, clinical characteristics and baseline markers were well balanced between the two groups.[2] The mean values for serum creatinine, CysC, log uNAG and SDMA remained stable within normal ranges in each trial arm and were comparable between the treatment groups across timepoints (Figure 1). Using the estimated difference in means between treatment groups at each timepoint demonstrated no statistically significant differences. The total number of samples available, respectively, at each timepoint (2, 12, 36 and 60 weeks) varied between the CyA (n = 47, 50, 41 and 39) and MTX (n = 44, 47, 34 and 31) arms.

Across all timepoints, 17 events affecting 14 (26.9%) participants in the CyA arm and 14 events affecting eight (15.7%) participants in the MTX arm demonstrated a 20% decrease in eGFR. In all cases, the eGFR reverted to baseline values when participants were encouraged to hydrate prior to a repeat test, which suggests that these were not treatment related. No patients were required to stop treatment due to renal impairment during the study (the full analysis details are available online at: https://figshare.com/articles/journal_contribution/TREAT_trial_renal_biomarker_analysis_report/25904470).

Our study findings provide trial data in children showing that CyA was not associated with decreased renal function compared with baseline or with worse renal outcomes than MTX over a 36-week treatment period. Both MTX and CyA are efficacious, with the cheaper drug option, MTX, inducing better disease control following cessation of treatment.

More frequent monitoring to detect kidney dysfunction adds little benefit, and reducing the number of blood tests would make the drugs more acceptable to children and young people who may be put off by the treatment due to the frequency of blood tests. Moreover, fewer blood tests would reduce the overall cost of treatment to healthcare providers, and we suggest monitoring 6-monthly once on a stable treatment regimen. To avoid potentially spurious drops in eGFR, children should be encouraged to maintain hydration when MTX or CyA is prescribed.

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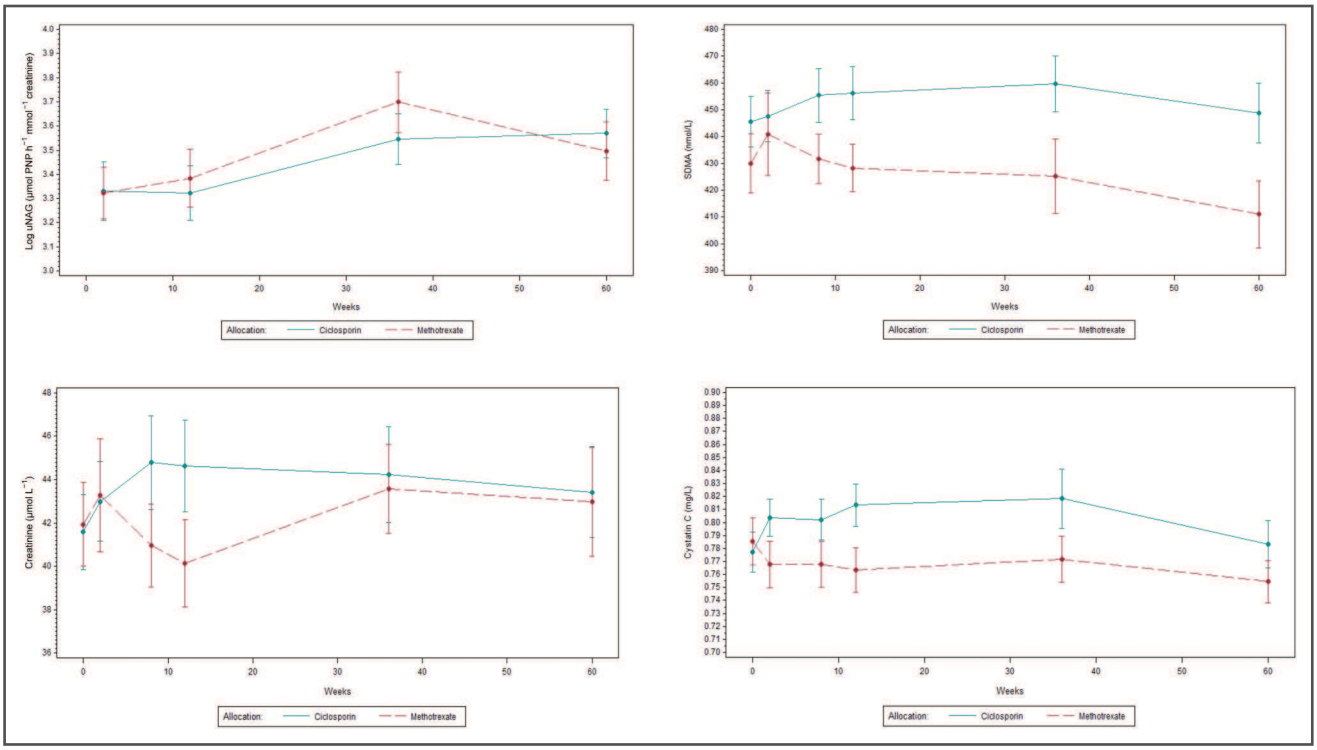

Figure 1 Mean (standard error bars) profile plots for log uNAG, SDMA, creatinine and cystatin C measurements. Normal ranges: uNAG: ≤56.0 PNP-NAG h^{-1} $mmol^{-1}$; SDMA: <533 nmol L^{-1}; creatinine: 1 month to 4 years, 13–39 μmol L^{-1}; 5–11 years, 29–53 μmol L^{-1}; ≥12 years, 40–90 μmol L^{-1}; cystatin C: 0.5–1.27 mg L^{-1}. PNP, *p*-Nitrophenyl; NAG, N-acetyl-β-D-glucosaminidase; SDMA, symmetric dimethylarginine; uNAG, urinary NAG.

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M.D.S. and C.F. contributed equally.

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Funding sources: The UK Medical Research Council/National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation Programme (EME) Board provided the financial resources for the conduct of the trial (grant code 15/EE/0328), provided ongoing support to the chief investigator to ensure that the trial progressed smoothly and monitored progress against key milestones via the submission of regular progress reports. The funders had no influence on participant enrolment and follow-up, data collection, data analyses and the writing of this manuscript.

Conflicts of interest: The full list of authors' conflicts of interest is provided in Appendix S2 in the Supporting Information.

Data availability: Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, can be made available to researchers who provide a methodologically sound proposal to the corresponding author with a signed data access agreement. All related documents are available on request at any point.

Ethics statement: The study was approved by the Cambridge Research Ethics Committee group (15/EE/0328). Written informed consent was received from each participant.

Patient consent: Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Full list of authors and affiliations.

Appendix S2 Full list of conflicts of interest.

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

Cosentyx® secukinumab

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

150+ clinical trials across indications[5]

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

8 indications[1–3]

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

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

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

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

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

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

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

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

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

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

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

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

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UK | August 2024 | FA-11239622

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

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

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

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Adverse Event Reporting:

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

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

Cosentyx® (secukinumab) Great Britain Prescribing Information.

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

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. 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If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com