DERMATOLOGY

HEALTHCARE
CELLTRION

Remsima®
Infliximab
SUBCUTANEOUS

Remsima®
Infliximab

SUBCUTANEOUS

The only subcutaneous infliximab formulation available in Australia[1]

Remsima® SC (infliximab) provides an alternative treatment option for patients with PsA, PsO, RA, CD, UC, and AS.[1,2]

Remsima® SC is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate.[1]

The availability of infliximab IV and a subcutaneous formulation of Remsima® provides a treatment approach tailored to the individual needs of your patients.

Remsima® SC can be an expanded treatment option with comparable efficacy and safety to infliximab IV.[3,4]

Available in a pre-filled pen and pre-filled syringe with needle guard

- Remsima® 120 mg solution for injection in pre-filled pen

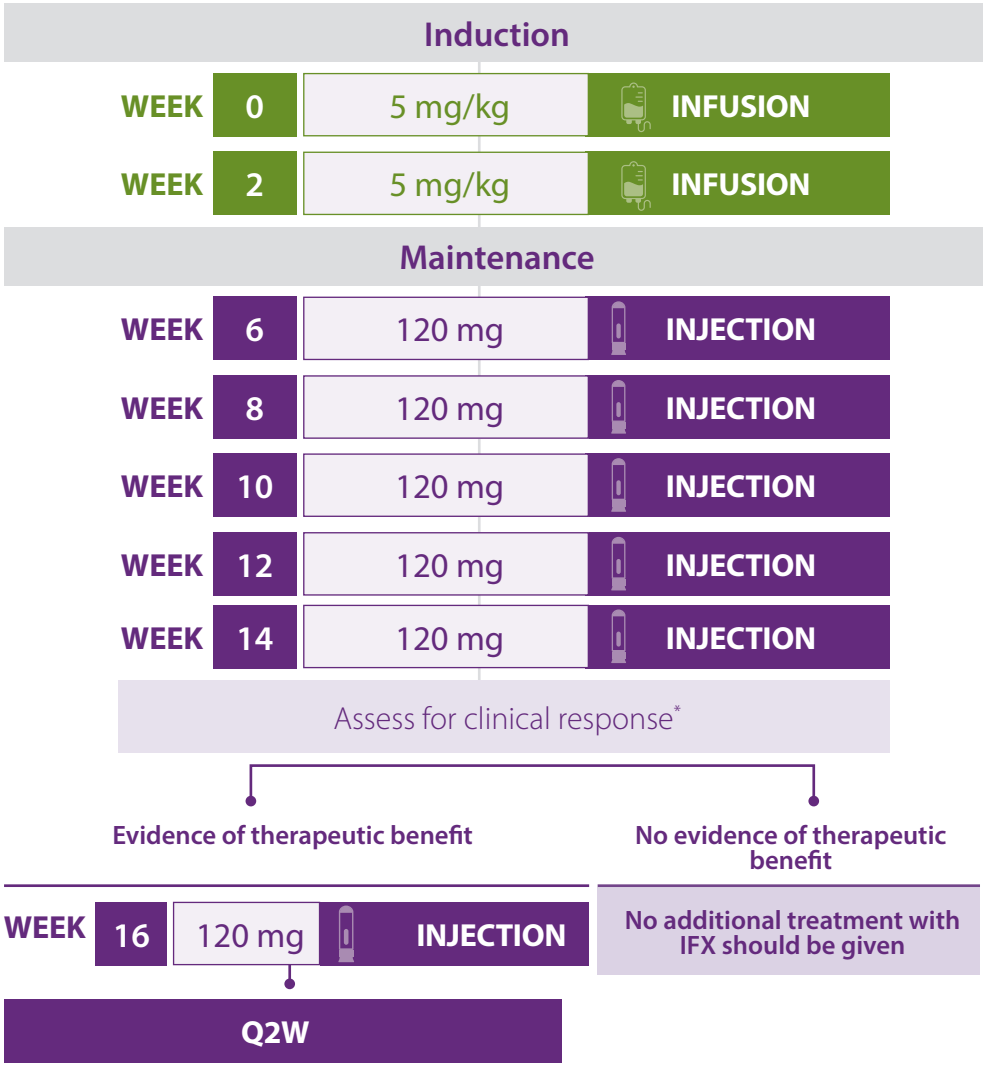
- Remsima® 120 mg solution for injection in pre-filled syringe with needle guard

AS, ankylosing spondylitis; CD, Crohn's disease; IV, intravenous; PsA, psoriatic arthritis; PsO, plaque psoriasis; RA, rheumatoid arthritis; SC, subcutaneous; UC, ulcerative colitis

Moderate to Severe Plaque Psoriasis in adults[1]

Posology[1]

- Remsima is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate.[1]



Safety and efficacy beyond 12 months have not been established.

Re-administration for Psoriasis

- Limited experience from re-treatment with one single intravenous infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen.
- Limited experience from re-treatment of intravenous infliximab following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance treatment of intravenous infliximab.

Q2W, Every two weeks; IFX, Infliximab

Extrapolation data

Remsima® SC (CT-P13 SC) is the same molecule as infliximab IV, but the formulation differs to enable SC administration.[5]

Remsima® is an approved biosimilar to the reference infliximab product. Comparability in safety, efficacy and quality between Remsima® and reference infliximab has been established.[1]

TGA allows extrapolation to other indications based on European Medicine Agency (EMA) Guidelines.[6]

The TGA has adopted a number of European guidelines that outline the quality, nonclinical and clinical data requirements specific to biosimilar medicines; and the ICH guideline on the assessment of comparability.[7]

Indication extrapolation refers to the extension of the efficacy and safety data from a condition for which the biosimilar has been clinically tested to other conditions for which the health outcomes for the reference biological medicine have been established.[8]

NOR-SWITCH Study[9,10]

NOR-SWITCH, a study to compare the effect of switching from reference infliximab to Remsima® IV in patients across all indications.[9]

Objective

NOR-SWITCH, a randomised, double-blind, non-inferiority parallel-group study to compare the effect of switching from reference infliximab (RMP*) to CT-P13** (infliximab - IV) in 482 patients across various indications.[9]

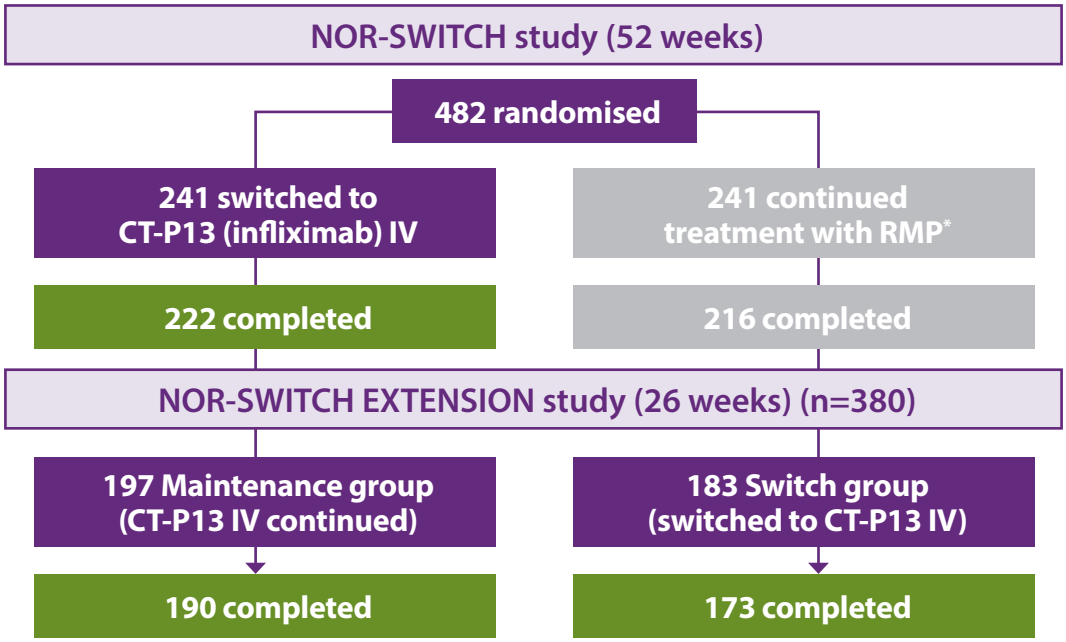
380 patients who completed the main study were then part of the extension trial. The NOR-SWITCH extension study aimed to assess efficacy, safety and immunogenicity in patients on infliximab IV (CT-P13) throughout the 78-week study period (maintenance group – 197 patients) versus patients switched to infliximab IV (CT-P13) at week 52 (switch group - 183 patients).[10]

Study design[9,10]

Exploring switching in stable patients.

Primary endpoint: Disease worsening (defined by worsening in disease-specific composite measures and/or a consensus on disease worsening between investigator and patient, leading to major change in treatment).

Note The study was not powered to show non-inferiority in individual diseases.



NOR-SWITCH study:[9]
N = 482 patients were randomly assigned,
- 241 assigned to switch to infliximab IV (CT-P13) but one withdrew consent and did not receive treatment. (n=240)
- 241 were assigned to receive continued treatment with originator reference infliximab IV. (n=241)

Patients were followed up for 52 weeks in each treatment.
The study was not powered to show non-inferiority in individual diseases.

NOR-SWITCH extension study:[10]
N = 380 of the 438 patients who completed the 52-week main trial. These patients were continued into the 26-week extension study.
- The patients treated with infliximab IV (CT-P13) in the main trial continued this treatment in the extension phase (maintenance group 197 patients).
- Patients treated with originator infliximab in the main trial switched to infliximab IV (CT-P13) at extension study baseline at week 52 (switch group 183 patients).

The study was not powered to show non-inferiority in individual diseases.
*RMP Reference medicinal product, **CT-P13 is marketed under different brand names including Inflectra®

NOR-SWITCH Study[9]

Efficacy at Week 52

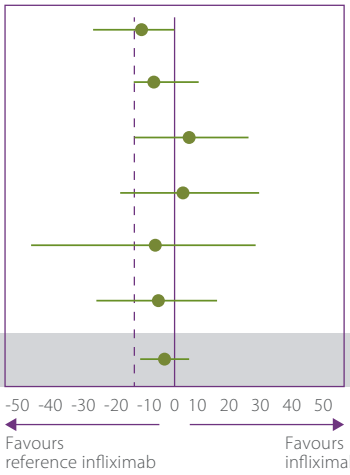
CTP-13 (infliximab) IV is non-inferior to the reference infliximab in disease worsening (primary endpoint) across various indications at Week 52.[9]

Stable patients switching to infliximab IV (CT-P13) experienced a similar percentage of disease worsening when measured across all indications compared to those remaining on reference infliximab therapy.

Primary endpoint met at Week 52

Switching from the reference infliximab to CT-P13 infliximab IV was not inferior to continued treatment with reference infliximab.

	RMP* n=202	CT-P13** n=206	Risk difference (95% CI***)	
Diagnosis				
Crohn's disease	21.2%	36.5%	-14.3%	-29.3 to 0.7
Ulcerative colitis	9.1%	11.9%	-2.6%	-15.2 to 10.0
Spondyloarthritis	39.5%	33.3%	6.3%	-14.5 to 27.2
Rheumatoid arthritis	36.7%	30%	4.5%	-20.3 to 29.3
Psoriatic arthritis	53.8%	61.5%	-8.7%	-45.4 to 28.1
Psoriasis	5.9%	12.5%	-6.7%	-26.7 to 13.2
Overall	26.2%	29.6%	-4.4%	-12.7 to 3.9



Adapted from Jorgensen K et. al.[9]

The study was not powered to show non-inferiority in individual diseases

NOR-SWITCH study: 482 patients were enrolled and randomised (241 to infliximab originator, 241 to CT-P13 group; one patient was excluded from the full analysis and safety set for CT-P13) and 408 were included in the per-protocol set (202 in the infliximab originator group and 206 in the CT-P13 group).[6]

Disease worsening at week 52: Forest plot of risk difference according to disease. Figure above shows data for the per-protocol set. Risk difference is adjusted for treatment duration of reference infliximab at baseline.[6]

Disease worsening according to disease-specific composite measures was defined as change from baseline in Harvey-Bradshaw Index of 4 points or more and a score of 7 points or greater for Crohn's disease, change from baseline in Partial Mayo Score of more than 3 and a score of 5 or greater for ulcerative colitis, change from baseline in Ankylosing Spondylitis Disease Activity Score of 1·1 or more attaining a minimum score of 2·1 for spondyloarthritis, change from baseline in Disease Activity Score in 28 joints of 1·2 or more with a minimum score of 3·2 for rheumatoid arthritis and psoriatic arthritis, and change in Psoriasis Area and Severity Index of 3 or more and a score of 5 or greater for chronic plaque psoriasis.

*RMP Reference medicinal product; **CT-P13 IV is marketed under different brand names including Inflectra®; *** CI: confidence interval.

NOR-SWITCH Extension Study[10]

Efficacy at Week 78

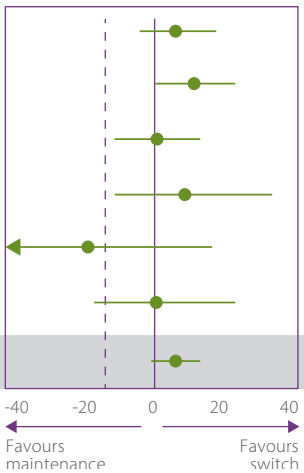
CTP-13 (infliximab) IV is non-inferior to the reference infliximab in disease worsening (primary endpoint) across all indications at Week 78.[10]

Disease worsening during the extension phase (week 78) occurred at a similar rate in the two groups, with no significant difference amongst those switched at main study baseline and those switched at extension study baseline.

Primary endpoint at week 78 met

Switching from the reference infliximab to CT-P13 infliximab IV was not inferior to continued treatment with reference infliximab.

	Maintenance* n=190	Switch** n=173	Risk difference (95% CI***)	
Diagnosis				
Crohn's disease	13/63 (20.6%)	8/61 (13.1%)	7.9%	-5.2 to 21
Ulcerative colitis	6/39 (15.4%)	1/35 (2.9%)	12.4%	-0.1 to 25
Spondyloarthritis	3/38 (7.9%)	2/28 (7.1%)	0.6%	-12.2 to 13.
Rheumatoid arthritis	9/26 (34.6%)	6/27 (22.2%)	10.5%	-13.6 to 34.
Psoriatic arthritis	1/8 (12.5%)	3/9 (33.3%)	-20.8%	-59.1 to 17.6
Psoriasis	0/16 (0%)	0/13 (0%)	0%	-20.6 to 24.
Overall	32/190 (16.8%)	20/173 (11.6%)	5.9%	-1.1 to 12.9



Adapted from Goll G et. al.[10]

The study was inadequately powered to detect non inferiority within individual diseases.[10]

NOR-SWITCH study: Full analysis set included 197 patients in the maintenance group and 183 patients in the switch group, and per-protocol set consisted of 190 and 173 patients in the maintenance group and the switch group.[10] Maintenance: CT-P13 infliximab IV biosimilar-CT-P13 infliximab IV biosimilar ; Switch: RMP-CT-P13 infliximab IV biosimilar.

Disease worsening at week 78: Forest plot of risk difference according to disease. The figure below shows data for the per-protocol set. Risk difference is adjusted for treatment duration of reference infliximab at extension study baseline (week 52).[10]

Disease worsening according to disease-specific composite measures was defined as ΔHBI ≥4 and HBI level ≥7 points for CD patients, ΔPMS >3 and PMS level ≥5 for UC patients, ΔASDAS≥1.1 and ASDAS level >2.1 for SpA patients, ΔDAS28 of ≥1.2 and DAS28 level >3.2 for RA and PsA patients, and ΔPASI ≥3 and PASI level ≥5 for Ps patients. Δ indicates change from time of switching (baseline week 52) to the end of the 26-week follow-up period (study end minus baseline).

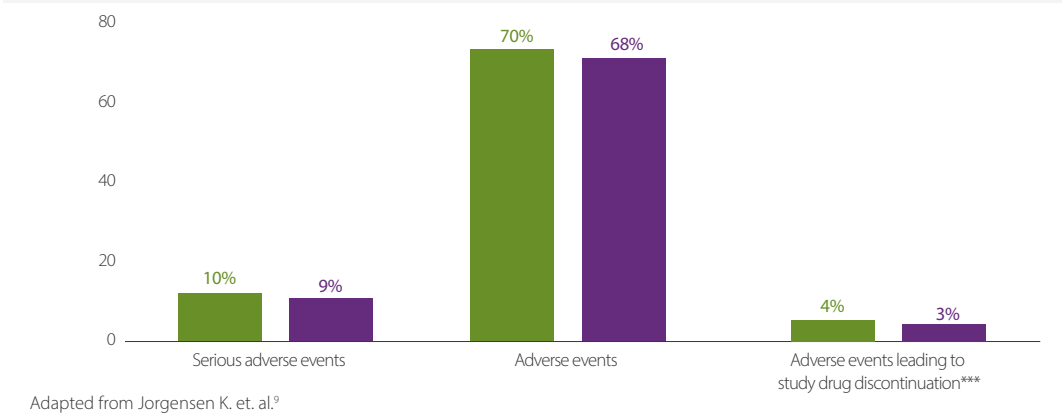
*Maintenance: CT-P13 IV - CT-P13 IV; **Switch: RMP - CT-P13 IV; ***CI: confidence interval.

NOR-SWITCH Study[9,10]

Safety

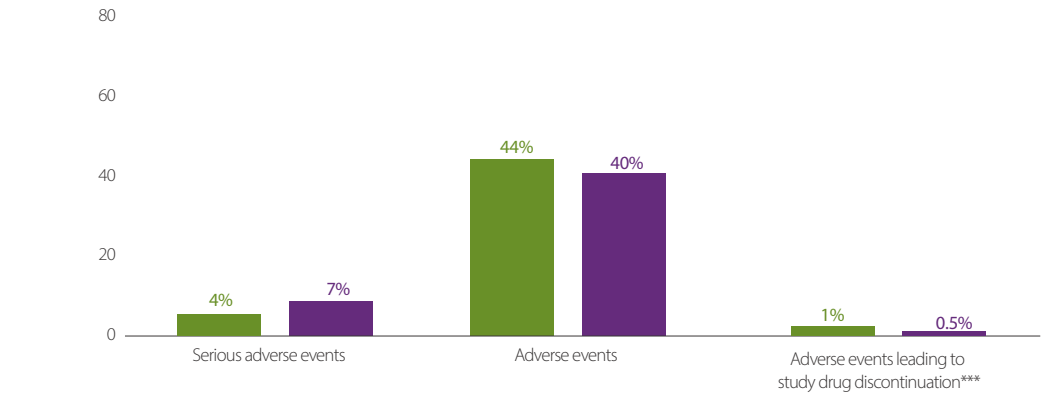
The safety profile was similar between stable patients switching from reference infliximab to CTP-13 IV, compared with those remaining on the reference infliximab[9]

Adverse events at Week 52[9] Figure 1



Adapted from Jorgensen K. et. al.[9]

Adverse events at Week 78[10] Figure 2



Adapted from Goll G. et. al.[10]
There were no new safety signals during the NOR-SWITCH extension study and adverse events were evenly distributed between study arms.

Conclusion

- Biosimilar infliximab IV (CT-P13) is non-inferior to the reference infliximab in efficacy and safety[9,10]
- Switching from the reference infliximab to CT-P13 IV was non inferior[9,10]
- No significant differences in immunogenicity were detected during the entire 78-week study period[10]

*RMP, reference medicinal product; **biosimilar infliximab IV referred to as CT-P13 in the study. Biosimilar IFX IV indicates patient group switched from RMP to biosimilar infliximab IV (CT-P13); +Maintenance: CT-P13 IV - CT-P13 IV; ++Switch: RMP - CT-P13 IV; ***Patients could have other primary reason for study drug discontinuation.

Remsima® Infliximab

SUBCUTANEOUS

The only subcutaneous infliximab available in Australia[1]

Flexibility and convenience through self-administration[1,11]

Citrate free and latex free[1]

Remsima® SC (CT-P13 SC) is the same molecule as infliximab IV, but the formulation differs to enable SC administration.[5]

Comparable efficacy and safety to IV administration[3,4]

Proven efficacy switching data from IV to SC formulation[3,4]

Comparable immunogenicity profile compared to IV[3,4]

The recommended dose is 120mg every other week.[1]

SC, subcutaneous; IV, intravenous; mg, milligrams

PBS Information: Authority required for the treatment of adults with severe chronic plaque psoriasis. Refer to PBS Schedule for full authority information.

Before prescribing, please review full Product Information available on request from the Celltrion Healthcare Medical Information Service (Phone: 1800 325 228) or www.ebs.tga.gov.au

MINIMUM PRODUCT INFORMATION REMSIMA® SC containing 120 mg infliximab (IFX) for subcutaneous (SC) injection in a 1-mL single dose pre-filled pen or syringe. **INDICATIONS**: adult patients with moderate to severe plaque PsO for whom phototherapy or conventional systemic treatments were inadequate or are inappropriate. **CONTRAINDICATIONS**: Severe infections (e.g. sepsis, abscesses, tuberculosis and opportunistic infections); history of hypersensitivity to IFX, other murine proteins or any excipient; concurrent administration with anakinra; congestive heart failure or moderate or severe heart failure (NYHA class III/IV). **PRECAUTIONS**: Systemic injection reactions, anaphylactic shock and delayed hypersensitivity reactions have been reported. Localised injection site reactions have been reported following SC administration; Malignancies and lymphoproliferative disorders, risk of development of lymphomas/other malignancies cannot be excluded. Caution with history of malignancy, with increased risk for malignancy, and treating patients who develop a malignancy; Skin Cancers, patients should be monitored for non-melanoma skin cancers, particularly those who have had prior prolonged phototherapy treatment; Infections, monitor closely for infections including TB before, during and up to 6 months after treatment. Caution with chronic infection or a history of recurrent infection. Suppression of TNF may mask symptoms of infection such as fever; Hepatitis B (HBV) reactivation, reactivation of HBV has occurred in chronic carriers when receiving IFX. Test for HBV infection before initiating treatment and closely monitor for symptoms of active HBV; Hepatobiliary events, jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed. Isolated cases of liver failure resulting in liver transplantation or death have occurred; Vaccinations/therapeutic infectious agents: prior to therapy vaccinations should be up to date. Live vaccines or therapeutic infectious agents not recommended. Min. 6-month waiting period after birth before use of live vaccines to infants exposed in utero to IFX; Autoimmune processes, discontinue treatment if symptoms suggestive of a lupus-like syndrome and positive for antibodies against double-stranded DNA; Neurological events, anti-TNF agents are associated with new onset or exacerbation of clinical symptoms and/or radiographic evidence of peripheral and CNS demyelinating disorders, including Guillain-Barré syndrome and multiple sclerosis; Heart failure, caution with mild heart failure (NYHA class I/II) and discontinue when new or worsening symptoms of heart failure develop; Haematologic reactions, consider discontinuation when significant haematologic abnormalities, including pancytopenia, leukopenia, neutropenia and thrombocytopenia; Use in the elderly, caution in the treatment of elderly patients (greater frequency of decreased hepatic, renal and/or cardiac function and concomitant disease and/or other drug therapy); Fertility, pregnancy and lactation, women of childbearing potential should consider adequate contraception to prevent pregnancy and continue use for ≥ 6 months after treatment. Not recommended for use during pregnancy and lactation. Breastfeeding should be discontinued for ≥ 6 months after treatment; Paediatric use, safety and efficacy of IFX SC therapy in children < 18 years is not established. **INTERACTIONS**: No specific drug interaction studies conducted. Combination with anakinra is contraindicated, use with abatacept as well as other biological therapeutics used to treat the same conditions not recommended. IFX should not be used in combination with immunosuppressive agents or phototherapy due to the possibility of excessive immunosuppression. Caution in patients with medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. **ADVERSE EFFECTS (AEs)**: Very common, localised injection site reactions; Common, viral infection, fever, serum-sickness-like reactions, headache, vertigo/dizziness, flushing, upper respiratory tract infection, lower respiratory tract infection, dyspnoea, sinusitis, nausea, diarrhoea, abdominal pain, dyspepsia, abnormal hepatic function, rash, pruritus, urticaria, increased sweating, dry skin, fatigue, chest pain, infusion-related reactions. The safety profile of REMSIMA® SC in clinical trials was overall similar to the safety profile of the IV formulation. For other less common and rarely reported AEs see full PI. **DOSAGE AND ADMINISTRATION**: treatment with Remsima® SC should be initiated as maintenance therapy 4 weeks after the last administration of two IV infusions of IFX 5 mg/kg given 2 weeks apart. The recommended dose for Remsima® SC is 120 mg once every 2 weeks.

References: 1. Remsima® Approved Australian Product Information available at https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-02558-1&d=20230223172310101. Last Accessed on 14.02.2023. **2.** The Pharmaceutical Benefit Scheme available at www.pbs.gov.au. **3.** Schreiber, S et al. Randomized Controlled Trial: Subcutaneous vs Intravenous Infliximab CT-P13 Maintenance in Inflammatory Bowel Disease; J. Gastroenterol. DOI: https://doi.org/10.1053/j.gastro.2021.02.068 Accessed 23 Feb 2023. **4.** Westhovens et al. Efficacy pharmacokinetics and safety of subcutaneous versus intravenous CT-P13 in rheumatoid arthritis: a randomized phase I/III trial. Rheumatology 2021;60:2277-2287. **5.** Celltrion Data on File (REF-00354 Jan 2023). **6.** European Medicines Agency. Guidelines on Similar Biological Medicinal Product containing biotechnology derived proteins. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf Last accessed: 17 Feb 2023. **7.** Australian Government Department of Health Therapeutic Goods Administration. Biosimilar Medicines Regulation. Version 2.2. April 2018. Available at: https://www.tga.gov.au/sites/default/files/biosimilar-medicines-regulation.pdf Last accessed: 17 Feb 2023. **8.** Australian Government Department of Health. Available at: https://www.health.gov.au/sites/default/files/documents/2022/04/biosimilar-medicines-the-basics-for-healthcare-professionals.pdf Last Accessed: 17 Feb 2023. **9.** Jørgensen K, Olsen I, Goll G, et al. NOR-SWITCH study group. The Lancet. 2017;389(10086):2304-2316. **10.** Goll G, Jørgensen K, Sexton J, Olsen I, et al. Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open label extension of the NOR-SWITCH trial. J Intern Med 2019; 285: 653–669. **11.** Cha JM et al. Physicians Should Provide Shared Decision-Making for Anti-TNF Therapy to Inflammatory Bowel Disease Patients. Journal Korean Med Sci 2017; 32:85–94.

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