Biosimilars in rheumatology: the Australian experience

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HAH New Zealand webinar: March 2022

Austin HEALTH

Acknolwedgement of Country

- I would like to acknowledge the Wurundjeri people who are the Traditional Custodians of this Land. I would also like to pay respect to the Elders past, present, and emerging of the Kulin Nation and extend that respect to other Indigenous Australians present, and to the First Nations people of the land you are on.

Disclosures

- Member, Australian Government Pharmaceutical Benefits Advisory Committee Drug Utilisation Subcommittee (PBAC DUSC)

What are biosimilar medicines?

- Biosimilar medicines are **highly similar versions of reference** (first brand to market) biologic medicines
  - Follow-on medicines (post-patent), but not generic medicines

- Biologic medicines
  - often (but not always) monoclonal antibodies (i.e. ‘mAbs’)
  - created from living cell lines
  - naturally variable production process
  - **cannot be created exactly the same**

- Biosimilar medicines **can be used to treat the same diseases in the same way** as the reference biologic medicines

But why should we care?

https://www1.health.gov.au/internet/main/publishing.nsf/content/biosimilar-what-are-biosimilar-medicines

Biosimilars: do they really matter?

Entrants to market

=

Competition

=

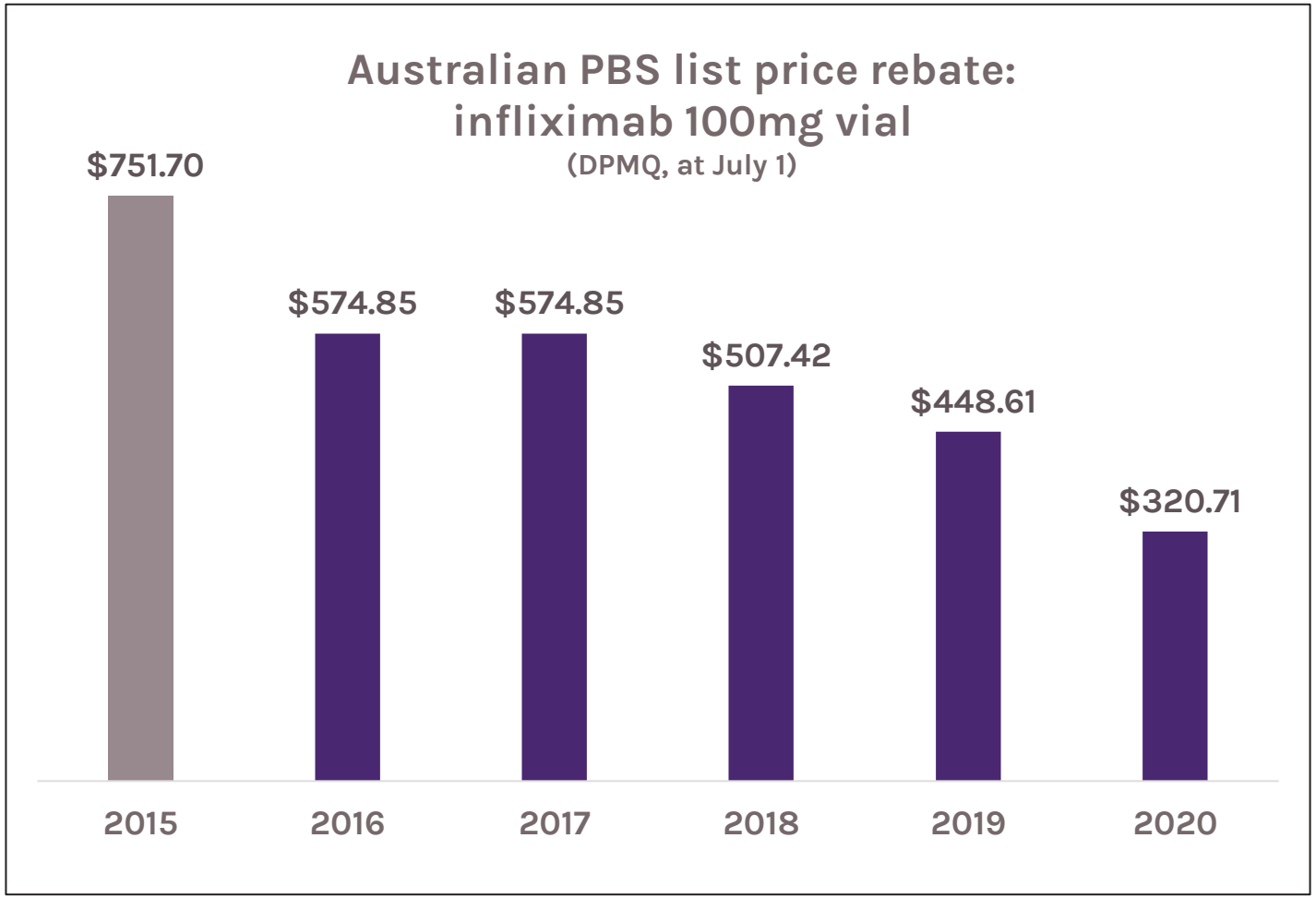
Reductions in price

=

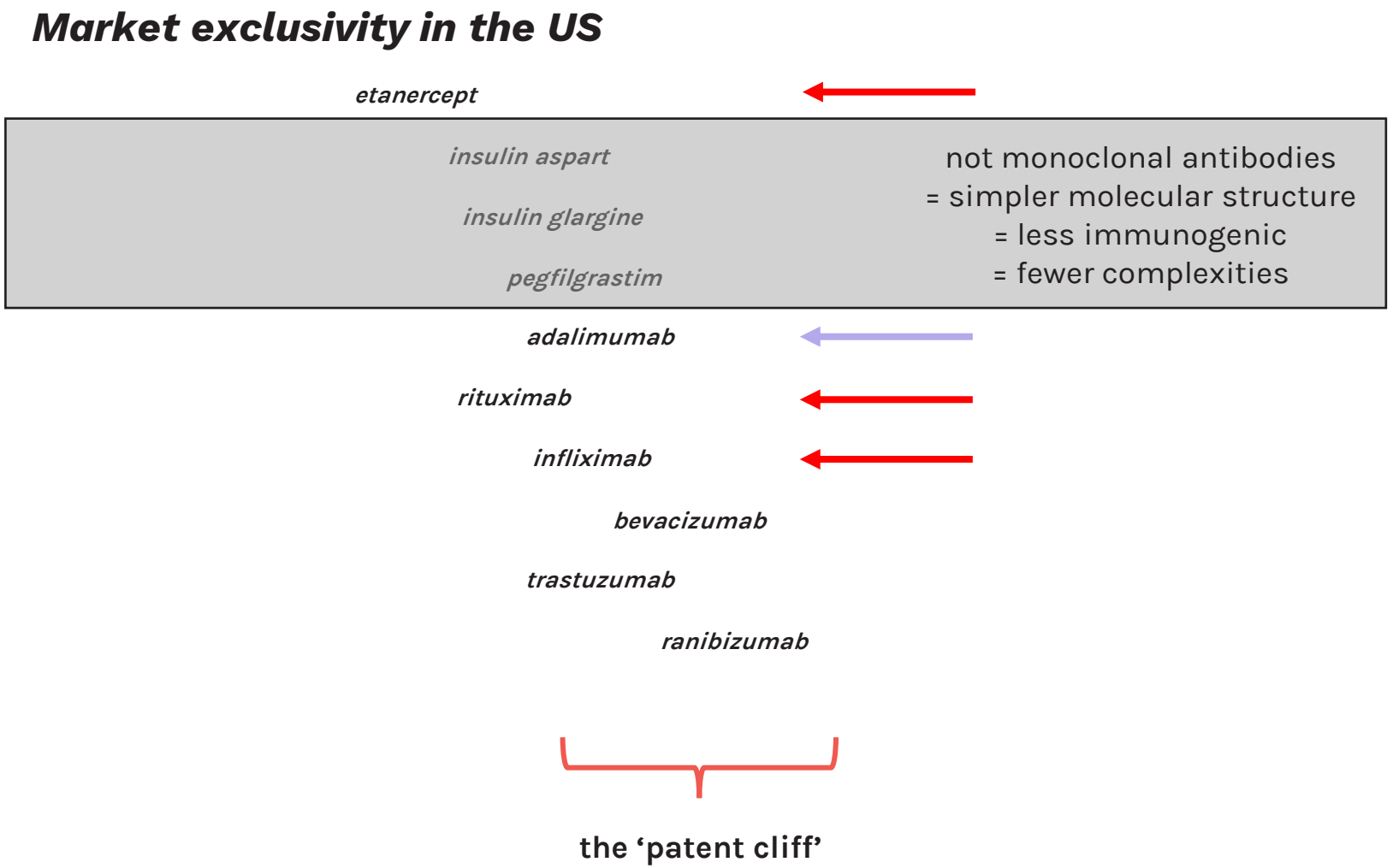
Better cost-effectiveness

=

Benefit
(sustainability/access)



TNF inhibitors: some of the first biosimilar mAbs amongst many



Calo-Fernandez et al Biosimilars: company strategies to capture value from the biologics market. Pharmaceuticals 2012

Theoretical Concerns

1. Small vs large molecules
2. Heterogeneity
3. Regulatory pathways

Small molecule vs large molecule drugs

Characteristic	Small molecule drug	Large molecule (biologics, monoclonal antibodies)
Size	Small (low MW)	Medium-large (high MW)
Manufacturing process	Chemically synthesised	Primarily produced in living cells
Complexity	Single homogenous structure	Complex, multiple levels of structure and post-translational modification (microheterogeneity)
Usual route of administration	Oral	Parenteral
Immunogenicity	Mostly non-immunogenic	Immunogenic
‘Follow-on’ drug	Generic	Biosimilar

Olech et al Biosimilars: Rationale and current regulatory landscape. Semin Arthritis Rheum 2016

Heterogeneity of biologics: production process

Batch-to-batch variation

- Manufacturing e.g. process, methods, packaging, technology
- Host cell impurities e.g. oxidation, deamidation, aggregation

Heterogeneity of biologics: production process

Has drift (unintended manufacturing change) and evolution (intended manufacturing change) created natural biosimilars?

Mehr et al. Is a Biologic Produced 15 Years Ago a Biosimilar of Itself Today? Am Health Drug Benefits 2016

Registration requirements for biosimilars

- Rigorous assessment
  - In vitro analysis
  - Clinical confirmation studies
- Clinically, need to prove:
  - Safe
  - Effective
  - Comparable immunogenicity

Infliximab: the test case

Focused attention given a potential model for whether more broadly feasible

First TNF inhibitor

- approved indications: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, ulcerative colitis

Large molecule – well known to be immunogenic

Originator (Remicade) versus biosimilar (CT-P13 – Inflectra)

Clinical confirmation studies: efficacy

Yoo et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther 2016

Immunogenicity

Immunogenicity is the ability of a substance to provoke an immune response

- Wanted immunogenicity eg vaccination
- Unwanted immunogenicity eg against therapeutic antigens

Unwanted immunogenicity occurs in many drugs

- Proteins are significantly more immunogenic than polysaccharides or simple molecules
- *Even small differences in 3D structure between foreign and native proteins lead to the production of anti-drug antibodies (ADAb)*

Biologic therapies, such as therapeutic monoclonal antibodies (mAbs), are often highly immunogenic

- Therapeutic failure
- Hypersensitivity

Clinical confirmation studies: immunogenicity

- Immunogenicity in infliximab biologic and biosimilar CTP13 comparable
- RA inherently more immunogenic than AS
- Comparable immunogenicity between biologic and biosimilar even in more immunogenic conditions

Dorner et al Biosimilars in rheumatology: current perspectives and lessons learnt. Nat Rev Rheumatol 2015

Switching studies

Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial

Kristin K Jørgensen, Inge C Olsen*, Guro L Goll*, Merete Lorentzen*, Nils Bolstad, Espen A Haavardsholm, Knut E A Lundin, Cato Mørk†, Jørgen Jahnsen†, Tore K Kvien†, on behalf of the NOR-SWITCH study group*

Lancet 2017; 389: 2304–16
Published Online
May 11, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30068-5

Summary

Background TNF inhibitors have improved treatment of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis, but are expensive therapies. The aim of NOR-SWITCH was to examine switching from originator infliximab to the less expensive biosimilar CT-P13 regarding efficacy, safety, and immunogenicity.

- NOR-SWITCH study including patients across all indications of infliximab
- Demonstrated that single switch is safe in non-oncological settings
- Concerns regarding switching in real-life: multiple switching, especially with interchangeability

Jorgensen et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH). Lancet 2017

Extrapolation of indications

- Use in an indication held by the reference product but not directly studied in a comparative clinical trial by the biosimilar
- Intended to reduce the expense of the clinical development program

Jurisdiction	EMA (Europe) (and TGA (Australia))	FDA (US)
In vitro analyses	Physico-chemical and structural analyses	Mechanism of action PK and biodistribution in various populations
Clinical data	Equivalent efficacy	Equivalent efficacy
Immunogenicity	Comparable immunogenicity data	In various populations including those with highest risk of immune response

Rituximab
NHL vs CLL
rheumatoid arthritis vs ANCA-associated vasculitis

fda.gov; ema.europa.eu
Dorner et al Biosimilars in rheumatology: current perspectives and lessons learnt. Nat Rev Rheumatol 2015

Practical data: summary

1. Biosimilars have equivalent impact in practice
   - Efficacy equivalent to reference biologic
   - Immunogenicity comparable to reference biologic

2. Data on biosimilar safety/efficacy dependent on use situation
   - New initiator: safe
   - Switch from reference biologic: safe

3. Extrapolation based on in vitro, clinical, and immunogenic considerations

Biosimilar drug pricing in Australia

Mechanisms to drive down price:

Legislated reductions: multiple PBS mechanisms

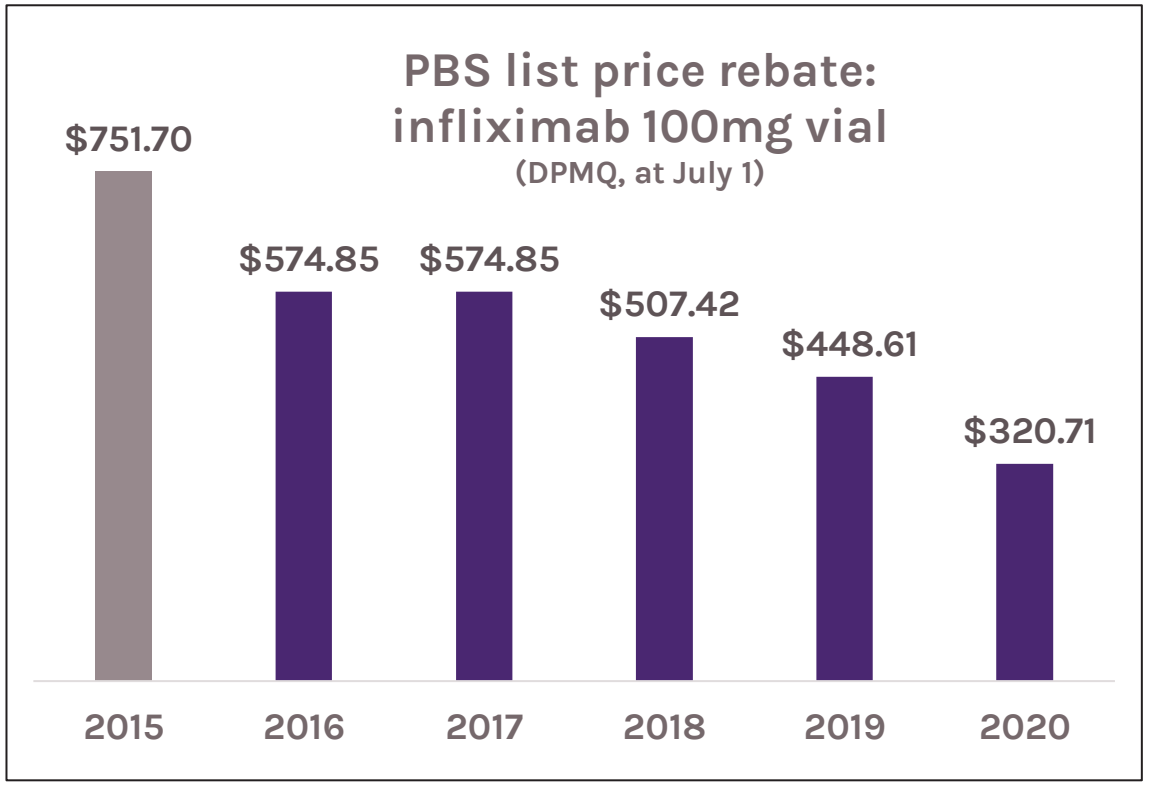
- First new brand price reduction (16%, now 25%)
- Anniversary price reductions
- Reference pricing

Market competition: PBS price disclosure cycle

Encourage biosimilar use (and thus entrants):

Government recommendation

'Biosimilar uptake drivers' influence use



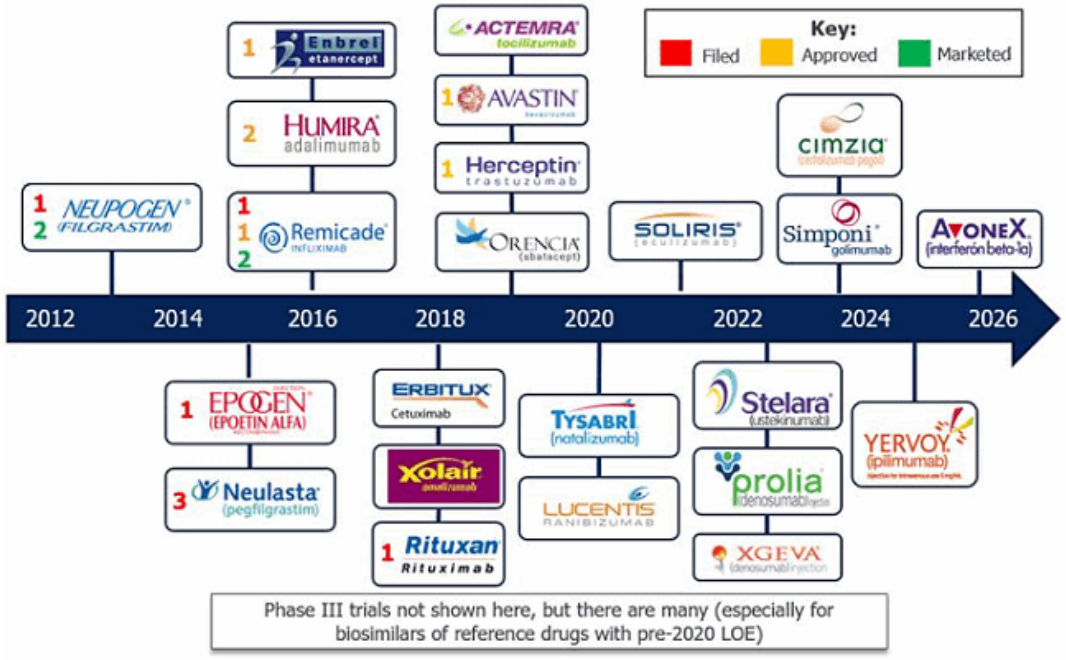
Biosimilars: what does the future hold?

- Ongoing patent expiry pipeline
- Is multiple switching safe?
- Will there continue to be additional biosimilar entrants to market?

- What will the development pathway look like?
  - Originator: greater focus on newer agents?
  - Biosimilar (and originator): innovation (points of differentiation)

- Will there be improvements in access?
  - Improved developing world access?
  - New indications: largely orphan or new diseases, likely require investigator-initiated studies

US Loss of Exclusivity timeline



www.biosimilardevelopment.com

Biosimilars: extended indications

18 OCTOBER 2021

RITUXIMAB IN LINE FOR OPEN PBS LISTING WITHOUT AUTHORITY

ANCA-ASSOCIATED VASCULITIS | LUPUS | MEDICATIONS | PBAC

By KARINA BRAY

IN A BONANZA MEETING FOR RHEUMATOLOGISTS, PBAC'S RECOMMENDATIONS INCLUDE UNRESTRICTED LISTING FOR RITUXIMAB,

https://rheuma.com.au/rituximab-in-line-for-open-pbs-listing-without-authority/20375

Two years following introduction of the rituximab biosimilar: open Australian PBS listing announced

COVID-19 and biosimilars

Subcutaneous Remsima launched in UK

2nd March 2020

THE LANCET

COMMENT | VOLUME 395, ISSUE 10234, P1407-1409, MAY 02, 2020

Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed

Marc Feldmann • Ravinder N Maini • James N Woody • Stephen T Holgate • Gregory Winter • Matthew Rowland • et al. Show all authors

Published: April 09, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)30858-8 • Check for updates

11 JUNE 2020 NEWS

Namilumab and Infliximab selected for CATALYST trial in UK

The Universities of Birmingham and Oxford in the UK have partnered with Izana Bioscience and Celltrion Healthcare for the CATALYST clinical trial, which is assessing drug candidates to treat Covid-19 in hospitalised patients.

Celltrion Healthcare UK will provide its anti-tumour necrosis factor (TNF) therapy, Infliximab (CT-P13), which binds to a protein involved in inflammation.

Under the brand name Remsima, Infliximab is indicated to treat inflammatory conditions, including eight autoimmune diseases, such as rheumatoid arthritis and irritable bowel syndrome.

Feldmann et al Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet 2020;
clinicaltrialsarena.com; pharmatimes.com

Biosimilar confidence, counselling

Clinician confidence: improves with familiarity

- In UK, with first two years of biosimilar introduction: infliximab (2015) 30%, rituximab (2017) 80%

Patient confidence: reliant on clinicians and education

- Nocebo (related to placebo): patients' negative expectations toward therapy change
- Minimising nocebo
  1. Positive framing
  2. Increase patient and healthcare professional understanding of biosimilars
  3. Coherent communication in a managed switching program, context

Kim et al Uptake of Biosimilar Infliximab in the UK, France, Japan, and Korea. Front Pharmacol 2020
Fleischmann et al Nonmedical Switching From Originators to Biosimilars. Rheumatol Ther 2020
Kristensen et al Non-pharmacological Effects in Switching Medication. BioDrugs 2018
Manai et al How to prevent, minimize, or extinguish nocebo effects in pain. Pain Rep 2019

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Phrase	Effect	Strategy
"You are going to feel a big bee sting; this is the worst part of the procedure"	More pain	• No explanation of rationale • Negative expectations
"We are going to give you a local anaesthetic that will numb the area and you will be comfortable during the procedure"	Less pain	• Explains rationale • Encouraging language

Encouraging:
Equality on assessment by independent regulators

Explains rationale:
Savings for system Reinvested into healthcare

Kim et al Front Pharmacol 2020; Fleischmann et al Rheumatol Ther 2020; Kristensen et al BioDrugs 2018