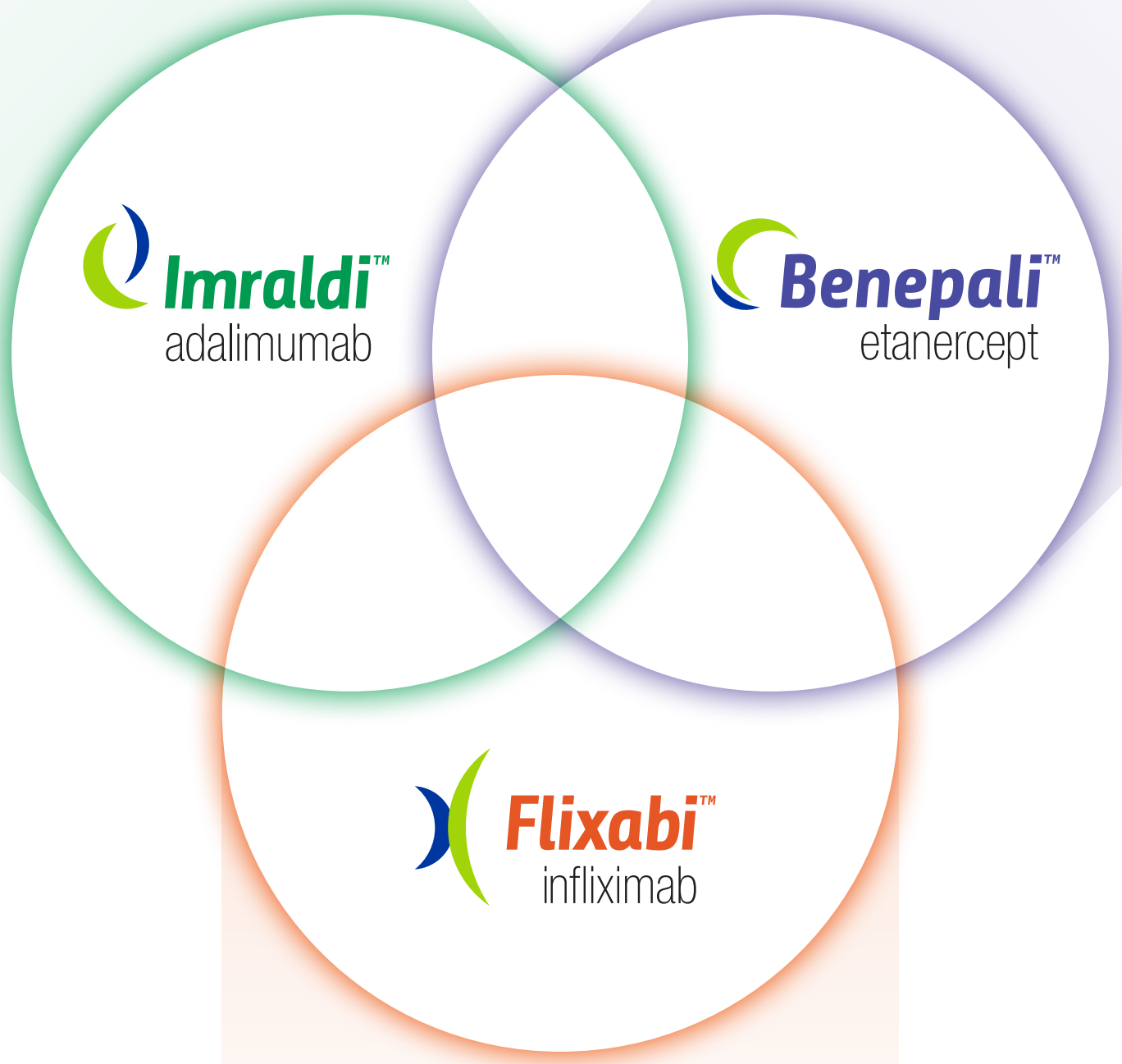
Biogen Anti-TNF PORTFOLIO DOSSIER



Immunology Portfolio

Biogen Biosimilars. Transforming *More* Lives.

Biogen

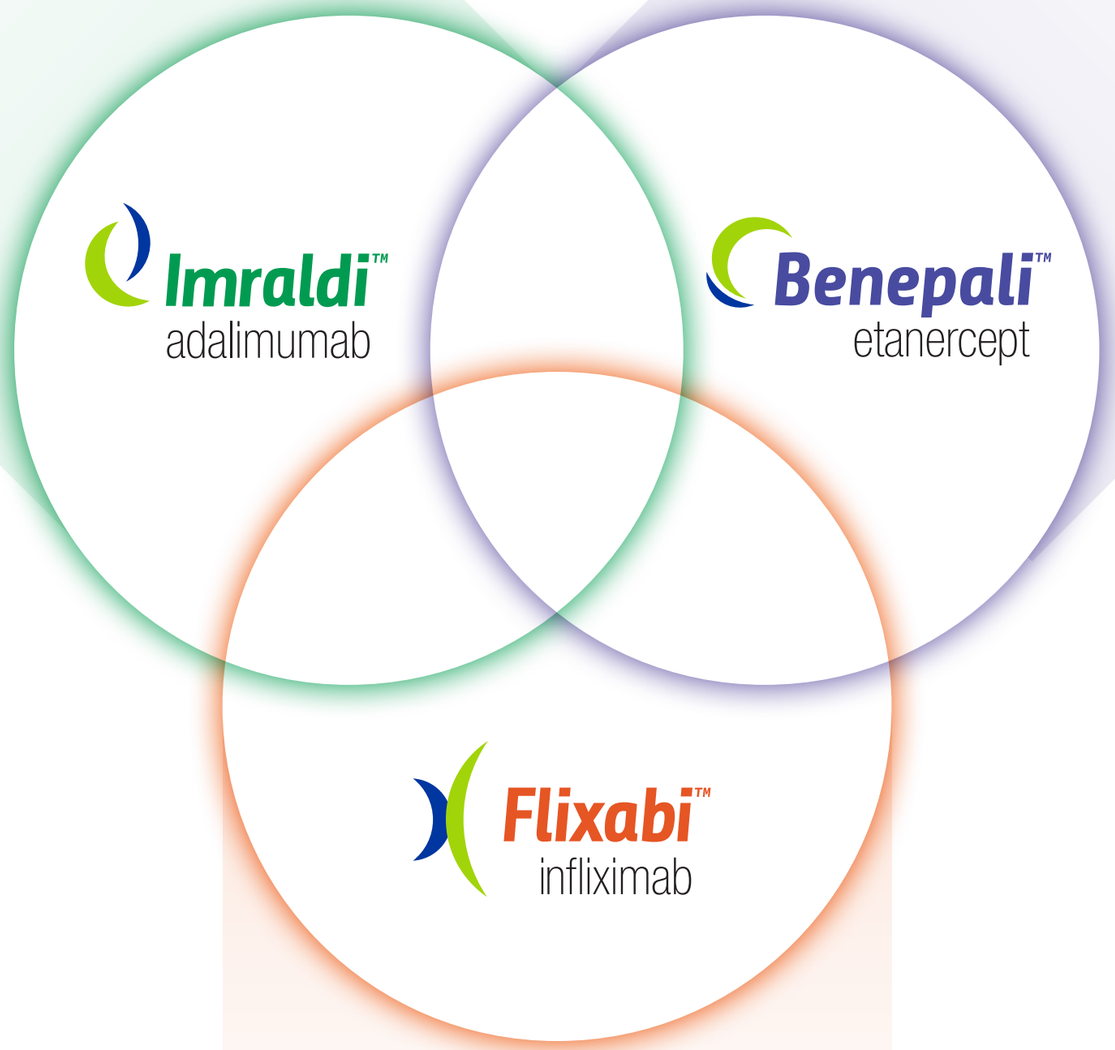


Table of contents

Note: For detailed and more in-depth information, please refer to the current product information and package inserts.

Overview

Biosimilars from the biologics expert

The manufacture of biotechnology products is complex and requires highly specialized knowledge. For more than 40 years, Biogen has successfully produced advanced biologics and is now one of a few companies that have the advanced manufacturing capabilities and extensive scientific expertise to produce biosimilars of consistent quality.

Biosimilars can help reduce spending on critically needed biopharmaceuticals, thereby increasing their availability to patients. Through significant savings, they also create financial headroom for further innovative medicines that benefit patients with severe diseases.

Biogen

Transforming *More* Lives

- **41% increase** in immune-mediated inflammatory disease treatment administration following introduction of Biosimilars[1] including Imraldi™[2], Benepali™[3] and Flixabi™[4]
- **More than 250.000 in Europe** are currently receiving a Biogen biosimilar[§]

	ADULT PATIENTS	Imraldi™ adalimumab	Benepali™ etanercept	Flixabi™ infliximab
Rheumatic Disease	Rheumatoid arthritis (RA)	■	■	■
	Axial spondyloarthritis (AS)	■	■	■
	Non-radiographic axial spondyloarthritis (nr-AxSpA)	■	■	
	Psoriatic arthritis (PsA)	■	■	■
Dermatologic Disease	Plaque psoriasis (PsO)	■	■	■
	Hidradenitis suppurativa	■		
IBD	Crohn's disease (CD)	■		■
	Ulcerative colitis (UC)	■		■
	Uveitis	■		

	PEDIATRIC PATIENTS#	Imraldi™ adalimumab	Benepali™ etanercept	Flixabi™ infliximab
Rheumatic Disease	Juvenile idiopathic arthritis (JIA)	■	■	
	Psoriatic arthritis (PsA)	■		
Dermatologic Disease	Plaque psoriasis (PsO)	■	■	
	Hidradenitis suppurativa	■		
IBD	Crohn's disease (CD)	■		■
	Ulcerative colitis (UC)	■		■
	Uveitis	■		

§ Q2 2022 – Financial Results and Business Update. https://investors.biogen.com/static-files/db762b3a-8c93-4913-85d9-22cc925e3d89.

1. IQVIA. The Impact of Biosimilar Competition in Europe [White paper]. https://www.iqvia.com/library/white-papers/the-impact-ofbiosimilar-competition-in-europe. Published: January 2021. Accessed September 2022. 2. IMRALDI™ 40 mg Summary of Product Characteristics, July 2021. 3. BENEPALI™ 25 mg/50 mg Summary of Product Characteristics, last revised in May 2021. 4.FLIXABI™ Summary of Product Characteristics, last revised in December 2021.

Shelf life and storage

IMRALDI™

Store the pen and syringe in the refrigerator (2–8°C). Do not freeze.

The pen and syringe can be stored once for up to 28 days at room temperature (up to 25°C) protected from light. If not used within this time, they must be discarded.

Store the pen and syringe in the outer carton in order to protect from light.

Keep the pen and syringe out of the sight and reach of children.

A suitable cooler bag is available for refrigerated transport of IMRALDI™.

BENEPALI™

Store the pen and syringe in the refrigerator (2–8°C). Do not freeze.

The pen and syringe can be stored once for up to 4 weeks at room temperature (up to max. 25°C) protected from light. However, if not used within this time, they must be discarded. Do not put them back in the refrigerator.

Store the pen and syringe in the outer carton in order to protect from light.

Keep the pen and syringe out of the sight and reach of children.

A suitable cooler bag is available for refrigerated transport of BENEPALI™.

FLIXABI™

Store FLIXABI™ 100 mg powder for concentrate for solution for infusion in a refrigerator (2–8°C).

Chemical and physical in use stability of the diluted solution has been demonstrated for up to 34 days at 2–8°C and for an additional 24 hours at 25°C after removal from refrigeration.*

The shelf life before reconstitution of the finished medicinal product is 4 years at 2–8°C.

Store FLIXABI™ out of the sight and reach of children.

FLIXABI™ may be stored at temperatures up to a maximum of 25°C for a single period of up to 6 months, but not beyond the original expiry date. The new expiry date must be noted in writing on the outer carton. Once removed from cold storage, FLIXABI™ must not be returned to cold storage.

*From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution etc. has taken place in controlled and validated aseptic conditions.

Overview of pack sizes and PCN

IMRALDI™ pack sizes

Not all pack sizes may be available in your country.

Medicinal product		Pack size	PCN
IMRALDI™ 40 mg pre-filled pen	N1	2 units	14155930
IMRALDI™ 40 mg pre-filled syringe	N1	2 units	14155982
IMRALDI™ 40 mg pre-filled pen	N3	6 units	14155953
IMRALDI™ 40 mg pre-filled syringe	N3	6 units	14156013

PRE-FILLED PEN
2 × 40 mg N1

Dimensions of the pack
70 × 182 × 40 mm

PRE-FILLED SYRINGE
2 × 40 mg N1

Dimensions of the pack
90 × 149 × 60 mm

PRE-FILLED PEN
6 × 40 mg N3

Dimensions of the pack
105 × 182 × 70 mm

PRE-FILLED SYRINGE
6 × 40 mg N3

Dimensions of the pack
150 × 150 × 90 mm

Each pack of IMRALDI™ contains one alcohol wipe per pen or syringe.

Shelf life and storage

IMRALDI™

Low-volume formulation.

Citrate-free formulation.

Store the pen and syringe in the refrigerator (2–8°C). Do not freeze.

The pen and syringe can be stored once for up to 31 days at room temperature (up to 25°C) protected from light. If not used within this time, they must be discarded.

Store the pen and syringe in the outer carton in order to protect from light.

Keep the pen and syringe out of the sight and reach of children.

A suitable cooler bag is available for refrigerated transport of IMRALDI™.

BENEPALI™

Store the pen and syringe in the refrigerator (2–8°C). Do not freeze.

The pen and syringe can be stored once for up to 4 weeks at room temperature (up to max. 25°C) protected from light. However, if not used within this time, they must be discarded. Do not put them back in the refrigerator.

Store the pen and syringe in the outer carton in order to protect from light.

Keep the pen and syringe out of the sight and reach of children.

A suitable cooler bag is available for refrigerated transport of BENEPALI™.

FLIXABI™

Store FLIXABI™ 100 mg powder for concentrate for solution for infusion in a refrigerator (2–8°C).

Chemical and physical in use stability of the diluted solution has been demonstrated for up to 34 days at 2–8°C and for an additional 24 hours at 25°C after removal from refrigeration.*

The shelf life before reconstitution of the finished medicinal product is 4 years at 2–8°C.

Store FLIXABI™ out of the sight and reach of children.

FLIXABI™ may be stored at temperatures up to a maximum of 25°C for a single period of up to 6 months, but not beyond the original expiry date. The new expiry date must be noted in writing on the outer carton. Once removed from cold storage, FLIXABI™ must not be returned to cold storage.

*From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution etc. has taken place in controlled and validated aseptic conditions.

Overview of pack sizes and PCN

IMRALDI™ pack sizes

Not all pack sizes may be available in your country.

Medicinal product		Pack size	PCN
IMRALDI™ 40 mg pre-filled pen	N1	2 units	14155930
IMRALDI™ 40 mg pre-filled syringe	N1	2 units	14155982
IMRALDI™ 40 mg pre-filled pen	N3	6 units	14155953
IMRALDI™ 40 mg pre-filled syringe	N3	6 units	14156013

PRE-FILLED PEN
2 × 40 mg N1

Dimensions of the pack
70 × 182 × 40 mm

PRE-FILLED SYRINGE
2 × 40 mg N1

Dimensions of the pack
90 × 149 × 60 mm

PRE-FILLED PEN
6 × 40 mg N3

Dimensions of the pack
105 × 182 × 70 mm

PRE-FILLED SYRINGE
6 × 40 mg N3

Dimensions of the pack
150 × 150 × 90 mm

Each pack of IMRALDI™ contains one alcohol wipe per pen or syringe.

Overview of pack sizes and PCN

BENEPALI™ pack sizes

Not all pack sizes may be available in your country.

Pharmaceutical form		Pack size	PCN
BENEPALI™ 50 mg pre-filled pen	N1	4 units	11557993
BENEPALI™ 50 mg pre-filled pen	N3	12 units	11558001
BENEPALI™ 50 mg pre-filled syringe	N1	4 units	11558030
BENEPALI™ 50 mg pre-filled syringe	N3	12 units	11558047
BENEPALI™ 25 mg pre-filled syringe	N1	8 units	13167173
BENEPALI™ 25 mg pre-filled syringe	N3	24 units	13167204

PRE-FILLED PEN
4 × 50 mg N1
(2 × 2 pens)

Dimensions of the pack
125 × 46 × 183 mm

PRE-FILLED PEN
12 × 50 mg N3
(3 × 4 pens)

Dimensions of the pack
128 × 151 × 192 mm

PRE-FILLED SYRINGE
4 × 50 mg N1
(2 × 2 syringes)

Dimensions of the pack
129 × 50 × 183 mm

PRE-FILLED SYRINGE
12 × 50 mg N3
(3 × 4 syringes)

Dimensions of the pack
192 × 132 × 162 mm

PRE-FILLED SYRINGE
8 × 25 mg N1
(2 × 4 syringes)

Dimensions of the pack
192 × 132 × 110 mm

PRE-FILLED SYRINGE
24 × 25 mg N3
(6 × 4 syringes)

Dimensions of the pack
262 × 192 × 162 mm

Overview of pack sizes and PCN

FLIXABI™ pack sizes

Not all pack sizes may be available in your country.

Concentrate for solution for infusion		Pack size	PCN
FLIXABI™ 100 mg	-	1 unit	11655945
FLIXABI™ 100 mg	N1	3 units	11655968
FLIXABI™ 100 mg	N1	4 units	11655974
FLIXABI™ 100 mg	N2	5 units	11655980

VIAL
1 × 100 mg

Dimensions of the pack
88 × 49.5 × 49.5 mm

VIAL
4 × 100 mg, N1

Dimensions of the pack
78 × 128.6 × 62.5 mm

VIAL
3 × 100 mg, N1

Dimensions of the pack
78 × 96.6 × 62.5 mm

VIAL
5 × 100 mg, N2

Dimensions of the pack
78 × 160.6 × 62.5 mm

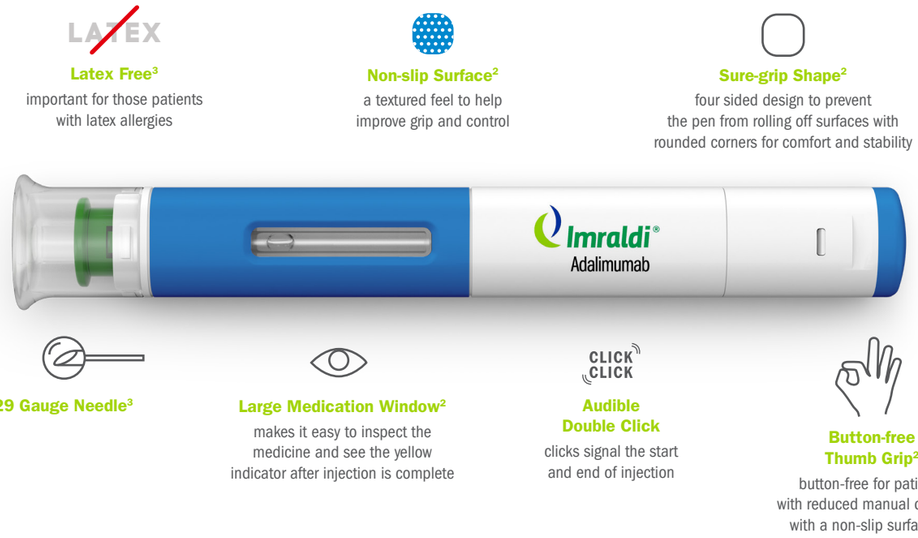
A suitable infusion filter is provided with each pack or bundle of packs of FLIXABI™.

IMRALDI™
Devices

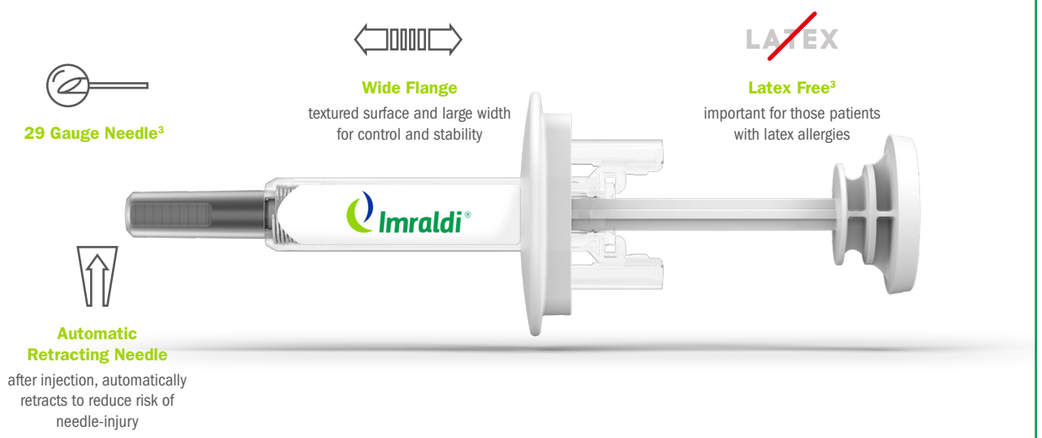
IMRALDI™ is administered by subcutaneous injection. After training in injection technique, your patients can self-inject IMRALDI™ using a 40 mg pre-filled pen or 40 mg pre-filled syringe.

The IMRALDI™ devices are designed to be as easy as possible for patients to use. Biogen will provide an IMRALDI™ training pen and an IMRALDI™ training syringe for training patients at the doctor's office.

IMRALDI™ pre-filled pen
Buttonless injection and good control



IMRALDI™ pre-filled syringe
Automatic needle retraction and good hold



IMRALDI™
Dosing schedule for Adults[1]

BENEPALI™ DOSAGE						
INDICATIONS FOR ADULTS	WEEK 0	WEEK 1	WEEK 2	WEEK 3	WEEK 4	MAINTENANCE THERAPY
Rheumatoid arthritis^# (comb. with methotrexate)	40 mg		40 mg		40 mg	every two weeks
Axial spondyloarthritis Ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis	40 mg		40 mg		40 mg	every two weeks
Psoriatic arthritis	40 mg		40 mg		40 mg	every two weeks
Plaque psoriasis^§	80 mg	40 mg		40 mg		every two weeks
Hidradenitis suppurativa	160 mg		80 mg		40 mg 80 mg	every week or every two weeks
Crohn's disease^~#	80 mg		40 mg		40 mg	every two weeks
Ulcerative colitis	160 mg		80 mg		40 mg	every two weeks
Uveitis¶†	80 mg	40 mg		40 mg		every two weeks

Rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis	If there is no response within 12 weeks, continuation of treatment should be reconsidered.
Psoriasis	If there is no response within 16 weeks, continuation of treatment should be carefully reconsidered.
Hidradenitis suppurativa	If there is no response within 12 weeks, continuation of treatment should be carefully reconsidered.
Crohn's disease	Some patients with no response to treatment at week 4 may benefit from continuation of maintenance therapy until week 12. If there is no response to treatment during this period, continuation of treatment should be carefully reconsidered.
Ulcerative colitis	If there is no clinical response within 2–8 weeks, treatment should not be continued.

For detailed information on posology, clinical response or possible discontinuation and resumption of treatment, please refer to the current Summary of Product Characteristics for IMRALDI™.[1]

$ Insight Health NVI-KT Regio Jan 2018-Dec 2020 data on file. # Depending on the indication, different lower limits for age and weight must be observed when starting treatment (see relevant Summary of Product Characteristics).

IMRALDI™
Dosing schedule for children and adolescents

BENEPALI™ DOSAGE						
INDICATIONS FOR CHILDREN AND ADOLESCENTS	WEEK 0	WEEK 1	WEEK 2	WEEK 3	WEEK 4	MAINTENANCE THERAPY
Juvenile idiopathic arthritis (JIA) Polyarticular juvenile idiopathic arthritis from the age of 2 years; ≥30 kg BW¶ Enthesitis-associated arthritis from the age of 6 years ≥30 kg BW¶	40 mg		40 mg		40 mg	every two weeks
Plaque psoriasis from 4 years of age ≥30 kg BW¶	40 mg	40 mg		40 mg		every two weeks
Hidradenitis suppurativa^~ from 12 years of age ≥30 kg BW	80 mg	40 mg		40 mg		every two weeks
Crohn's disease^~# from 6 years of age ≥40 kg BW¶	80 mg		40 mg		40 mg	every two weeks
Ulcerative colitis <40 kg BW ≥40 kg BW	80 mg 80 mg		40 mg 40 mg		40 mg 40 mg	every two weeks
Uveitis¶† (in combination with methotrexate) from 2 years of age ≥30 kg BW	40 mg		40 mg		40 mg	every two weeks

Polyarticular juvenile idiopathic arthritis	If there is no response within 12 weeks, continuation of treatment should be carefully reconsidered.
Plaque psoriasis	If there is no response within 16 weeks, continuation of treatment should be carefully reconsidered.
Hidradenitis suppurativa	If there is no response within 12 weeks, continuation of treatment should be carefully reconsidered.
Crohn's disease	If there is no response within 12 weeks, continuation of treatment should be carefully reconsidered.

For detailed information on posology, clinical response or possible discontinuation and resumption of treatment, please refer to the current Summary of Product Characteristics for IMRALDI™.[1]

^ The dosage may be increased to 40 mg weekly or 80 mg every 2 weeks in

Patients on monotherapy with inadequate response to 40 mg every 2 weeks.

§ Inadequate response to 40 mg every 2 weeks at 16 weeks. If sufficient response is achieved with dose increase, then reduce to 40 mg every 2 weeks.

~ Loss of efficacy at 40 mg every 2 weeks.

If more rapid response to treatment is required, the dose may be increased: 160 mg at week 0 (as 4 injections per day or 2 injections per day for 2 consecutive days), 80 mg at week 2 (as 2 injections per day) and then 40 mg every 2 weeks.

¶ Children <30 kg with JIA, plaque psoriasis, or uveitis, or <40 kg with Crohn's disease require a form of adalimumab that allows dosage per kg of body weight.

† If treatment is initiated with IMRALDI™, an induction dose of 80 mg may be administered one week prior to the start of maintenance therapy in patients ≥30 kg. No clinical data are available on the use of an adalimumab induction dose in children < 6 years of age.

IMRALDI™
Information kits

The IMRALDI™ training kit with training pen or training syringe and a presentation aid will help you train your patients to self-inject.

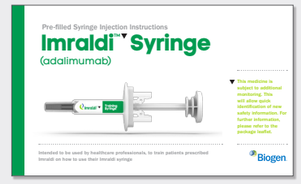
Your patients can use the reusable training pen and training syringe, which do not contain a needle or solution for injection, to practice the injection process and handling of the devices under your guidance.

The clear illustrations in the presentation aid will help you to explain the injection process with the pre-filled pen or pre-filled syringe to your patients step by step.

Training kits

IMRALDI™ training pen

IMRALDI™ training syringe



The IMRALDI™ training devices do not contain a needle or solution for injection. With the help of the training pen/syringe, patients can practice self-injection several times at the doctor's office.

Patient kits

For further information, you can refer your patients to the Quick Start Guides, Patient Leaflet and Injection Video, in addition to the package insert.

Patient information kit

Includes:

- Patient brochure
- Injection calendar
- Travel certificate
- Care+ registration card
- Card for syringe injection video

Syringe injection videos
www.imraldi.eu

IMRALDI™
Real-world evidence

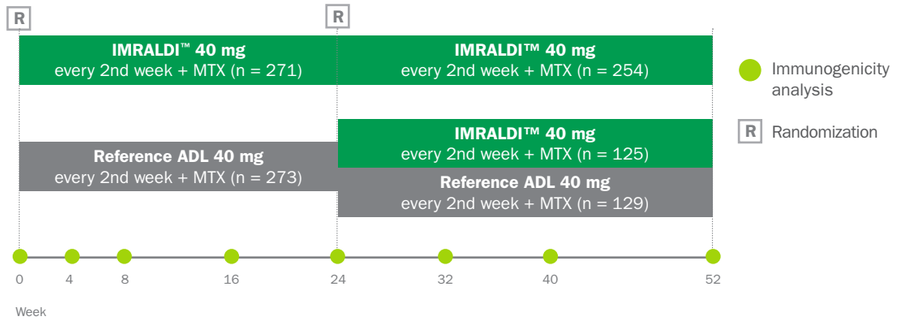
Clinical data show similar efficacy and tolerability to the reference adalimumab whether used first line[5,6] or after switching[6]

IMRALDI™. Phase III study design.

Patients with rheumatoid arthritis and prior methotrexate treatment, n = 544

Primary endpoint:
ACR20 at Week 24

Secondary endpoints: including DAS28, ACR20/50/70 to 52 weeks, tolerability, and immunogenicity



ACR20/50/70 = American College of Rheumatology 20% / 50% / 70% improvement score. Reference ADL = Reference adalimumab Humira® , Humira® is a registered trademark of AbbVie Biotechnology Ltd. DAS28 = Disease Activity Score 28. MTX = methotrexate

Figure adapted from Weinblatt ME et al. 2018

IMRALDI™. ACR response rates show comparable efficacy to the reference adalimumab, sustained over 52 weeks even after switching from Humira® # to IMRALDI™.

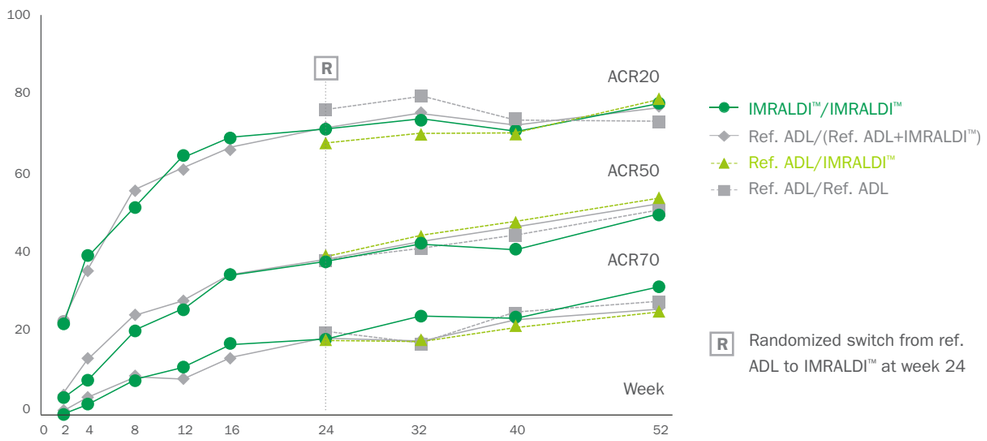


Figure adapted from Weinblatt ME et al.4, Ref. ADL = reference adalimumab Humira® , Humira® is a registered trademark of AbbVie Biotechnology Ltd.

IMRALDI™
Real-world evidence

IMRALDI™. Mean DAS28 scores show sustained improvement in disease activity over 52 weeks, similar to the reference adalimumab and after switching from Humira® # to IMRALDI™.

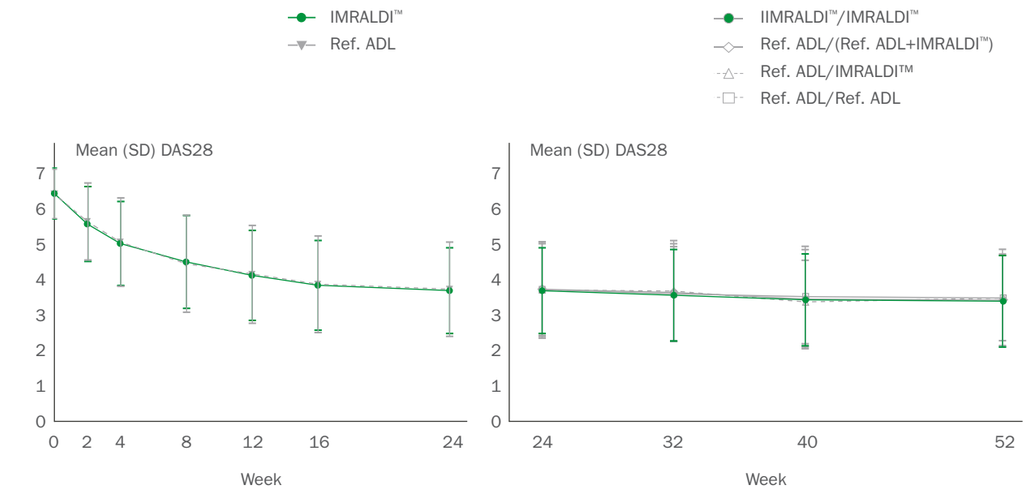


Figure adapted from Kay J et al.[7]

Figure adapted from Weinblatt ME et al.[6]

IMRALDI™. Good tolerability at the injection site, comparable to the reference adalimumab.

Patients with injection site reactions (ISR) in %

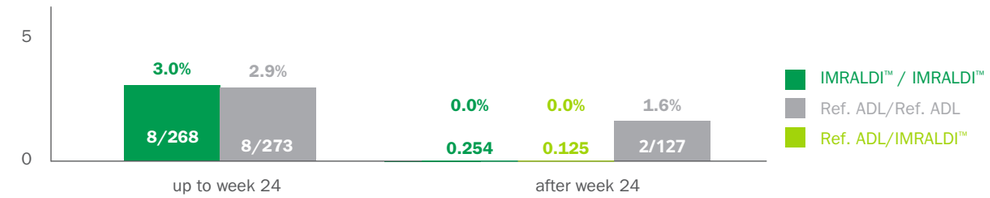


Figure adapted from Weinblatt ME et al.[5,6]

AUTHORS' CONCLUSION

IMRALDI™ was well tolerated over the one-year study period and showed comparable efficacy, tolerability and immunogenicity to the reference adalimumab. Switching from Humira® # to IMRALDI™ had no impact on tolerability, immunogenicity, and efficacy.

BENEPALI™
Devices

Benepali™ pre-filled pen

Compact and lightweight
discreet and portable for patients

Audible Double Click
clicks signal the start and end of injection

Latex Free
Reassurance for patients with latex allergies or their family

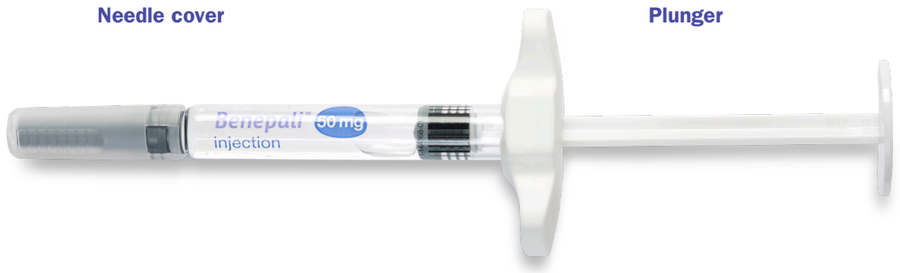
Medication Window
confirms full dose delivery, maximising patient benefit

Button-free
Simple to use

Benepali™ pre-filled syringe

Needle cover

Plunger



Latex Free[2]
Reassurance for patients with latex allergy or their family

Ergonomic Finger Grip

Stainless steel[1]
27 gauge needle

BENEPALI™
Dosing schedule for adults

BENEPALI™ DOSAGE	
INDICATIONS FOR ADULT PATIENTS	WEEKLY
Rheumatoid arthritis (administration in combination with methotrexate)	1 × / week: 50 mg or 2 × / week: 25 mg
Axial spondyloarthritis • Ankylosing spondylitis • Non-radiographic axial spondyloarthritis	50 mg or 25 mg
Psoriatic arthritis	50 mg or 25 mg
Plaque psoriasis	50 mg or 25 mg; alternatively 50 mg 2 × / week for up to 12 weeks
ASSESSMENT OF TREATMENT RESPONSE IN ADULTS	
Rheumatoid arthritis, axial spondylitis, psoriatic arthritis	If there is no response within 12 weeks, continuation of treatment should be carefully considered.
Plaque psoriasis	If there is no response after 12 weeks, treatment should be discontinued. If reinitiation of treatment is indicated, the same guidance on treatment duration should be followed (see Posology); the dose should be 25 mg twice weekly or 50 mg once weekly.

Dosing schedule for children and adolescents[1]

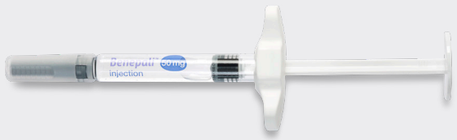
BENEPALI™ DOSAGE	
INDICATIONS CHILDREN AND ADOLESCENTS FROM 62.5 kg BW#	WEEKLY
Juvenile idiopathic arthritis • Polyarthritis and oligoarthritis from the age of 2 years • Enthesitis-associated arthritis from the age of 12 years Psoriatic arthritis from the age of 12 years	50 mg or 25 mg
Plaque psoriasis from the age of 6 years	50 mg
ASSESSMENT OF TREATMENT RESPONSE – CHILDREN AND ADOLESCENTS	
Juvenile idiopathic arthritis, psoriatic arthritis	Treatment discontinuation should be considered in patients who do not respond to treatment after 4 months.
Plaque psoriasis	Treatment should be discontinued in patients who have not responded after 12 weeks. If reinitiation of treatment is indicated, the same guidance on treatment duration should be followed (see Posology); the dose should be 0.8 mg/kg body weight (up to a maximum of 50 mg per dose) once weekly.

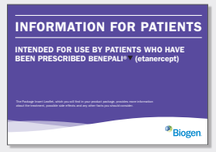
BENEPALI™ is only available as a 50 mg pre-filled pen and as a 50 mg or 25 mg pre-filled syringe. BENEPALI™ can therefore not be used in children and adolescents who require less than a full 50 mg or 25 mg dose. Patients who weigh 62.5 kg or more may receive the dose using a pre-filled syringe or a pre-filled pen with a fixed dose.

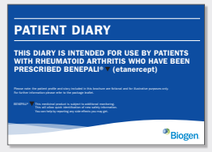
BENEPALI™
Information kits

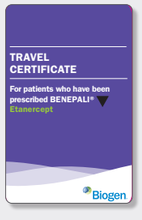
BENEPALI™ Patient Information Kit

Pen and pre-filled syringe injection videos **www.benepali.eu**









The BENEPALI™ training pen and a graphic presentation aid will help you to instruct your patients on how to self-inject. The BENEPALI™ training pen does not have a needle and does not contain any solution for injection. With the reusable training pen, patients can practice injecting themselves several times in the doctor's office.

The BENEPALI™ Patient Information Kit includes a link to a self-injection video with the pre-filled pen, the product information leaflet and a travel certificate.

* Store the pre-filled pens/pre-filled syringes in the outer carton in order to protect from light. BENEPALI™ may be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks after which, it should not be refrigerated again. BENEPALI™ should be discarded if not used within 4 weeks of removal from refrigeration.

BENEPALI™

Clinical data confirm the long-term efficacy of BENEPALI™ whether used at initiation of treatment or after switching[4]

BENEPALI™ Mean DAS28 scores remained stable over 100 weeks both with continuous BENEPALI™ treatment and after switching from reference etanercept# to BENEPALI™.

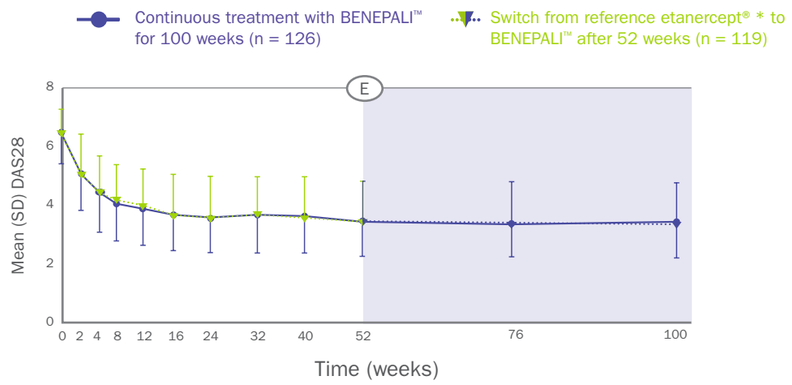
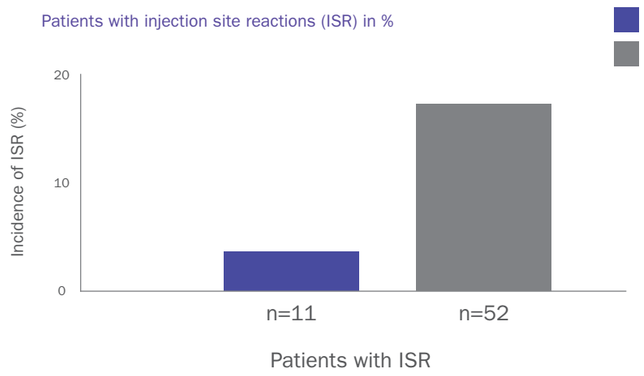


Figure adapted from Emery P et al. 20175. DAS28 = Disease Activity Score 28. E = Extension. # reference etanercept Enbrel® , Enbrel® is a registered trademark of Pfizer Inc.

BENEPALI™ The lower incidence of ISR vs. reference etanercept# indicates better injection site tolerability[5]



BENEPALI™

Reference etanercept#

Injection site reactions (ISRs) were mostly mild and transient.

Figure adapted from Girolomoni G et al. 2017[6]

Reference etanercept Enbrel® , Enbrel® is a registered trademark of Pfizer Inc.

AUTHORS' CONCLUSION

BENEPALI™ has the same efficacy as reference etanercept with less immunogenicity and fewer injection site reactions.[5,6]

Evidence from everyday practice: Registry data show high retention rates with BENEPALI™ whether used at initiation of treatment[7] or after switching[8]

Data from the longitudinal RABBIT+ registry: 86% retention with BENEPALI™ vs. 68% with reference etanercept# after 6 months of therapy in biologic-naive patients

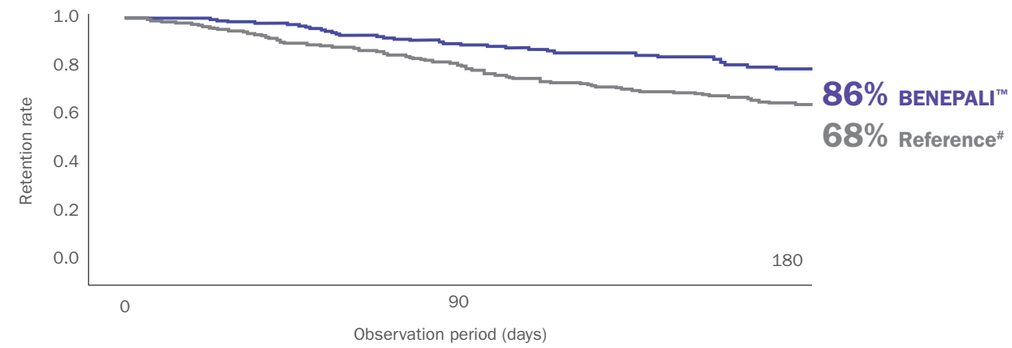


Figure adapted from Strangfeld A et al. 2018[7]. Registry data collected through December 2017; biologic-naive patients: 250 on BENEPALI™, 317 on Enbrel® #. Adjustment of curves for disease duration and comorbidities had no significant effect on results. # Reference etanercept Enbrel® , Enbrel® is a registered trademark of Pfizer Inc. + RABBIT = Rheumatoid arthritis: Observation of biologic therapy.

Data from the DANBIO registry: Retention rates at 1 year were significantly higher after switching to BENEPALI™ than with continued treatment with reference etanercept#.

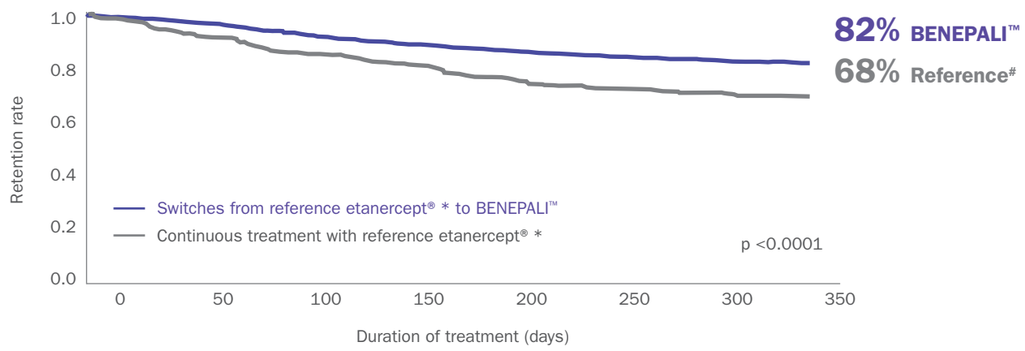


Figure adapted from Glintborg B et al. 2017[8] #Reference etanercept Enbrel® , Enbrel® is a registered trademark of Pfizer Inc.

- Danish DANBIO registry: prospective evaluation of 1-year retention rates of etanercept patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (AxSpA).
- n = 2061 (1621 switchers to BENEPALI™, 440 non-switchers); switch for economic reasons per national guideline in April 2016; mean duration of treatment with etanercept before switch: 6 years (RA), 4.3 years (PsA), 4.6 years (AxSpA).

FLIXABI™
Preparation of infusion (step by step)

1

Remove the cap from the bottle and clean the top with 70% alcohol.

Under aseptic conditions, insert a 21G (0.8 mm) or smaller needle through the center of the rubber stopper.

Allow 10 mL of water for injection per vial to run along the inner wall of the vial.

2

To dissolve the powder, gently turn the bottle, do not move it for too long or vigorously, do not shake!

Foaming is not uncommon but should be avoided.

3

Let the solution stand for 5 minutes.

Examine the solution: It should be colorless to pale yellow and opalescent; fine translucent particles may be present.

Do not use solutions with opaque particles, discoloration or foreign particles.

4

Dilute the total volume of infliximab solution required to 250 mL with 0.9% sodium chloride (NaCl) solution for infusion.

To do this, first withdraw the corresponding volume of FLIXABI™ solution(s) from the 250 mL 0.9% NaCl solution.

Slowly add the FLIXABI™ solution from the vials to the infusion bag and mix gently. Ensure that the concentration of the solution for infusion does not exceed 4 mg/mL.

5

Administer the solution for infusion over at least the recommended infusion time.

The appropriate infusion filter is included with each pack or bundle pack of FLIXABI™ or is available from Biogen.

Do not co-administer FLIXABI™ with other agents via the same intravenous line.

FLIXABI™
Infusion instruction

Recommended duration of infusion and follow-up in practice

FLIXABI™ is administered intravenously over a 2-hour period. All patients should be monitored for acute infusion-related reactions for at least 1–2 hours after infusion.

INDUCTION PHASE

1st Infusion

Infusion: **2 hrs** Observation: **1–2 hrs**

2nd Infusion

Infusion: **2 hrs** Observation: **1–2 hrs**

3rd Infusion

Infusion: **2 hrs** Observation: **1–2 hrs**

MAINTENANCE THERAPY: shortened infusion as an option in adults after induction phase

In carefully selected patients who have tolerated at least 3 initial 2-hour FLIXABI™ infusions and are receiving maintenance therapy, subsequent infusions may be shortened, as long as they administered over at least 1 hour. If an infusion reaction occurs with the shortened infusion, the infusion rate should be slowed for subsequent infusions. Shortened infusions at doses >6 mg/kg have not been studied.

Infusion: **min 1 hr** Observation: **1–2 hrs**

FLIXABI™
Dosing schedule[1]

FLIXABI™ DOSAGE				
INDICATIONS	WEEK 0	WEEK 2	WEEK 6	MAINTENANCE THERAPY
Crohn's disease ・with fistula formation ・incl. children and adolescents from 6 years of age	**5 mg/kg BW**	**5 mg/kg BW**	**5 mg/kg BW**	every 8 weeks
Ulcerative colitis incl. children and adolescents from 6 years of age	**5 mg/kg BW**	**5 mg/kg BW**	**5 mg/kg BW**	every 8 weeks
Rheumatoid arthritis (administration in combination with MTX)	**3 mg/kg BW**	**3 mg/kg BW**	**3 mg/kg BW**	every 8 weeks
Ankylosing spondylitis from 6 years of age ≥40 kg BW¶	**5 mg/kg BW**	**5 mg/kg BW**	**5 mg/kg BW**	every 6–8 weeks
Psoriatic arthritis	**5 mg/kg BW**	**5 mg/kg BW**	**5 mg/kg BW**	every 8 weeks
Psoriasis	**5 mg/kg BW**	**5 mg/kg BW**	**5 mg/kg BW**	every 8 weeks

MTX = methotrexate
BW = body weight

Assessment of treatment response

Moderate to severe CD in adults:	no response after 2nd dose→ treatment should not be continued
CD with fistula formation in adults:	no response after 3rd dose→ treatment should not be continued
UC:	no response after 3rd dose→ treatment should be continued with careful monitoring
RA:	no therapeutic benefit within the first 12 weeks or after dose adjustment→ continuation of treatment should be carefully reconsidered. In case of inadequate response and loss of response after 12 weeks, the dose may be gradually increased by approx. 1.5 mg/kg BW to a maximum of 7.5 mg/kg BW every 8 weeks, or alternatively 3 mg/kg BW every 4 weeks
AS:	no response after 2nd dose→ treatment should not be continued
Pso:	no response after 4th dose→ treatment should not be continued
CD in children/adolescents:	current data do not support continuation of treatment if there is no response within the first 10 weeks
UC in children/adolescents	current data do not support continuation of treatment if there is no response within the first 8 weeks

For detailed information on dosing, clinical response or possible discontinuation or resumption of treatment, please refer to the current Summary of Product Characteristics for FLIXABI™.
AS, Ankylosing spondylitis; BW, body weight; CD, Crohn's disease; Pso, Psoriasis; RA, rheumatoid arthritis; UC, Ulcerative colitis.

FLIXABI™
Follow-up

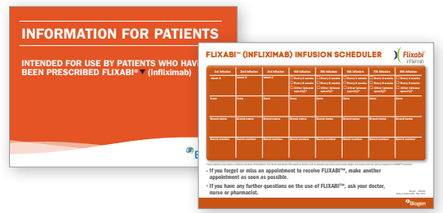
A FLIXABI™ case report form may be used to monitor the course of treatment.

FLIXABI™ Case Report Form

Materials for patients

FLIXABI™ Package Leaflet

FLIXABI™ Patient Card



Contents of the patient information kit. Patient brochure and infusion calendar

Shelf life and storage of the ready-to-use solution

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Chemical and physical in use stability of the diluted solution has been demonstrated for up to 34 days at 2°C to 8°C and for an additional 24 hours at 25°C after removal from refrigeration.

From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

The storage time should not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution etc. has taken place in controlled and validated aseptic conditions.

Unused portions of the solution should not be reused.

Prospective data on switching from reference infliximab to FLIXABI™ in IBD# patients[3]

Prospective 80-week study of switching from Remicade® # to FLIXABI™ in everyday clinical practice in Germany n = 144 patients (n = 94 Crohn's disease, n = 50 ulcerative colitis)

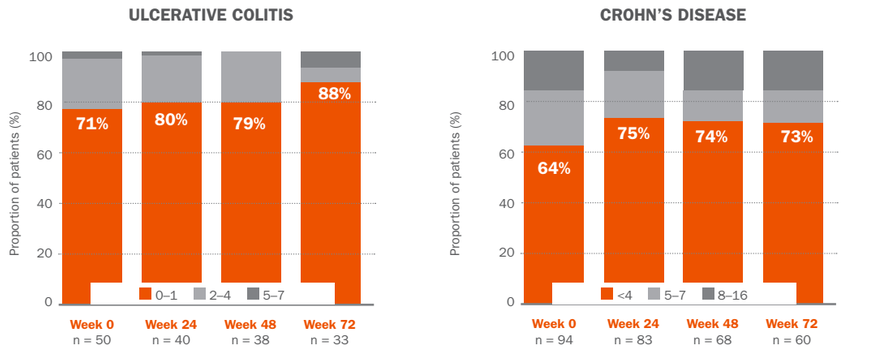
University Hospital Erlangen

Median duration of treatment with Remicade® # before switch: 30.5 months (2–110), median age 39.5 years (19–78)

Assessment of disease activity: Harvey-Bradshaw Index (Crohn's Disease), Partial Mayo Score (Ulcerative Colitis)

Evaluation of infliximab trough levels, anti-drug antibodies (ADAs) and adverse effects

Sustained high remission rates after switching to FLIXABI™



Partial Mayo score

0–1	Remission
2–4	Mild disease activity
5–7	Moderate disease activity
8–9	Severe disease activity

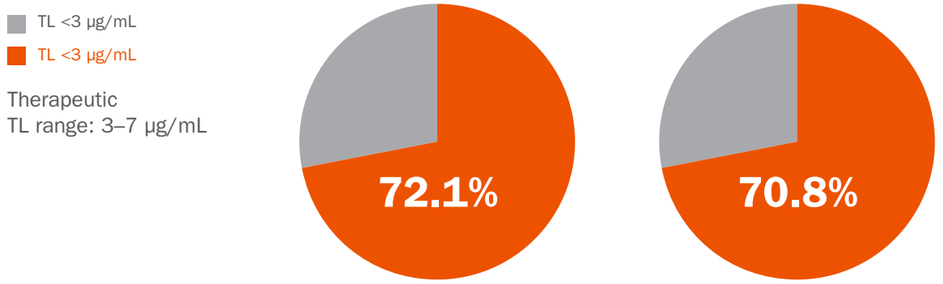
Harvey Bradshaw Index

<4	Remission
5–7	Mild disease activity
8–16	Moderate disease activity
>17	Severe disease activity

Figures adapted from Fischer S et al. 2021[3].

FLIXABI™
Clinical data – Gastroenterology

Changes in infliximab trough levels (TL) over time



Before the switch to FLIXABI™
Week 0

During treatment with FLIXABI™
Week 24

With FLIXABI™, 70.8% of the measured infliximab trough levels were within or above the therapeutic TL range at week 24.[4]

Anti-drug antibody (ADA) determination

Before switching to FLIXABI™ (week 0), 11 patients (9.8%) were ADA-positive, of whom 5 were ADA-positive over the 80-week follow-up period after the switch and 4 became ADA negative.[3]

After switching to FLIXABI™, 7 patients had new-onset and persistent ADAs, 2 patients discontinued treatment. New-onset and transient ADAs were observed in 4 patients at only one time point.[3]

AUTHORS' CONCLUSION

IBD# patients can be switched from Remicade® # to FLIXABI™ in everyday practice.

Data show that switching has no impact on disease activity, immunogenicity or tolerability over the 80-week observation period.[3]

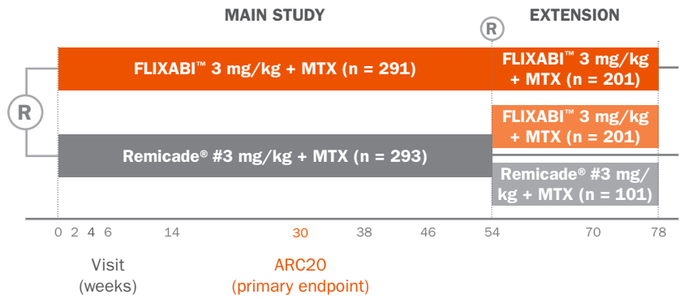
Remicade® is a registered trademark of MSD Sharp & Dohme GmbH.
Inflammatory Bowel Disease.

FLIXABI™

Clinical data – Rheumatology

Phase III study to demonstrate the similar safety and safety of FLIXABI™ and the reference infliximab drug including in patients with rheumatoid arthritis who switched to FLIXABI™[4,5]

Head-to-head study in patients with rheumatoid arthritis (RA) previously treated with methotrexate (MTX) with a 54-week main study followed by a 24-week switching period[4,5]



- Randomized, double-blind, parallel-group Phase III study: Patients received either FLIXABI™ or Remicade® # (3 mg/kg IV + MTX).
- Primary endpoint of the main study: ACR20 response rates[#] at 30 weeks
- At week 54, patients previously receiving Remicade® # were re-randomized 1:1 to either FLIXABI™ or continued treatment with Remicade® [#]; in patients who received FLIXABI™ in the main study, treatment was continued until week 70.
- Efficacy, safety, and immunogenicity were recorded in the main study and in the switching period (up to week 78).

MTX = methotrexate. R = randomization. [#] according to American College of Rheumatology (ACR) criteria.

Figures adapted from Smolen JS et al. 2017[6]

- The primary endpoint was met: ACR20 response rates for FLIXABI™ (64.1%) and Remicade® [#] (66.0%) were equivalent at week 30.[4]
- The secondary efficacy endpoints (including DAS28, ACR50, and ACR70) confirmed their comparability.[4]
- The safety profiles and immunogenicity of FLIXABI™ and Remicade® [#] were comparable in both the main study and the extension study.[5]

[#] Remicade® is a registered trademark of MSD Sharp & Dohme GmbH.

Extension of the Phase III study with switch from the infliximab reference drug to FLIXABI™[6]

The course of disease activity remained similar across all three groups even after the switch to FLIXABI™ at week 54.

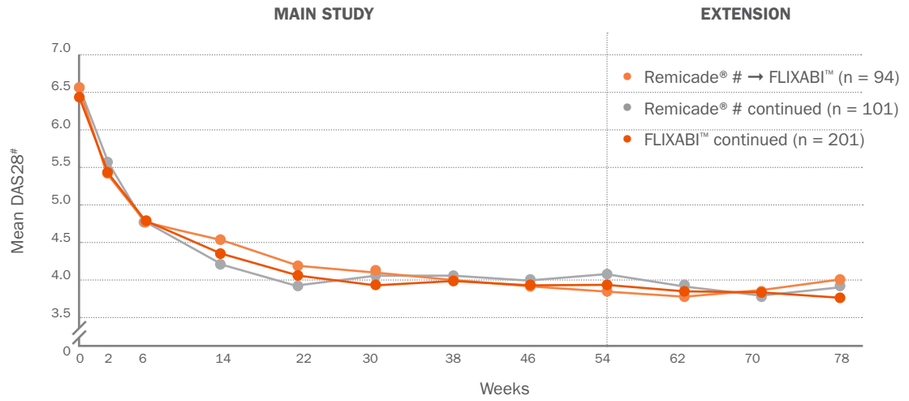


Figure adapted from Smolen JS et al. 2017[6]

Adverse events
The incidence of adverse events remained similar between groups during the switching period from week 54 to 78 (36.2% in patients who switched from Remicade® [#] to FLIXABI™, 35.6% in patients who continued to receive Remicade® [#], and 40.3% in patients who continued to receive FLIXABI™).

Immunogenicity
Of the patients who did not have antidrug antibodies (ADAs) at week 54, 14.6% who switched from Remicade®
[#] to FLIXABI™ developed ADAs. The percentage of patients who developed ADAs was similar among those who continued to receive Remicade® [#] (14.9%) and FLIXABI™ (14.1%).

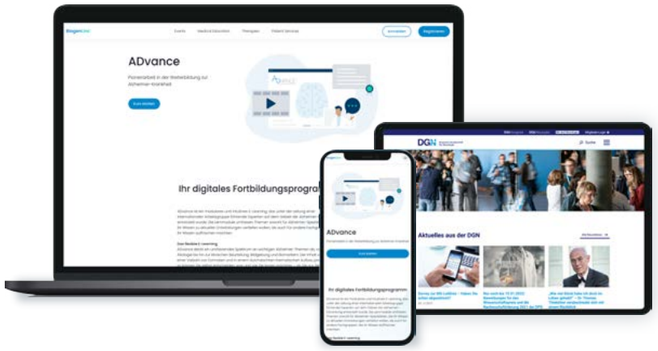
AUTHORS' CONCLUSION

FLIXABI™ showed sustained efficacy and comparable tolerability and immunogenicity to reference infliximab in the main study and after switching from reference infliximab.

[#] Remicade® is a registered trademark of MSD Sharp & Dohme GmbH . [#] Disease Activity Score 28.

Biosimilar Medical Academy – the biologics department of Biogen

For Healthcare Professionals



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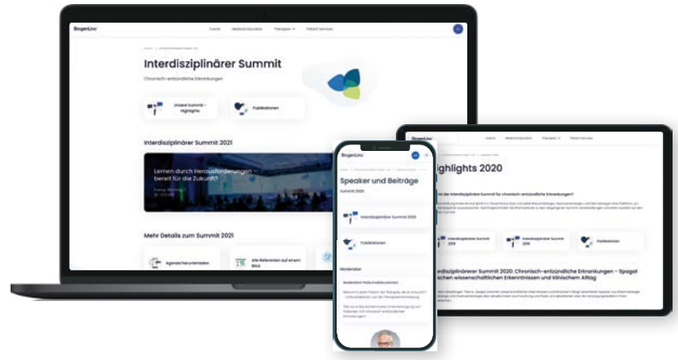

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MyCarePlus – a Biogen service for patients

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Share your inspirational stories – people want to read them!

The MyCarePlus app, a mobile all-rounder, is another service at your disposal. Compact, user-friendly, interactive: This digital service makes it easier for patients to manage their inflammatory disease through numerous functions such as medication reminders, doctor's appointments or keeping track of patients' health. This gives patients more freedom and easier access to their personal information. A good tip for your patients.

www.meincareplus.de

Information resources on exercise, work, education, social law, nutrition, travel and relationships

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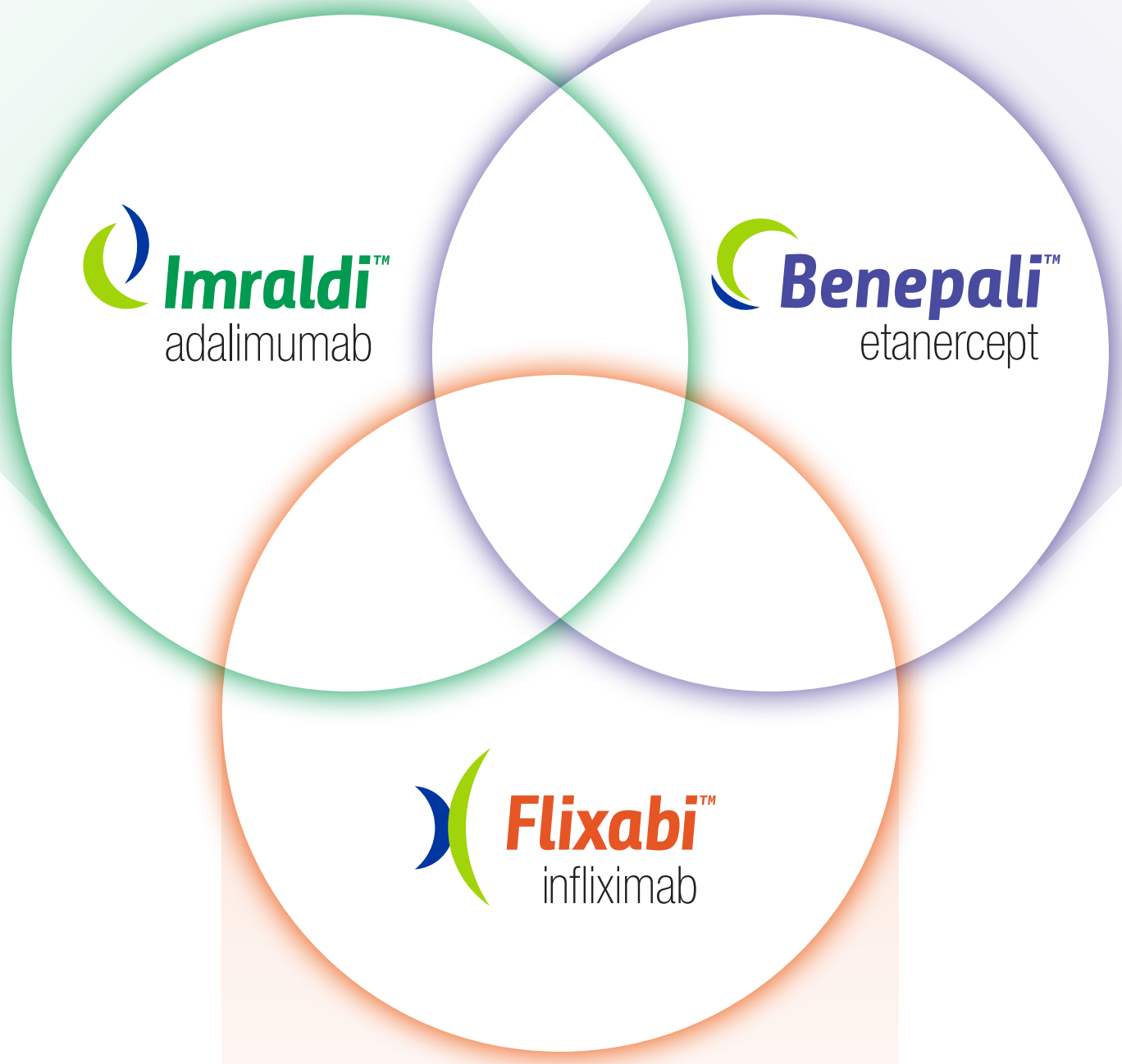

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