



High cost drugs pathway for psoriasis

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Version 2.1

This supersedes version

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DOCUMENT CONTROL

REVISION DATE	ACTIONED BY	SUMMARY OF CHANGES	VERSION
Jan 2017	Prof Richard Warren Dr Zenas Yiu	Version 1 updated to update secukinumab NICE TA status, add ixekizumab, and add apremilast.	1.1
Jan 2017	Sarah Jacobs	Changed to same format as other GMMMG biologics pathways. Added links to NICE guidance.	1.2
May 2017	Working group	Updated following NICE TA442 (ixekizumab)	1.3
June 2017	Prof Warren	Added detail around sequential use	1.4
June 2017	Sarah Jacobs	Final formatting. Added flowchart.	1.5
September 17	Prof R Warren S Jacobs	Changes following consultation. Added dimethyl fumarate	1.6
May 2018	Prof R Warren S Jacobs	Added brodalumab	2.1

Changes to version 1.0

The pathway has been updated with the following additions:

- Brodalumab added as an additional core drug
- Changed title to 'high cost' rather than biologics
- Ixekizumab added as an additional core drug
- Reference to non-biologic treatments, apremilast and dimethyl fumarate
- Biosimilars
- IFRs
- Research recruitment
- Flowchart
- Contraindications, special warnings and precautions
- Special situations
- Vaccinations

The number of drug options has increased from 3 to 4 before an IFR needs to be submitted when the patient is being treated at Salford Royal FT. The clinical reasons for this decision have been included.

Approvals

This document must be approved by the following before distribution:

TITLE	DATE OF ISSUE	VERSION
Psoriasis working group	31/07/2017	1.5
Psoriasis working group	18/09/2017	1.6
GMMMG high cost drugs subgroup	05/10/2017	1.6
GMMMG	19/10/2017	2.0
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Distribution

Final version available on GMMMG website

Contents	Page
1. Introduction	4
2. Aims	4
3. NICE guidance	5
4. Clinical reasoning for using 4 biologic drugs	6
5. Drug choice	7
1 st , 2 nd , 3 rd and 4 th choice	7
Apremilast	8
Dimethyl fumarate	8
6. Biosimilars	8
7. Individual funding requests	9
8. Research recruitment	9
9. Biologics treatment flow chart	10
10. Contraindications, special warnings and precautions	11
11. Special situations:	12
a) Peri-operative risk	
b) Pregnancy and breast feeding	12
i) Pregnancy	
ii) Breast feeding	
c) Vaccination of infants	13
12. Vaccinations	13
a) Live vaccines	
b) Non-live vaccines	14
c) Vaccination scheduling during biologic therapy	14
13. Suggested checklist for patient screening on pre-admission for biologic agents	15
14. References	16

Biologics Pathway for Psoriasis

1. Introduction

Psoriasis is a common inflammatory skin condition which is frequently (30%) associated with an inflammatory arthropathy known as psoriatic arthritis (PsA). It is often life ruining if left untreated. Compelling data demonstrate that the impact on quality of life for patients living with psoriasis is comparable or worse than diabetes, heart disease and cancer¹. Thus, it is imperative that, for those with the most severe disease, effective treatment strategies are utilised.

The National Institute for Health and Care Excellence (NICE) has published individual HTAs for the 7 licensed systemic biological therapies for psoriasis; namely adalimumab, etanercept, infliximab (Anti-TNF's), ustekinumab (IL12/23 inhibitor), secukinumab, ixekizumab and brodalumab (IL 17A inhibitors). See section 3.

Apremilast, (oral phosphodiesterase 4 inhibitor) and dimethyl fumarate have been approved by NICE for use with the same requirements as for the biologic therapies for psoriasis, (see section 5 for further details).

NICE guidance allows for treating with 2 biologic drugs, after which supra- specialist advice should be sought. This GMMMG pathway supports the use of 4 lines of biologic use before submitting an individual funding request (IFR).
3rd and 4th line treatment options are restricted to being used at Salford Royal Foundation Trust (SRFT) tertiary centre.

The vast majority of biologic prescribing for psoriasis within Greater Manchester is undertaken via the tertiary referral psoriasis clinic at SRFT. This clinic has a cohort of patients with severe psoriasis and often receives referrals from other centres from across the UK, when patients have failed several biologic therapies.

In line with NICE we propose that all biologics can be used 1st line. The 5 core agents in the algorithm are adalimumab, ustekinumab, secukinumab, ixekizumab and brodalumab.

The following rarer scenarios are also applicable:

- Infliximab for patients who have unstable disease and rapid control is required.
- Etanercept when infection risk is a significant concern.

2. Aims

The aims of the biologics pathway for psoriasis are:

1. To present the evidence behind the use of each biologic in order to enable consistent evidence based clinical practice.
2. To reduce the number of Individual Funding Requests (IFRs) across the region.
3. To illustrate particular instances where the use of a particular biologic drug may be preferred over another, based on mode of action and current safety data.
4. To alert clinicians about on-going recruitment into clinical trials/studies where appropriate.
5. To promote cost containment by using the most appropriate biologic therapy, by supporting the use of biosimilar drugs and by promoting dose reduction, where appropriate.
6. To improve patient care by ensuring appropriate use of biologics for psoriasis and reducing the number of dermatology hospital admissions.

3. NICE guidance

The relevant NICE guidelines links are listed below.

The NICE recommendations also apply to biosimilar products of the technologies that have a marketing authorisation, allowing the use of the biosimilar for the same indication.

[NICE psoriasis pathways overview](#)

[NICE TA146: Adalimumab for the treatment of adults with psoriasis; June 2008](#)

Adalimumab is recommended as a treatment option for adults with plaque psoriasis only if:

- Their condition is severe as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more **and** a Dermatology Life Quality Index (DLQI) of more than 10.
and
- their condition has not improved with other treatments such as ciclosporin, methotrexate **and** PUVA (psoralen and long-wave ultraviolet radiation), or they have had side effects with these in the past or there is a medical reason why they should not be given these treatments
- Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either:
 - a 75% reduction in the PASI score (PASI 75) from when treatment started, **or**
 - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment

[NICE TA180: Ustekinumab for the treatment of adults with moderate to severe psoriasis; Sep 2009](#)

As adalimumab.

[NICE TA103: Etanercept \(and efalizumab\) for the treatment of adults with psoriasis; July 2006](#)

As adalimumab.

[NICE TA350: Secukinumab for treating moderate to severe plaque psoriasis; July 2015](#)

As adalimumab plus:

- The company provides secukinumab with the discount agreed in the patient access scheme
- Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks.

[NICE TA442: Ixekizumab for treating moderate to severe plaque psoriasis; April 2017](#)

As secukinumab.

[NICE TA511: Brodalumab for treating moderate to severe plaque psoriasis; March 2018](#)

As secukinumab.

[NICE TA134: Infliximab for the treatment of adults with psoriasis; Jan 2008](#)

Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met.

- The disease is **very severe** as defined by a total Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18.
- The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant to or has a contraindication to these treatments.
- Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either:
 - a 75% reduction in the PASI score from when treatment started (PASI 75) or
 - a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment

[NICE TA419: Apremilast for treating moderate to severe plaque psoriasis; Nov 2016](#)

As adalimumab plus:

- The company provides apremilast with the discount agreed in the patient access scheme.

[MHRA Drug Safety Update: Apremilast \(Otezla▼\): Risk of suicidal thoughts and behaviour; Feb 2017](#)

- Apremilast is associated with an increased risk of psychiatric symptoms, including depression, suicidal thoughts, and suicidal behaviours
- Suicidal thoughts and behaviour, including completed suicide, have been reported in patients with or without a history of depression
- Carefully assess the benefits and risks of starting or continuing treatment in patients with a history of psychiatric symptoms, or in those who are taking other medicines likely to cause psychiatric symptoms
- Stop treatment if patients experience new psychiatric symptoms or if existing symptoms get worse
- Advise patients to inform a healthcare professional if they notice changes in their mood

[NICE TA475: Dimethyl fumarate \(Skilarence®\) for treating moderate to severe plaque psoriasis; September 2017](#)

Dimethyl fumarate is recommended as an option for treating plaque psoriasis in adults, only if the disease:

- is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 and
- Has not responded to other systemic therapies, including, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet A radiation), or these options are contraindicated or not tolerated.

4. Clinical reasoning for using 4 biologic drugs

- Each of the 5 core drugs targets a different cytokine, or has varying affinity or avidity where the target is the same cytokine: adalimumab (TNF); ustekinumab (IL 23); secukinumab (IL17), ixekizumab (IL17), brodalumab (IL17). It is likely that the key driver of any individual's disease is one of these 5 cytokines so if one agent fails, a subsequent line of therapy is likely to work. Published data supports this. ²⁻⁴
- Each of the 5 drugs has clinical trial data demonstrating a 75% reduction in PASI, (PASI 75) of at least 70% ⁵⁻⁷
- Ustekinumab, secukinumab and ixekizumab have demonstrated superiority to etanercept in large well designed clinical trials. ^{5, 7, 8}
- Secukinumab and ixekizumab have demonstrated superiority to ustekinumab in a large well-designed clinical trial. ^{9, 10}
- Although all 4 drugs are highly efficacious in the short term, biologic drugs do have an attrition rate year on year of approximately 15% such that, if switches are not allowed, longer term disease control, for what is a life-long condition, will be lost. Ustekinumab has a lower attrition rate than adalimumab¹¹. No such data is currently available for secukinumab or ixekizumab.
- Consideration can be given to escalating the dose of biologic therapy in adults when feasible when an inadequate primary response may be due to insufficient drug dosing, for example in obese patients or when psoriasis relapses during the treatment cycle. Take into account that this may be associated with an increased risk of infection. Dose escalation must be within the product license and included in the relevant NICE guidance.
- Clinicians at SRFT have audited the use of ustekinumab and adalimumab locally and led on a national ustekinumab study showing that both these drugs are effective following failure of other biologics. All studies have been published in the British Journal of Dermatology. ²⁻⁴
- As secukinumab and ixekizumab have come to the market later, many patients in the clinical trial programmes had failed prior biologics and both biologics were shown to be efficacious in such scenarios. ^{7, 12}
- It is not known if sequential use of secukinumab and ixekizumab is effective. Sequential use is being audited at SRFT and the pathway will be adapted if it is unsuccessful.
- All 4 drugs have efficacy for psoriatic arthritis ¹³⁻¹⁷ although the anti-TNF drugs (adalimumab from core set) are the gold standard drugs in this scenario. Secukinumab and ixekizumab demonstrate a TNF like response in published clinical trials and may, in time, challenge this position. ^{13, 16}

5. Drug choice

1st Line

- There are numerous factors which would influence the choice of which drug should be used at which point in the pathway.
- In those with psoriasis without signs of, or risks of psoriatic arthritis, **ustekinumab is the 1st line treatment option**, in accordance with NICE, on the basis of better drug survival and a now well established safety record.¹¹
- In those with both psoriasis and PsA (or signs of early PsA / risk of PsA) **adalimumab is the 1st line treatment option** in accordance with NICE.
- There are other clinical factors which will inform the decision around choice of drug. These include, but are not limited to:
 - Presence of inflammatory bowel disease would mean that caution would be needed when using secukinumab and ixekizumab
 - Body weight – ustekinumab has 2 dosing regimens with those > 100kg getting access to the higher dose of drug; for heavier patients this may be of relevance
 - Immunogenicity risk –emerging data show that certain biologics may be neutralised by anti-drug antibodies. It is not immediately clear which populations are at risk of this but ongoing work will help inform this
 - Genetic factors - Certain HLA subtypes may make patients more or less likely to respond to ustekinumab
- Whilst safety data is being accrued, secukinumab /ixekizumab would only be 1st choice options where there are concerns or possible problems with the other 2 drugs e.g. demyelination risk / tuberculosis risk OR when a patient is looking for a very high level of clinical response. Local and national access costs also need to be considered as some of the newer therapies are being made available to the NHS at competitive prices. Thus, agents such as secukinumab and ixekizumab may, in a short period of time (1-2 years), be considered 1st line in an increasing range of scenarios as experience is gained in the real world setting.
- Shared decision making between clinicians and patients plays an important role in the choice of treatment. Clinicians and patients should utilise suitable clinical decision aids (e.g. as suggested in the BAD guidelines for biologic therapies 2017¹⁸) to tailor the most appropriate biologic therapy to the patients' wishes and values.

2nd Line

NICE guidance recommends considering changing to an alternative biological drug in adults if:

- the psoriasis does not respond adequately to a first biological drug as defined in NICE technology appraisals (at 10 weeks after starting treatment for infliximab, 12 weeks for etanercept, ixekizumab, secukinumab and brodalumab, and 16 weeks for adalimumab and ustekinumab [primary failure]) **or**
- the psoriasis initially responds adequately but subsequently loses this response (secondary failure) **or**
- the first biological drug cannot be tolerated or becomes contraindicated.
- After failing either adalimumab or ustekinumab, either secukinumab, ixekizumab or brodalumab would be used based on the high efficacy levels in psoriasis, as the clinical trial data shows that these agents will work in patients who have failed other biologics and are efficacious for the treatment of PsA.
- If secukinumab or ixekizumab has been used 1st line we would recommend either ustekinumab or adalimumab depending on signs of, or risk of PsA (adalimumab) or not (ustekinumab).
- In the rare scenarios when etanercept or infliximab has been used 1st line we would recommend secukinumab or ixekizumab based on the same logic given above.

3rd and 4th Line

- NICE guidance allows for treating with 2 biologic drugs, after which supra- specialist advice should be sought. Only those trusts who are commissioned to treat severe psoriasis should be treating patients in line with this pathway.
- 3rd and 4th line treatment options, including dimethyl fumarate and apremilast, are restricted to being used at Salford Royal Foundation Trust (SRFT) tertiary centre.

- The use of consecutive treatment with IL-17's used 2nd, 3rd or 4th line is being audited at SRFT.
- Acknowledging that PsA often develops in patients with psoriasis, those patients who have failed ustekinumab, secukinumab or ixekizumab, or who go on to develop PsA whilst on these agents, would be best treated with adalimumab based on its efficacy for both psoriasis and PsA.
- In those patients who have failed adalimumab and secukinumab / ixekizumab / brodalumab we would suggest either ustekinumab based on the completely differing mechanism of action for these agents compared with the 1st two agents and the documented tolerability and persistence data that support the use of ustekinumab in people who develop adverse events on other biologic drugs.

Apremilast

- In patients with significant comorbidities and therefore at higher risk of developing adverse effects OR when laboratory parameters may preclude other therapies, apremilast can be considered as an alternative for patients with either psoriasis alone or psoriasis in combination with PsA.

Dimethyl fumarate

- When compared indirectly, dimethyl fumarate is less effective than systemic biologic therapies but it is also less costly.
- In patients with a significant risk of infection or significant comorbidities, such as demyelination, OR when laboratory parameters may preclude other therapies, dimethyl fumarate can be considered as an alternative for patients with moderate to severe psoriasis in the absence of psoriatic arthritis.
- Fumaderm® is unlicensed for the treatment of psoriasis in the UK, and should no longer be initiated now that Skilarence® is available.

6. Biosimilars

[Prescribing-of-high-cost-biosimilar-biological-medicines](#) position statement has been approved by **GMMMG** and is included in this pathway:

Initiating treatment with a biologic

- The choice of biologic used should be guided by clinical judgement, national or local guidance and the overall value proposition offered by the individual medicines. The rationale for choice should be documented.
- **If more than one treatment is suitable, the least expensive should be chosen** (taking into account administration costs, dosage and price per dose). You may be expected to retrospectively audit your practice, for which we recommend keeping an accurate record of the cheapest biologic for your trust (and update this on a 6-12 monthly basis).
- When the biologic treatment has been selected, the least expensive product, either biosimilar or originator should be prescribed.
- If the least expensive product is not prescribed, the reasons why must be documented and made available to commissioners if required.
- Where NICE has already recommended the originator biological medicine, the same guidance will apply to the biosimilar medicine.
- In line with MHRA guidelines: [Gov.uk/drug-safety-update/biosimilar-products](#) biologics, including biosimilars must be prescribed by brand name to support on-going pharmacovigilance of the individual products.
- Pharmacovigilance is essential for any new biological medicine including biosimilars and additional monitoring is indicated through the black triangle. Patients prescribed a biologic should be enrolled on to relevant registries which gather data on the safety and effectiveness of the medicine in clinical practice.

Changing from originator to a biosimilar

- There is evidence that patients who are in a stable clinical response or remission may be changed over to the biosimilar at the same dose and dose interval. This should be done after discussion and agreement with individual patients.
- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing and in discussion with the hospital pharmacy department.
- There should be no automatic substitution of a biologic with a biosimilar at the point of dispensing.

7. Individual Funding Requests (IFR)

- IFRs for psoriasis will not be required for up to 4 biologics included in this pathway, if prescribed in accordance with this pathway.

All other treatment options outside of this pathway will require an IFR to be approved prior to treatment being started.

- Blueteq forms which comply with these pathways are available. Where Blueteq has been introduced to the trust as part of the contractual arrangements, funding approval for the PbR excluded high cost drugs will be made by meeting the accepted criteria outlined on completion and submission of a Blueteq form.

8. Research Recruitment

All free of charge schemes and clinical trials should be approved in accordance with trust guidance and GMMMG guidance when available. Approval should be agreed at the trust's medicines management committee. There must be clear exit criteria that does not place financial burden on commissioners and does not raise patient's expectations of continuation of treatment.

British Association of Dermatologists Biologic Interventions Register (BADBIR):

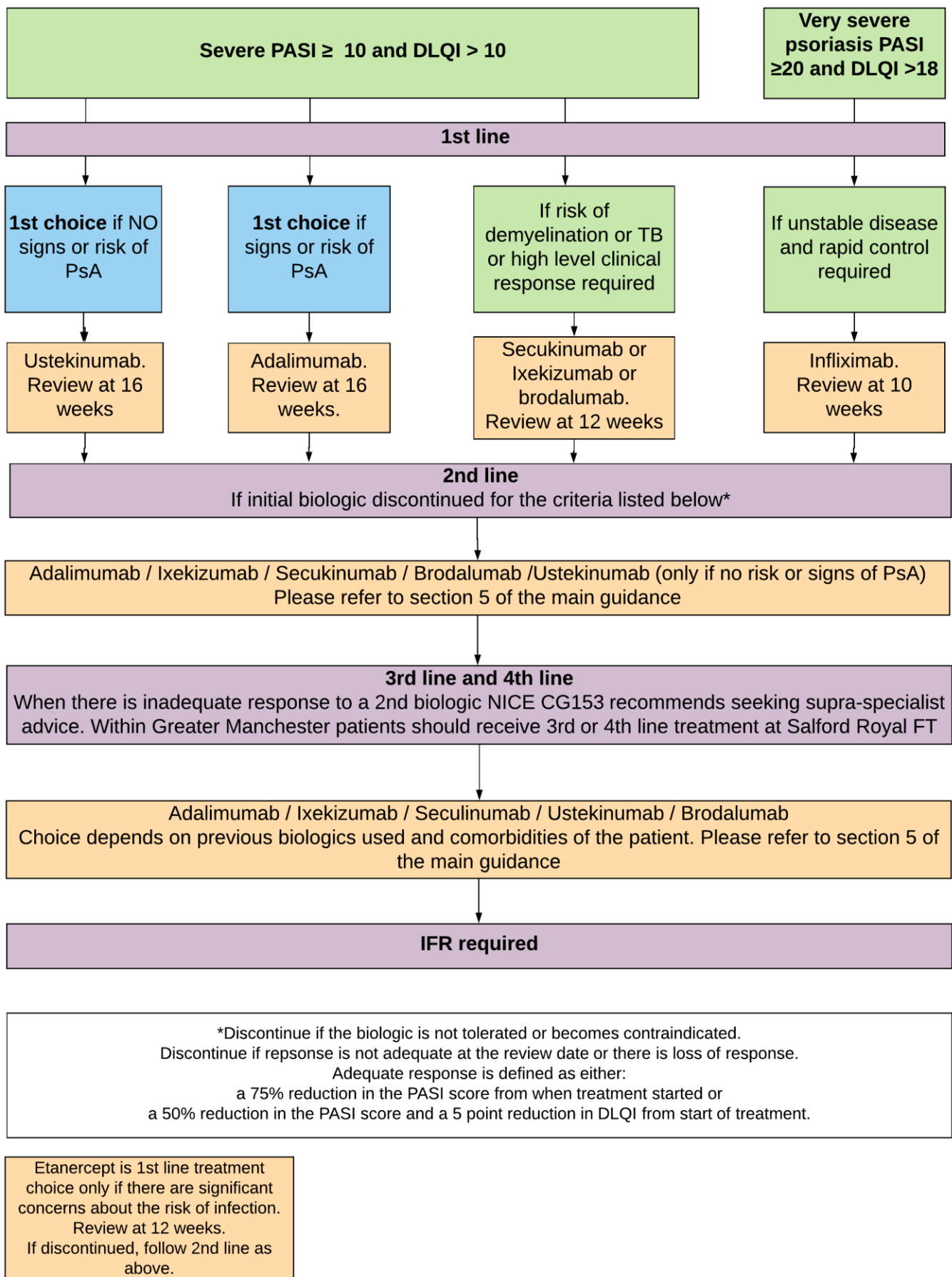
- All patients starting a biologic therapy should be given the opportunity to participate in BADBIR, a national long-term safety registry within 6 months of initiation in accordance with NICE recommendations.

Clinical trials:

- Where possible consideration should be made to enter patients into observational/clinical studies.
- Many sites host early and later phase clinical trials of biologic therapies, both biologic naïve and biologic experienced.

9. Biologics treatment flow chart

**Greater Manchester biologics pathway for psoriasis v2.1
May 2018**



10. Contraindications, special warnings and precautions

a) **Contraindications to ustekinumab, secukinumab and ixekizumab**

- Hypersensitivity to the active substance or to any of the excipients.
- Clinically important, active infection (e.g. active tuberculosis)

Special warnings and precautions for use with ustekinumab

[Medicines.org.uk: Ustekinumab special warnings and precautions](https://www.medicines.org.uk/ustekinumab/special-warnings-and-precautions)

Special warnings and precautions for use with secukinumab

[Medicines.org.uk: Secukinumab special warnings and precautions](https://www.medicines.org.uk/secukinumab/special-warnings-and-precautions)

Special warnings and precautions for use with ixekizumab

[medicines.org.uk: Ixekizumab special warnings and precautions](https://www.medicines.org.uk/ixekizumab/special-warnings-and-precautions)

b) **Contraindications to anti-TNF's (infliximab, adalimumab)**

- Moderate to severe heart failure (NYHA class III/IV heart)
- Active tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections
- History of hypersensitivity to the active substance, to other murine proteins, or to any of the excipients

Special warnings and precautions for use with infliximab:

[Medicines.org.uk: Infliximab special warnings and precautions](https://www.medicines.org.uk/infliximab/special-warnings-and-precautions)

Special warnings and precautions for use with adalimumab:

[Medicines.org.uk: Adalimumab special warnings and precautions](https://www.medicines.org.uk/adalimumab/special-warnings-and-precautions)

c) **Contraindications to etanercept**

- Hypersensitivity to the active substance or to any of the excipients
- Sepsis or risk of sepsis
- Treatment with etanercept should not be initiated in patients with active infections including chronic or localised infections

Special warnings and precautions for use with etanercept:

[Medicines.org.uk: Etanercept special warnings and precautions](https://www.medicines.org.uk/etanercept/special-warnings-and-precautions)

d) **Contraindications to apremilast**

- Hypersensitivity to the active substance(s) or to any of the excipients
- Pregnancy

Special warnings and precautions for use with apremilast:

[Medicines.org.uk: Apremilast special warnings and precautions](https://www.medicines.org.uk/apremilast/special-warnings-and-precautions)

e) **Contraindications to brodalumab**

- Hypersensitivity to the active substance or to any of the excipients
- Active Crohn's disease
- Clinically important active infections (e.g. active tuberculosis)

Special warnings and precautions for use with brodalumab:

[Medicines.org.uk: Brodalumab special warnings and precautions](https://www.medicines.org.uk/brodalumab/special-warnings-and-precautions)

f) **Contraindications to dimethyl fumarate**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe gastrointestinal disorders.
- Severe hepatic or renal impairment.
- Pregnancy and breast-feeding.

Special warnings and precautions for use with dimethyl fumarate:

https://www.medicines.org.uk/emc/medicine/33813#CLINICAL_PRECAUTIONS

11. Special Situations

a) Peri-operative risk

Prevention of potential post-operative infection risk by temporarily stopping a patient's biologic treatment should be carefully balanced against the possibility of a peri-operative flare of psoriasis.

Should treatment be stopped prior to surgery, consider stopping the drug 3-5 times the half-life for the relevant drug (Level IV evidence, grade of recommendation C).⁷

Treatment should be recommenced post-operatively once infection is excluded and the wound is healed (Level IV evidence, grade of recommendation C).⁷

Biologic	Half-life*	Time to stop treatment prior to surgery
Etanercept	3 days (approx. 70 hours)	9- 15 days
Adalimumab	12-14 days	6 – 10 weeks
Infliximab	9 days	4 – 7 weeks
Ustekinumab	Median half-life 3 weeks (15-32 days)	9 – 15 weeks
Secukinumab	Median half-life 27 days (18-46 days)	12 – 19 weeks
Ixekizumab	13 days	6 – 10 weeks

*summary of product characteristics (SPC)

b) Pregnancy and breast feeding

i) Pregnancy

There is limited data for safety of biologic drugs in pregnancy and lactation. The decision to continue biologic agents in pregnancy needs to be individualised. This needs to take into account alternative therapies, the severity of the mother's condition prior to therapy, the risk of a disease flare by cessation of therapy, and the impact of a flare on the mother and the unborn child. This should be discussed by a multi-disciplinary team.

Patients who stop therapy during pregnancy should be re-loaded with biological therapy soon after delivery. Consideration should be given to stopping biologic therapy in a woman who becomes pregnant as listed below:

Biologic	Compatible with 1st trimester	Compatible with 2 nd / 3rd trimester
Etanercept	Yes	Second but not third
Adalimumab	Yes	Second but not third
Infliximab	Yes	Stop at 16 weeks
Ustekinumab	No data	No data
Secukinumab	No data	No data
Ixekizumab	Limited data	Limited data
Brodalumab	Limited data	Limited data
Apremilast	Limited data	Limited data
Dimethyl fumarate	Limited data	Limited data

To ensure low/no levels of drug in cord blood at delivery, etanercept and adalimumab should be avoided in the third trimester and infliximab stopped at 16 weeks. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age.

ii) Breast feeding

There is insufficient information on the excretion of biologics in breast milk. Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot be excluded. A decision on whether to breastfeed or to continue/discontinue therapy should be made taking into account the benefit of breastfeeding to the child and the benefit of therapy to the woman.

The manufacturers recommend that it is not advisable to breast feed during drug treatment or for the duration specified below after treatment has stopped.

Biologic	Time to elapse between stopping treatment and starting breastfeeding
Etanercept	
Adalimumab	5 months
Infliximab	6 months

Ustekinumab	15 weeks
Secukinumab	20 weeks
Ixekizumab	-
Brodalumab	No data
Apremilast	No data
Dimethyl fumarate	No data

c) Vaccination of Infants

Any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible.

In the case of in utero exposure to an anti-TNF and other biological medicines, this period should be until the infant is aged 7 months, after which time vaccination should be considered.

MHRA has received 4 Yellow Card reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to an anti-TNF in utero; they were probably not known to be immunosuppressed at the time of vaccination⁹.

Current vaccination strategies with non-live vaccines for infants who have been exposed to anti-TNF in utero do not differ from those for unexposed infants⁹.

The risk of a natural rotavirus infection is high. Although the vaccine is a live attenuated virus, with the exception of severe combined immune-deficiency (SCID), the benefit from vaccination may exceed any risk in other forms of immunosuppression. Therefore, there are very few infants who cannot receive rotavirus vaccine. Vaccination should be discussed on an individual basis.

12. Vaccinations

a) Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents.

It is safe to administer a live vaccine 4 weeks prior to commencing biologic therapy, when necessary.

There is no contra-indication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs.

The table below shows all live vaccines available in the UK.

Live Vaccine	Brand Name
BCG	Bacillus Calmette-Guerin Vaccine
Influenza	Fluenz Tetra®
Measles, Mumps and Rubella combined vaccine (MMR)	MMRvaxPRO®, Priorix®
Poliomyelitis (Live oral vaccine)	Poliomyelitis Vaccine, live (oral) GSK OPV
Rotavirus (Live oral vaccine)	Rotarix®
Typhoid (Live oral vaccine)	Vivotif®
Varicella-Zoster Vaccine	Varilrix®, Varivax®, Zostavax®
Yellow Fever	Stamaril®

For patients on established conventional DMARD treatment, immunosuppression treatment should be stopped for 6 months before administration of a live vaccine. Therapy may then be restarted 2 to 4 weeks after the administration of the live vaccine.

When a live vaccine is required by a patient on a biologic, the cessation of treatment may permit a necessary vaccination to be administered. The table below shows the time period required to elapse off each biologic therapy, prior to the administration of a live vaccination.

Biologic	Time to elapse before giving a live vaccine
Adalimumab	3 months
Infliximab	2 months
Etanercept	1 month
Ustekinumab	6 months
Secukinumab	6 months
Ixekizumab	6 months
Brodalumab	6 months

b) Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on biologic therapies.

Pneumococcal vaccine should be given 2-4 weeks before starting a biologic as response after starting treatment can be poor.

The table below gives a list of non-live vaccines available in the UK.

Vaccine	Brand Name
Cholera Vaccine (Oral preparation only)	Dukoral®
Diphtheria	Given as combined adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation.
Hepatitis A	Avaxim®, Epaxal®, Havrix Monodose®, Vaqta Paediatric®
Hepatitis B	Engerix®, Fendrix®, HBvaxPRO®
Hepatitis A and B Combined	Ambirix®, Twinrix®
Influenza	Agrippal®, Begrivac®, Enzira®, Fluarix®, Fluvirin®, Imuvac®, Influvac® Sub-unit, Mastafu®, Optafu® and Viroflu®
Pneumococcal	Pneumovax II® (Adults and Children over 5 years), Prevenar® (Primary childhood immunisation)
Poliomyelitis (Injection)	Inactivated Poliomyelitis Vaccine (non-proprietary) IPV
Meningococcal Group C	Menjugate Kit®, NeisVac-C®
Meningococcal polysaccharide A,C, W135 and Y vaccine	ACWY Vax®
Rabies	Rabipur®
Tetanus	*Single preparation no longer available. Combined Adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation given.
Tick-borne encephalitis	TicoVac®
Typhoid (Polysaccharide injection for vaccination)	Typherix®, Typhim Vi®

c) Vaccination scheduling during biologic therapy

Influenza vaccine – receive annually

Pneumococcal vaccine – receive once. Check titres every 5-10 years.

13. Checklist for patient screening on pre-admission for biologic agents

Name:.....Number:.....Consultant:.....

Screening Investigations Requested in Clinic			
	Y/N	Initial	Results/Details
FBC/U&E/LFT/ESR/CRP			
Rheumatoid Factor (if negative check anti-CCP) <i>Don't repeat if previously positive result</i>			
ANA (If positive also order ENA/dsDNA/C3/C4)			
HIV, HBV (surface antigen, core antibody)*, HCV (antibody test) <i>If positive result please refer to Hepatology/GUM</i> <small>*Reactivation has been reported in HBsAg-ve as well as HbsAg +ve patients stressing the importance of measuring not only HBsAg but also antibodies against HBc antigen to identify positive carrier status</small>			
Varicella Zoster IgG (If negative inform GP and patient)			
TB screening (g-IFN testing) <i>If positive refer to respiratory</i>			
Chest X-Ray (within the last 6 months) <i>(± pulmonary function tests/HRCT thorax)</i> CXR checked by/date			

Screening questions asked in clinic			
	Y/N	Initial	Details
Previous TB/TB contact <i>(details)</i>			
Recent travel abroad (i.e. TB high risk countries) <i>Which Country/Dates</i>			
History of heart failure (NYHA class III or IV) <i>(details)</i>			
History of recurrent infection <i>(details)</i>			
History of interstitial lung disease <i>(details such as extent of ILD²¹)</i>			
History of cancer <i>(Type/Date when occurred/Date of all clear)</i>			
Date of last mammogram (50yr +) <i>(Encourage patient to visit GP if >3 years)</i>			
Date of last smear (25yr +) <i>(Encourage patient to visit GP if >3 years)</i>			
History of infusion reaction to any agent <i>(To what/type of reaction)</i>			
Allergy <i>(details)</i>			

Education and funding		
	Initial	Details
Request for funding		
Pregnancy/breastfeeding advice given		
Annual influenza vaccination advice given		
Pneumococcal vaccination advice given		
Patient counselled and educated		
Patient education pack given		
Patient consent to be approached for research		

Completing Clinician Signature..... Date.....

Nurse Practitioner Signature..... Date.....

References

1. Rapp, S.R., Feldman, S.R., Exum, M.L., Fleischer, A.B., Jr. & Reboussin, D.M. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* **41**, 401-7 (1999).
2. Warren, R.B., Brown, B.C., Lavery, D., Ashcroft, D.M. & Griffiths, C.E. Biologic therapies for psoriasis: practical experience in a U.K. tertiary referral centre. *Br J Dermatol* **160**, 162-9 (2009).
3. Warren, R.B., Brown, B.C., Lavery, D. & Griffiths, C.E. Adalimumab for psoriasis: practical experience in a U.K. tertiary referral centre. *Br J Dermatol* **163**, 859-62 (2010).
4. Laws, P.M. et al. Practical experience of ustekinumab in the treatment of psoriasis: experience from a multicentre, retrospective case cohort study across the U.K. and Ireland. *Br J Dermatol* **166**, 189-95 (2012).
5. Griffiths, C.E. et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* **362**, 118-28 (2010).
6. Menter, A. et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol* **58**, 106-15 (2008).
7. Langley, R.G. et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *New England Journal of Medicine* **371**, 326-38 (2014).
8. Griffiths, C.E. et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet* **386**, 541-51 (2015).
9. Thaci, D. et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *Journal of the American Academy of Dermatology* **73**, 400-9 (2015).
10. Reich, K. et al. (25th European Academy of Dermatology and Venereology (EADV) Congress: Abstract D3T01.1K. Presented October 1, 2016, 2016).
11. Warren, R.B. et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Journal of Investigative Dermatology* **135**, 2632-40 (2015).
12. Gottlieb, A.B. et al. Treatment outcomes with ixekizumab in patients with moderate-to-severe psoriasis who have or have not received prior biological therapies: an integrated analysis of 2 Phase III randomised studies. *J Eur Acad Dermatol Venereol* (2016).
13. McInnes, I.B. et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **386**, 1137-46 (2015).
14. Mease, P.J. et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* **52**, 3279-89 (2005).
15. Mease, P.J. et al. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. *N Engl J Med* **373**, 1329-39 (2015).
16. Mease, P.J. et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* (2016).
17. McInnes, I.B. et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* **382**, 780-9 (2013).
18. Smith, C.H. et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *British Journal of Dermatology* (2017).