Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2196

risankizumab 75mg solution for injection in pre-filled syringe (Skyrizi®)

AbbVie Ltd

06 September 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

risankizumab (Skyrizi®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

SMC restriction: for patients who have failed to respond to conventional systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contraindication to these treatments.

Risankizumab was superior to placebo, a tumour necrosis factor antagonist, and an interleukin 12/23 antagonist in improving symptoms of adult patients with moderate to severe plaque psoriasis.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of risankizumab. This SMC advice is contingent upon the continuing availability of the patient access scheme, or a list price that is equivalent or lower, in NHSScotland.

Chairman
Scottish Medicines Consortium

Indication

The treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.[1]

Dosing Information

The recommended dose is 150mg administered by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Risankizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

Refer to the Summary of Product Characteristics (SPC) for further details.[1]

Product availability date

1 May 2019[1]

Summary of evidence on comparative efficacy

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that binds to the p19 subunit of human interleukin 23 (IL23) cytokine thereby inhibiting IL23-dependent cell signalling and release of proinflammatory cytokines.[2] The submitting company has requested that SMC considers risankizumab when positioned for use in patients who have failed to respond to conventional systemic therapies (including ciclosporin, methotrexate and phototherapy), or are intolerant to, or have a contraindication to these treatments.

The evidence supporting the efficacy and safety of risankizumab comes from three similarly designed studies: UltIMMa-1, UltIMMa-2, and IMMvent. All three studies were multicentre, randomised, double-blind, double-dummy, active controlled, phase III studies. Patients aged ≥18 years old were required to have moderate to severe plaque psoriasis, defined as static Physician's Global Assessment (sPGA) score ≥3, Psoriasis Area and Severity Index (PASI) score ≥12, and body surface area (BSA) involvement of ≥10%, for at least six months. Patients were also required to be eligible for systemic treatment or phototherapy, as assessed by investigator.[3]

In the UltIMMa studies, patients were randomised 3:1:1 to receive risankizumab 150mg by subcutaneous (SC) injection at week 0, 4, 16, 28 and 40 (n=304 in UltIMMa-1; n=294 in UltIMMa-2), ustekinumab 45mg or 90mg (based on screening weight) SC at week 0, 4, 16, 28, and 40 (n=100 in UltIMMa-1; n=99 UltIMMa-2) or placebo (n=102 in UltIMMa-1; n=98 in UltIMMa-2). The studies comprised two parts: Part A from week 0 to 16 and Part B from week 16 to 52. At week 16, the placebo group was switched to risankizumab treatment whilst other groups continued on their respective treatments.[3] Randomisation was stratified according to bodyweight (≤100kg or >100kg) and previous exposure to tumour necrosis factor (TNF) inhibitor (yes or no).[3]

IMMvent comprised two parts. Patients were randomised equally in Part A to receive risankizumab 150mg SC at week 0 and 4 (n=301) or adalimumab 80mg SC at week 0, followed by 40mg SC every other week (n=304). In Part B (week 16 onwards), patients who had an intermediate response (PASI 50 to PASI<90) were re-randomised 1:1 to receive risankizumab 150mg SC at week 16, 20, and 32 (n=53) or adalimumab 40mg SC every 2 weeks through to week 41 (n=56). Patients who had PASI<50 in Part A were given risankizumab 150mg SC at week 16, 20 and 32 (n=38). Patients with PASI≥90 at week 16 continued on their original treatment; the risankizumab group received 150mg SC at week 16 and week 28 (n=294) and the adalimumab group received 40mg SC every 2 weeks through to week 41 (n=144). Randomisation was stratified in Part A according to weight (≤100kg or >100kg) and prior TNF inhibitor exposure (yes or no).[4, 5]

The co-primary outcomes used for UltIMMa-1, UltIMMa-2, and IMMvent were the proportion of patients achieving 90% improvement in PASI from baseline (PASI 90) and sPGA score of 0 (clear) or 1 (almost clear) at week 16. In addition, IMMvent had a primary outcome for Part B; the proportion of patients achieving PASI 90 at week 44 in those who had achieved an intermediate response (PASI 50 to PASI<90) with adalimumab at week 16. Efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomisation, and those who underwent re-randomisation in IMMvent. A hierarchical testing strategy was used to control for the risk of type I error associated with multiple testing for the primary outcomes and ranked secondary outcomes. No formal testing of primary or key secondary outcomes was performed after the first non-significant outcome in the hierarchy. Missing efficacy data for categorical variables were handled with non-responder imputation and for continuous variables with a last observation carried forward approach.[3-5]

In both UltIMMa-1 and UltIMMa-2, risankizumab was superior to placebo and to ustekinumab for the two co-primary outcomes. A statistically significant higher proportion of patients achieved a PASI 90 response and sPGA score of 0 or 1 at week 16 on risankizumab compared with placebo and ustekinumab. IMMvent also met all primary outcomes; at week 16 a statistically significantly higher proportion of patients treated with risankizumab achieved PASI 90 and sPGA score of 0 or 1 versus adalimumab. Among adalimumab-treated patients with PASI 50 to PASI<90 responses at week 16, a significantly higher proportion of patients switching to risankizumab achieved PASI 90 responses at week 44 compared with patients continuing on adalimumab. Table 1 presents the results obtained from the primary analyses.[3]

Table 1. Primary outcome results from UltIMMa-1, UltIMMa-2, and IMMvent.[3-5]

	UltIMMa-1			UltIMMa-2		
	RIS	**UST**	**PBO**	**RIS**	**UST**	**PBO**
Number of patients	n=304	n=100	n=102	n=294	n=99	n=98
PASI 90 at Week 16	75%[A]	42%	4.9%	75%[A]	48%	2.0%
sPGA 0 or 1 at Week 16	88%[A]	63%	7.8%	84%[A]	62%	5.1%

IMMvent				
	RIS	**ADA**	**ADA to RIS at week 16***	**ADA to ADA at week 16***
Number of patients	n=301	n=304	n=53	n=56
PASI 90 at Week 16	72%[B]	47%	-	-
sPGA 0 or 1 at Week 16	84%[B]	60%	-	-
PASI 90 at Week 44	-	-	66%	21%

RIS = risankizumab; UST = ustekinumab; PBO = placebo; ADA = adalimumab; PASI 90 = improvement of 90% in psoriasis area and severity index (PASI); sPGA = static physician global assessment of psoriasis score (assessed on 5-point scale, where 0 = clear and 1 = almost clear); A = comparison versus ustekinumab and placebo, p<0.001; B = comparison versus adalimumab, p<0.001; *Patients had an intermediate response (PASI 50 to PASI<90) at Week 16 on adalimumab, and were randomised to either risankizumab or adalimumab for Part B of the study.

All pre-specified key secondary outcomes were met across the three studies. Risankizumab achieved statistically significant and consistent improvements over placebo, ustekinumab, and adalimumab across various PASI and sPGA outcomes. Of particular note was PASI 75; in UltIMMa-1 and UltIMMa-2 respectively, 87% and 89% of patients receiving risankizumab achieved a PASI 75 response at Week 12 versus 70% and 70% in the ustekinumab groups; in IMMvent, 91% of patients receiving risankizumab achieved a PASI 75 response at Week 16 versus 72% in the adalimumab group (all p<0.001). Additionally, risankizumab was shown to maintain superiority over placebo and ustekinumab for PASI 90 and sPGA score of 0 or 1 at Week 52. In non-key secondary outcome analysis of nail, palmoplantar, and scalp psoriasis at Week 16, risankizumab was found to have higher levels of improvement in extent and severity when compared with placebo. Higher levels of improvement were reported with risankizumab compared with ustekinumab at Week 52 for nail and scalp psoriasis.[2-5]

Quality of life (QoL) was evaluated using two outcome measures in UltIMMa-1 and UltIMMa-2: Dermatology Life Quality Index (DLQI) and Psoriasis Symptom Scale (PSS). IMMvent measured QoL with DLQI only. The DLQI is a validated, patient-reported, dermatology-specific outcome measure,

which has a score range of 0 to 30, with higher scores indicating a greater impairment of quality of life. PSS is a four-item instrument used to assess the severity of pain, redness, itching, and burning symptoms associated with psoriasis. DLQI 0 or 1 response and PSS 0 response at Week 16 featured as key secondary outcomes in the UltIMMa studies. The proportion of patients with DLQI 0 or 1 and PSS 0 response was significantly higher in the risankizumab group versus placebo and ustekinumab at Week 16. Similarly, a higher proportion of DLQI 0 or 1 responses were observed in the risankizumab group versus adalimumab in IMMvent. See Table 2 for further details.[3, 6]

Table 2. Patient reported outcomes for UltIMMa-1, UltIMMa-2, and IMMvent.[2, 3]

	Number of responders at Week 16 (%)				Number of responders at Week 52 (%)			
	RIS	UST	PBO	p-value	RIS	UST	PBO to RIS	p-value
UltiMMa-1								
DLQI 0 or 1	66%	43%	7.8%	p<0.001*	75%	47%	62%	-
PSS 0	29%	15%	2.0%	p<0.001*	57%	30%	51%	-
UltIMMa-2								
DLQI 0 or 1	67%	46%	4.1%	p<0.001*	71%	44%	68%	-
PSS 0	31%	15%	0	p<0.001*	54%	30%	48%	-
IMMvent								
	RIS	ADA						
DLQI 0 or 1	66%	49%	-	-	-	-	-	-

RIS = risankizumab; UST = ustekinumab; PBO = placebo; ADA = adalimumab; DLQI = Dermatology Life Quality Index; PSS = Psoriasis Symptom Scale; *p<0.001 for both placebo and ustekinumab comparisons.

Subgroup analyses results were performed in the UltIMMa-1, UltIMMa-2, and IMMvent studies for the primary outcomes PASI 90 and sPGA score of 0 or 1 at Week 16. Treatment effects in all pre-specified subgroups favoured risankizumab over placebo and adalimumab. No subgroup analyses were presented for risankizumab versus ustekinumab. The treatment effect of risankizumab appeared consistent across all prior exposure to treatment strata.[2]

In the absence of direct evidence comparing risankizumab to other relevant biologic medicines for the treatment of moderate to severe plaque psoriasis, the submitting company presented Bayesian Network Meta-analyses (NMAs) for the following outcome measures: PASI score (60 studies), DLQI (33 studies), adverse events (AEs) (42 studies), serious AEs (44 studies), and withdrawal due to AEs (42 studies), all measured between Week 10 to 16. A meta-analysis was also undertaken to assess PASI response at Weeks 44 to 66 (21 studies). The relevant comparators included in the networks were adalimumab, apremilast, brodalumab, certolizumab pegol, dimethyl fumarate, etanercept, guselkumab, infliximab, ixekizumab, secukinumab, tildrakizumab, and ustekinumab. An adjusted random effects model, using meta-regression to adjust for placebo response was used for the NMAs.

For all relevant levels of PASI response (PASI 75/90/100) in the 10 to 16 week analysis, risankizumab was likely to produce a greater response than etanercept regimens, adalimumab, ustekinumab, secukinumab, apremilast, dimethyl fumarate, and infliximab. Risankizumab was

likely to produce similar response to guselkumab, brodalumab, and ixekizumab. The results of the meta-analysis suggested that risankizumab was more efficacious than apremilast, etanercept, infliximab, adalimumab and ustekinumab across all levels of PASI response. Broadly, the longer-term efficacy of risankizumab was comparable to secukinumab, ixekizumab, brodalumab and guselkumab.

The results of the DLQI NMA suggested that risankizumab was associated with a higher probability of achieving a DLQI 0/1 compared with apremilast, etanercept, adalimumab, ustekinumab and secukinumab, and comparable improvement to ixekizumab, brodalumab, and guselkumab. The analysis of AE suggested that risankizumab had a similar probability of experiencing any adverse event compared with etanercept, adalimumab, ustekinumab, and guselkumab, and a lower probability of experiencing an adverse event compared with apremilast, dimethyl fumarate, infliximab, secukinumab, ixekizumab and brodalumab.

The NMA of serious AE suggested that the probability of experiencing a serious adverse event was similar for all treatment included in the network.

The NMA of withdrawal due to an AE suggested that there was a lower probability of withdrawing risankizumab due to an AE compared with adalimumab, secukinumab, apremilast, brodalumab, dimethyl fumarate, infliximab, ixekizumab, and a likely similar probability of withdrawal due to an AE compared with ustekinumab, etanercept, and guselkumab.

Summary of evidence on comparative safety

The European Medicines Agency (EMA) concluded that risankizumab 150mg was a well-tolerated treatment associated with low discontinuation rates and mostly mild adverse events (AEs). These conclusions were drawn from three safety data sets, with 2,234 patients exposed to risankizumab.[2]

In Part A of both UltIMMa-1 and UltIMMa-2 combined, for the risankizumab (n=598), ustekinumab (n=199), and placebo (n=200) groups respectively: 48%, 52%, and 48% of patients reported at least one AE; 2.2%, 5.5%, and 2.0% reported at least one serious AE; and 0.5%, 1.0%, and 2.5% discontinued study treatment because of an AE. Common AEs reported included: viral upper respiratory tract infection (5.0%, 5.5%, 4.0%), upper respiratory tract infection (4.7%, 5.0%, 2.0%), psoriasis (0%, 1.0%, 5.0%), and diarrhoea (1.0%, 3.5%, 2.5%).[2,3]

For patients who continued on treatment with risankizumab (n=297), ustekinumab (n=99), or switched from placebo to risankizumab (n=97) in Part B of UltIMMa-1, the following AEs were reported: viral upper respiratory tract infection (14%, 18%, 16%), upper respiratory tract infection (10%, 11%, 8.2%), urinary tract infection (1.0%, 5.1%, 0%), influenza (2.0%, 2.0%, 1.0%), and headache (1.7%, 5.1%, 3.1%).[3]

For patients who continued on treatment with risankizumab (n=291), ustekinumab (n=94), or switched from placebo to risankizumab (n=94) in Part B of UltIMMa-2, the following AEs were reported: viral upper respiratory tract infection (12%, 18%, 15%), upper respiratory tract infection (8.2%, 9.6%, 8.5%), urinary tract infection (2.1%, 1.1%, 0%), influenza (1.4%, 2.1%, 5.3%), and headache (2.4%, 3.2%, 2.1%).[3]
Further information on the safety profile of risankizumab can be found in the SPC.[1]

Summary of clinical effectiveness issues

Psoriasis is a chronic, immune-mediated, relapsing-remitting, inflammatory skin disease, which is characterised by red, scaly patches, plaques and pustules that usually itch. Plaque psoriasis, which typically affects the elbows, knees, scalp and back, is the most common type of psoriasis. Treatment options include topical therapy initially, then, in patients inadequately controlled with topical therapy, phototherapy or photochemotherapy followed, in non-responders, by conventional systemic therapy (for example, methotrexate and acitretin, with ciclosporin usually reserved for induction only in severe cases). Biologic medicines are generally used in patients who have failed to respond to conventional systemic therapies.[7, 8] Biologic therapies licenced for the treatment of moderate to severe plaque psoriasis in adults, and have been approved for restricted use in NHSScotland, include tumour necrosis factor (TNF) inhibitors (infliximab, etanercept, adalimumab and certolizumab pegol), IL12/IL23 inhibitor (ustekinumab), IL23 inhibitor (guselkumab), IL17 inhibitors (secukinumab and ixekizumab) and the IL17A receptor antagonist (brodalumab). Clinical experts consulted by SMC consider that risankizumab offers an additional biologic therapy.

The submitting company has requested that SMC considers risankizumab when positioned for use in patients who have failed to respond to conventional systemic therapies (including ciclosporin, methotrexate and phototherapy), or are intolerant to, or have a contraindication to these treatments.

Findings from the key phase III studies UltIMMa-1, UltIMMa-2, and IMMvent have shown that risankizumab is an effective treatment for moderate to severe plaque psoriasis. At Week 16, risankizumab was superior to ustekinumab, adalimumab, and placebo in achieving PASI 90 and sPGA 0 or 1 responses. Key secondary analyses demonstrated that this benefit was maintained through to Week 44/52, and was also supported by statistically significant and clinically meaningful improvements in patient reported DLQI 0 or 1 scores. However, the populations used in the key studies, although large and heterogeneous, were broader than the positioning proposed by the company. Patients were not required to have an inadequate response, an intolerance to, or a contra-indication to conventional systemic treatment, and consequently only a proportion of patients had failed to respond to at least one conventional systemic therapy. Subgroup analyses reassuringly demonstrated a consistent treatment effect with risankizumab, including subgroups of patients with varying levels of prior treatment exposure. These results should be interpreted with caution however, as the subgroup analyses were not powered to detect differences.[3-5]

No patients enrolled in the three key studies were from the UK. In order to address this potential issue of generalisability, the submitting company compared baseline characteristics of the key studies against registry data of an adalimumab group (n=5657) drawn from the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR).[9] Although broadly similar, there were some minor differences between the UltIMMa-1, UltIMMa-2, IMMvent, and BADBIR populations, namely mean baseline PASI score (20, 20, 20 versus 15) and baseline DLQI score (12 to 15 versus 17). The female population was under represented in the key studies; approximately 30% of study participants were female across UltIMMa-1, UltIMMa-2, and IMMvent, which was lower than data taken from BADBIR (41%). These minor differences may introduce some uncertainty in the applicability of results to the Scottish population.[3-5, 9-12]

The UltIMMa studies and IMMvent were 52 week and 44 week studies respectively, demonstrating a maintained treatment effect with risankizumab over this period. The duration of these studies is in line with what has previously been seen in plaque psoriasis. However, in a condition that is both chronic and relapse-remitting, longer follow-up data would have been informative. IMMhance is an ongoing, randomised, double-blind, placebo-controlled, phase III study that will monitor efficacy through to Week 156.[3-5, 10, 11]

Although risankizumab has been compared with two relevant active comparators in Scottish clinical practice, there remains a paucity absence of direct comparative evidence for several other valid treatment options. This was addressed through the use of NMAs, which had some limitations: the populations were broader than the company's proposed positioning and it is uncertain if the results from the NMA are likely to reflect the effect size and relative differences that would be seen in patients who have failed to respond to conventional systemic therapies; there was heterogeneity in baseline patient characteristics, including age, weight, duration of disease, and DLQI score; there were important differences in the PASI levels reported and assessment times across the studies included in the networks which may have confounded results. Despite these limitations, the indirect evidence is acceptable.

Clinical experts consulted by SMC considered that the availability of risankizumab would offer patients another biologic treatment option for moderate to severe plaque psoriasis after failure of response to conventional non-biologic systemic therapies. The 12-weekly maintenance dosing of risankizumab can be self-administered, and may be more convenient for patients compared with some (but not all) of the other treatment options available.

*Other data were also assessed but remain confidential.**

Summary of comparative health economic evidence

The submitting company provided an economic evaluation of risankizumab within its licensed indication for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The company applied an additional restriction, for patients who have failed to respond to conventional systemic therapies (including ciclosporin, methotrexate and phototherapy), are intolerant to, or have a contraindication to these treatments.

The company provided comparisons against three comparators: adalimumab, ustekinumab and secukinumab. This was justified based on previous market share data, alongside British Association of Dermatologists guidelines stating that these are the most commonly chosen first-line biologics. However, SMC clinical expert input suggested that risankizumab is initially likely to be used as a later line treatment, therefore additional comparisons against more recently available treatments (guselkumab, brodalumab and ixekizumab) were provided upon request.

The company provided two analyses against all of the comparators: a cost-utility analysis (CUA) and a cost-minimisation analysis (CMA). Pairwise comparisons were provided against each of the comparators. Both took the perspective of NHS Scotland and social care, as appropriate.

The CUA structure comprised three health states ('primary response', 'subsequent maintenance period', 'best supportive care' [BSC]) which were subdivided according to PASI categories. An additional four health states were used: three tunnel health states within the primary response period and an absorbing state of death. Patients entered the model in the primary response period, transitioning through the tunnel states and either transitioning to the maintenance period (for patients with PASI ≥75) or into BSC (for patients with a response of PASI ≤75). Patients in the maintenance phase could only transition into BSC or death, as no additional lines of treatment were included in the model. A 4-week cycle length and lifetime (42 year) time horizon was applied.

The CMA utilised a simpler four-state structure, comprising 'primary response period' (to week 16), 'maintenance period', 'no treatment' and 'death'. The PASI75 criteria was again applied to determine the portion of patients entering the maintenance period. In this case, a weekly cycle length and ten year time horizon was applied.

As only direct evidence was available against placebo, adalimumab and ustekinumab, the NMA described above was used to compare against the key treatments within Scottish clinical practice. Treatment discontinuation data were obtained from the UK BADBIR observational study and assumed to be consistent across all treatments, while resource use and costs data were applied from a retrospective cohort of 76 patients from a London teaching hospital. Utility estimates for the different PASI levels were derived using EQ-5D-5L data from the risankizumab clinical trials, pooled across treatment arms and mapped to EQ-3D-3L using the crosswalk approach. Adverse

event rates were assumed to be consistent and minimal between the interventions, and neither costs nor disutilities were included in the analysis.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group [PASAG] as acceptable for implementation in NHS Scotland. Prices for the other medicines were obtained from the Monthly Index of Medical Specialties (MIMS) MIMS and dose and duration estimates were obtained from the applicable SPCs. Costs of best supportive care were based on the publication from the retrospective study mentioned above, after adjusting to 2017 prices. PAS discounts are in place for ustekinumab, secukinumab, guselkumab, brodalumab and ixekizumab and these were included in the results used for decision-making by using estimates of the comparator PAS prices.

Incremental cost-effectiveness ratios (ICERs) were provided for each cost-utility analysis as a pairwise comparison, and incremental costs were provided for the cost-minimisation analysis. Base case and key sensitivity analyses are presented in the tables below.

The results presented do not take account of the PAS for the comparators or the PAS for risankizumab but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for the comparators due to commercial confidentiality and competition law issues.

Table 3: Base case results: CUA pairwise comparisons [list price for all medicines]

Risankizumab versus:	**ICER**
Adalimumab	£191,663
Ustekinumab	£183,900
Secukinumab	dominant
Guselkumab	£3,282
Brodalumab	dominant
Ixekizumab	-£394,240

Abbreviations: ICER: Incremental cost effectiveness ratio; QALY: Quality-adjusted life year;

Table 4: Base case results: CMA 10-year time horizon (list prices for all medicines)

Risankizumab versus:	**Incremental costs***
Adalimumab	£21,420
Ustekinumab	£19,121
Secukinumab	-£192
Guselkumab	£858
Brodalumab	-£3,762
Adalimumab	£21,420
Ixekizumab	-£1,335

* A negative sign indicates risankizumab is cost-minimising

Sensitivity analysis presented by the submitting company suggested that the model is most sensitive to changes in the acquisition costs of risankizumab and the relevant comparator, as well as the relative efficacy of the comparator and risankizumab. Key scenario analyses are presented in the table below.

Table 5: Key scenario analyses: CUA & CMA (list price for all medicines)

Cost-utility (ICERs)	**ADA**	**UST**	**SEC**	**GUS**	**BRO**	**IXE**
Reduced time horizon (5 years)	£199,225	£189,140	dominant	£809	dominant	dominant
Reduced time horizon (10 years)	£193,228	£184,984	dominant	£184,984	dominant	dominant
Alternative response criteria	£191,663	£183,900	dominant	£3,282	dominant	dominant
Cost-minimisation*	**ADA**	**UST**	**SEC**	**GUS**	**BRO**	**IXE**
Reduced time horizon (5 years)	£17,608	£15,372	-£326	£753	-£2,365	-£1,387
Alternative response criteria	£21,420	-£192	-£161	-£1,335	-£4,248	-£1,252

ADA: Adalimumab, UST: Ustekinumab, SEC: Secukinumab, GUS: Guselkumab, BRO: Brodalumab, IXE: Ixekizumab.

* A negative sign indicates risankizumab is cost-minimising

The key uncertainties with the evaluation include:

- Comparisons against key comparators using the CUA approach rely on indirect comparisons to derive treatment differences, which are associated with uncertainty. However, the use of a CMA provides alternative estimates for a scenario where no clinical difference is applied.
- It is unclear whether the stopping rules related to the primary response period apply to all comparator medicines included in this evaluation.
- Uncertainty exists regarding the generalisability of the best supportive care costs to a post-treatment population within NHS Scotland, although these have previously been estimated to be higher in other submissions to SMC than assumed within this evaluation (representing a conservative assumption).
- Lack of baseline utility estimate poses challenge in evaluating face validity, however does not influence the ICER calculations.

Despite these issues, the economic case was considered demonstrated.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from The Psoriasis Association and the Psoriasis and Psoriatic Arthritis Alliance (PAPAA). PAPAA is a registered charity and The Psoriasis Association is a charitable incorporated organisation.

- The Psoriasis Association has received 5.63% pharmaceutical company funding in the past two years, including from the submitting company. PAPAA has not received any pharmaceutical company funding in the past two years.

- Psoriasis is a relentless lifelong condition which affect all parts of an individual's life. Owing to the highly visible nature of psoriasis, patients may adopt negative coping mechanisms such as avoiding social situations, making the condition both isolating and lonely. Psoriasis in high impact areas such as the hands, feet, face or genitals is particularly disabling.

- Although there have been advancements in therapy, there are always individuals who find the existing treatments either do not work or begin to fail. These people need further choice and therefore more options are welcomed.

- Risankizumab would offer another treatment option that could lead to an improved quality of life for some people, allowing them to experience a life that is not blighted and restricted by the impact of the physical and mental aspects of psoriasis.

Additional information: guidelines and protocols

In October 2010 the Scottish Intercollegiate Guidelines Network (SIGN) published SIGN number 121, Diagnosis and management of psoriasis and psoriatic arthritis in adults: A national clinical guideline. The SIGN website notes "some recommendations may be out of date, declaration of interests governance may not be in line with current policy." The guidance recommends that patients with psoriasis who do not respond to topical therapy should be offered narrow band UVB (NBUVB) phototherapy. Psoralen UVA (PUVA) photochemotherapy should be considered for those patients who do not respond to NBUVB. Patients with severe or refractory psoriasis should be considered for systemic therapy with ciclosporin, methotrexate or acitretin, following discussion of benefits and risks. Patients with severe psoriasis who fail to respond to, or have a contraindication to, or are intolerant of phototherapy and systemic therapies including ciclosporin and methotrexate, should be offered biologic therapy unless they have contraindications or are at increased risk of hazards from these therapies. For severe psoriasis, the guideline recommends biologic treatment options in alphabetical order: adalimumab (loading regimen then 40mg every other week), etanercept (25mg twice weekly or 50mg weekly), infliximab (5mg/kg at weeks 0, 2, 6

and repeated every two months) or ustekinumab (45mg for patients weighing under 100kg and 90mg for patients weighing over 100kg given at weeks 0 and 4 then every 12 weeks).[7]

The National Institute for Health and Care Excellence (NICE) published Psoriasis: assessment and management; Clinical guideline 153 in October 2012. The guidance was subsequently updated in September 2017 but did not review evidence for use of a first biological agent because guidance was available in existing NICE technology appraisals. Reference is made in the guidance to technology appraisals for adalimumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab in adult patients. The guidance recommends that consideration is given to changing to an alternative biological drug, in adult patients, 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 and secukinumab, and 16 weeks for adalimumab and ustekinumab; referred to as 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.[8]

The British Association of Dermatologists (BAD) published Guidelines for biologic therapy for psoriasis in April 2017. The guidance recommends that biologic therapy is offered to patients with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated, and if psoriasis has a large impact on physical, psychological or social functioning (for example, a DLQI or cDLQI of >10 or clinically relevant depressive or anxiety symptoms), and one or more of the following disease severity criteria apply: the psoriasis is extensive (defined as BSA >10%, or a PASI ≥10), or the psoriasis is severe at localised sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals). The guidance also recommends that consideration is given to commencing biologic therapy earlier in the treatment pathway (for example, if methotrexate has failed, is not tolerated or is contra-indicated) in patients with psoriasis, who fulfil the disease severity criteria and who have active psoriatic arthritis or who have psoriasis that is persistent (that is psoriasis that relapses rapidly off a therapy that cannot be continued long-term).[13]

The guidance stipulates that the choice of first-line biologic therapy should be tailored to the needs of the individual patient and take into account the psoriasis and patient choice. Initial response to biologic therapy should be assessed at time points appropriate for the drug in question, and then on a regular basis during therapy (for example, every 6 months). It is also recommended that consideration is given to changing to an alternative therapy, including another biologic therapy, if any of the following apply: the psoriasis does not achieve the minimum response criteria (primary failure); the psoriasis initially responds but subsequently loses this response (secondary failure); or the current biologic therapy cannot be tolerated or becomes contraindicated. The choice of second-line biologic therapy may include any of the currently licensed biologic therapies. BAD guidance recommends that consideration should be given to reserving infliximab for use in patients with very severe disease or where other available biologic agents have failed or cannot be used. Furthermore, the guidance states that consideration is given

to escalating the dose of biologic therapy in adults, where this is feasible and funded, when an inadequate primary response may be due to insufficient drug dosing (for example, in people who are obese or whose psoriasis relapses during the treatment cycle). The guidance highlights that this may be associated with an increased risk of infection, and, depending on the drug, off-licence.[13]

Additional information: comparators

Other biologic medicines licensed for the treatment of adults with moderate to severe plaque psoriasis, including adalimumab, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, secukinumab, tildrakizumab and ustekinumab.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
risankizumab	**Initially 150mg SC, then 150mg after 4 weeks, then maintenance 150mg every 12 weeks.**	First year: 16,630 Subsequent years: 14,967
brodalumab	210mg SC at weeks 0, 1, and 2, then every 2 weeks.	First year: 17,280 Subsequent years: 16,640
ixekizumab	160mg SC at week 0, then 80mg at weeks 2, 4, 6, 8, 10 and 12, then 80mg every four weeks.	First year: 19,125 Subsequent years: 14,625
secukinumab	300mg SC at weeks 0, 1, 2, 3 and 4 and then monthly.	First year: 19,500 Subsequent years: 14,625
tildrakizumab	Initially 100mg subcutaneously (SC), then 100mg after 4 weeks, then maintenance 100mg every 12 weeks. A dose of 200mg may provide greater efficacy.	First year: 16,205 Subsequent years: 14,043
guselkumab	100mg SC at weeks 0 and 4, then every 8 weeks.	First year: 15,750 Subsequent years: 14,625

infliximab	5mg/kg IV at weeks 0, 2 and 6, then every 8 weeks.	First year: 12,064 Subsequent years: 9,802
ustekinumab	45mg (or 90mg) SC at weeks 0 and 4, then every 12 weeks.	First year: 10,735 Subsequent years: 9,304
certolizumab pegol	400mg SC at week 0, 2, and 4, then 200mg every 2 weeks.	First year: 10,368 Subsequent years: 9,295
etanercept	25mg SC twice weekly or 50mg SC weekly, alternatively 50mg twice weekly for up to 12 weeks, followed by 25mg twice weekly, alternatively 50 mg once weekly.	8,366 to 10,296
adalimumab	80mg SC at week 0, then 40mg SC every two weeks.	First year: 8,319 Subsequent years: 8,011

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 04 July 2019. Costs calculated using a bodyweight of 70kg and the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. SC=subcutaneously; IV=intravenously.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. King AC, Pappacena JJ, Tallman MS, Park JH, Geyer MB. Blinatumomab administered concurrently with oral tyrosine kinase inhibitor therapy is a well-tolerated consolidation strategy and eradicates measurable residual disease in adults with Philadelphia chromosome positive acute lymphoblastic leukemia. Leukemia Research. 2019;79:27-33.
2. European Medicines Agency (EMA). European Public Assessment Report. Risankizumab (Skyrizi). EMEA/H/C/004759/0000. 28 June 2019. www.ema.europa.eu.
3. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y*, et al.* Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. The Lancet. 2018;392(10148):650-61.
4. Reich K, Gooderham M, Thaci D, Crowley JJ, Ryan C, Krueger JG*, et al.* Efficacy and safety of risankizumab (RZB) compared with adalimumab (ADA) in patients with moderate-to-severe plaque psoriasis: Results from the phase 3 IMMvent trial. Experimental Dermatology. 2018;27 (Supplement 2):9-10.
5. Reich K, Gooderham M, Thaci D, Crowley JJ, Ryan C, Kruger JG*, et al.* Efficacy and safety of Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis: Results from the Phase 3 IMMvent trial. Experimental Dermatology. 2019;28 (3):e24-e5.
6. Feldman S, Krueger G. Psoriasis assessment tools in clinical trials. Annals of the rheumatic diseases. 2005;64(suppl 2):ii65-ii8.
7. Scottish Intercollegiate Guidelines Network. Diagnosis and management of psoriasis and psoriatic arthritis in adults: A national clinical guideline. SIGN 121. Edinburgh; 2010. Available at: https://www.sign.ac.uk/assets/sign121.pdf (Accessed 22.02.19).
8. National Institute for Health and Care Excellence. Psoriasis: assessment and management. Clinical guideline 153. London; 2012. Available at: https://www.nice.org.uk/guidance/cg153 (Accessed 22.02.19).
9. Burden A, Warren R, Kleyn C, McElhone K, Smith C, Reynolds N*, et al.* The British Association of Dermatologists' biologic interventions register (BADBIR): design, methodology and objectives. British Journal of Dermatology. 2012;166(3):545-54.
10. Blauvelt A, Papp K, Gooderham M, Langley RG, Leonardi C, Lacour JP*, et al.* Efficacy and Safety of Risankizumab, in IL-23 Inhibitor, in Patients with Moderate-to-Severe Chronic Plaque Psoriasis: 16-Week Results from the Phase 3 IMMhance. Maui Derm for Dermatologists; Grand Wailea, Hawaii.
11. Langley RG, Blauvelt A, Gooderham M, Papp K, Philipp S, Wu JJ*, et al.*, editors. Efficacy and Safety of Continuous Q12W Risankizumab versus Treatment Withdrawal: Results from the Phase 3 IMMhance Trial. American Academy of Dermatology Meeting; 2019; Washington, D.C.
12. DynaMed. Psoriasis. 19 November 2018 [cited 08 February 2019]; Available from: http://www.dynamed.com.knowledge.idm.oclc.org/topics/dmp~AN~T116742/Psoriasis.
13. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, Bale T, Burden AD, Coates LC*, et al.* British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. Br J Dermatol. 2017;177(3):628-36. Epub 2017/05/18.

This assessment is based on data submitted by the applicant company up to and including 15 August 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: https://www.scottishmedicines.org.uk/media/3572/20180710-release-of-company-data.pdf*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.