Cost-effectiveness of risankizumab (Skyrizi®) for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of risankizumab (Skyrizi®). Following assessment of the Applicant's submission, the NCPE recommends that risankizumab (Skyrizi®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The Health Service Executive (HSE) asked the NCPE to carry out a review of the Applicant's (AbbVie Ltd) Health Technology Assessment of risankizumab (Skyrizi®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **August 2021**

Summary

In October 2020, AbbVie Ltd submitted a dossier of clinical, safety and economic evidence on risankizumab (Skyrizi®) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. AbbVie Ltd are seeking reimbursement on the High Tech Drug Arrangement. Final data was submitted by the Applicant in April 2021.

Psoriasis is a chronic inflammatory, immune-mediated condition that primarily affects the skin and joints. Plaque psoriasis is characterised by red, scaly plaques; it is the most common form of the condition, affecting 90% of people with psoriasis. The Psoriasis Area and Severity Index (PASI) is one of the most common tools used by clinicians to assess disease severity and clinical response to treatments. For example, a 75% reduction from baseline PASI score is referred to as PASI 75.

Risankizumab is a humanised monoclonal antibody that selectively blocks interaction of human interleukin 23 (IL-23) cytokine with its receptor complex, leading to inhibition of IL-23 dependant release of pro-inflammatory cytokines. The recommended dose of risankizumab is 150mg (two 75mg injections) administered by subcutaneous (SC) injection at week 0, week 4, and once 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. The product licence does not provide a definition for 'response'. However, clinical opinion suggests that, in Irish clinical practice, PASI 75 would be considered appropriate. Given the chronic nature of the condition, it is anticipated that risankizumab will be used continuously by patients once initiated and where there is evidence of response.

Systemic treatments for plaque psoriasis may be categorised as non-biologic or biologic therapies. Risankizumab is a biologic therapy. Non-biologic, systemic treatment options licensed for moderate to severe plaque psoriasis include methotrexate, ciclosporin, acitretin, apremilast, and dimethyl fumarate. Alternative biologic systemic treatment options include the tumour necrosis factor-alpha (TNF-α) inhibitors (adalimumab and

etanercept), the IL-23 inhibitors (guselkumab and tildrakizumab), the IL-12/23 inhibitor (ustekinumab), and the IL-17 inhibitors (brodalumab, ixekizumab, and secukinumab). Clinical opinion to the Review Group indicated that, in Irish clinical practice, most patients are initiated on methotrexate as the first-line systemic treatment option. Patients who fail methotrexate are subsequently initiated on biologic therapy. It was acknowledged, however, that there would be a small proportion of patients, who for various reasons, would be commenced on biologic therapy first-line. Most (but not all) clinicians indicated that they would consider biosimilar adalimumab for first-line biologic treatment. The licensed indication for risankizumab positions it such that it may be used as either a first-, second-, or third-line systemic treatment option. The Review Group considered all systemic therapies, both biologic and non-biologic, to be relevant comparators to risankizumab. However, the comparison of risankizumab with biosimilar adalimumab was of particular interest to the Review Group.

1. Comparative effectiveness of risankizumab

Clinical evidence is available from five pivotal, phase III, randomised, double-blind, placebo- and active-controlled trials. UltIMMA-1 (n=506) and UltIMMA-2 (n=491) were replicate clinical trials; both trials compared risankizumab to both placebo monotherapy and to ustekinumab monotherapy. IMMvent (n=605) compared risankizumab to adalimumab. IMMhance (n=507) and IMMerge (n=327) compared risankizumab to placebo and secukinumab, respectively. Co-primary endpoints for all five trials were the number of patients achieving a 90% improvement from baseline in Psoriasis Severity Index Score (PASI 90), and the number of patients achieving static Physician's Global Assessment (sPGA) of clear (0) or almost clear (1), at week 16. Risankizumab demonstrated improved outcomes, with respect to co-primary endpoints, at week 16 versus all comparators; the results were statistically significant.

The pivotal clinical trials provided direct comparative evidence for risankizumab versus placebo, adalimumab, secukinumab, and ustekinumab. However, indirect evidence was required to compare risankizumab with the remaining systemic therapy comparators The Applicant conducted a network meta-analysis (NMA), informed by 66 studies, to generate comparative clinical evidence pertaining to short-term PASI response (between week 12 and

week 16) for risankizumab versus the remaining systemic therapies. The Review Group noted there was heterogeneity among the trials particularly with respect to the prior treatment history of patients included in the trials, and also with respect to time points at which primary efficacy end-point data was collected. The results of the NMA suggest that risankizumab is more effective than placebo and the non-biologic medicines in achieving various levels of short-term PASI response. With respect to other biologic medicines, similar levels of efficacy are observed between risankizumab, the IL-17 inhibitors (brodalumab, ixekizumab, and secukinumab), and the IL-23 inhibitor, guselkumab. The NMA results also suggest that risankizumab is more effective than both TNF-α inhibitors (adalimumab and etanercept); however, the difference appears to be more pronounced in its comparison with etanercept.

2. Safety of risankizumab

The safety profile of risankizumab was demonstrated to be comparable, if not more favourable, to the comparators used in the five pivotal clinical trials. The most frequently reported adverse drug reaction (ADR) associated with risankizumab treatment was upper respiratory tract infection, which occurred in 13% of patients. Other commonly reported ADRs included headache, arthralgia, fatigue, back pain, and pruritus. Common ADRs were predominantly mild (>97%). Overall, risankizumab was well tolerated with discontinuation in clinical trials due to ADRs less than 2%. The Applicant used an NMA, as described in section 1, to generate indirect clinical evidence comparing the relative safety of risankizumab to its comparators at 16 weeks. Results suggest that the probability of experiencing an ADR is similar for risankizumab, adalimumab, etanercept, guselkumab, tildrakizumab, and ustekinumab. The probability of experiencing an ADR is higher with apremilast, dimethyl fumarate and the IL-17 inhibitors (brodalumab, ixekizumab, and secukinumab).

3. Cost effectiveness of risankizumab

Cost effectiveness was assessed using a Markov model with a life-time horizon. Model cycle length was four weeks; a half-cycle correction was not applied. Treatment effectiveness was determined by PASI response. The model assumed that patients were treated with a sequence of three active drug treatments (the intervention or comparator, followed by two other active drug treatments) followed by treatment with best supportive care. The model

consisted of four mutually exclusive treatment-related states: the primary response state, maintenance treatment state, best supportive care, and death. Within each state (except death) patients were categorised according to PASI response (PASI 0 to 49, PASI 50 to 74, PASI 75 to 89, PASI 90 to 99, and PASI 100). Duration of the primary response period varied (either 12 or 16 weeks) between active treatments and aligned with the recommended timing for primary response assessment specified in the product licence for each drug. At the end of the primary response period, patients who achieved PASI 75 response were classified as responders and transitioned to maintenance treatment; patients who achieved less than PASI 75 response were classified as non-responders and transitioned to the next treatment in sequence. Patients who entered maintenance treatment were assumed to retain the same level of PASI response until discontinuation due to any cause. Patients who entered the best supportive care state were assumed to retain PASI 0 to 49 response. Transition to death was possible from all states, and was modelled according to national mortality rates for the general population. The Applicant applied treatment specific discontinuation rates which were informed by published literature and also from the NMA. It was assumed that the discontinuation rate for each treatment was constant and would not vary over time. The structure with respect to primary response period, response-based stopping rule, and maintenance treatment was replicated for each active drug treatment.

Whilst the Review Group considered the model structure to be appropriate overall, several limitations were identified. PASI score measures disease severity according to area of skin affected, level of redness, and thickness of psoriasis. It is commonly used as a measure of treatment effectiveness in economic models for psoriasis. However, clinical opinion to the Review Group indicated that disease severity may also be determined by particular body areas affected by psoriasis and the impact of psoriasis on patients' daily lives, which may not be fully captured by PASI. The product licence for risankizumab states that patients who demonstrate an initial partial response may subsequently benefit from continued treatment beyond 16 weeks. Whilst PASI 75 is considered a reasonable threshold for response to treatment, the model structure does not account for patients who are partial responders. In efforts to address this, scenarios using response criteria of PASI 50 (instead of PASI 75) were provided by the Applicant. With respect to subsequent treatments, the Review Group considers that model structure facilitating multiple lines of treatment is appropriate.

However, the model structure did not account for variation in second or third line treatment options. The Applicant assumed that all patients in a treatment arm will receive the same second and third line treatments. However, in practice the choice of follow on therapy will likely vary depending on patient factors. There was also a paucity of data to inform what the most likely treatment sequences would be in Irish clinical practice.

Health outcomes in the cost-effectiveness model were measured as incremental quality-adjusted life year (QALY) gains. Each level of PASI response corresponded to a specific utility increment measure, which was assumed to be the same irrespective of treatment. The Applicant used EQ-5D-3L-based utility values derived from a technology appraisal of brodalumab, conducted by the National Institute for Health and Care Excellence (NICE) in the UK (2018; TA511), for their base case results. However, the Review Group considered the application of utility values collected during the UltIMMA-1 and UltIMMA-2 trials to be more appropriate. As cost-effectiveness results were highly sensitive to the choice of health outcome data used, several scenario analyses were presented.

The Review Group made a number of necessary adjustments to cost inputs in the Applicant's base case model. The Review Group made a number of additional changes to establish the NCPE-adjusted base case:

- EQ-5D-3L data mapped from EQ-5D-5L data collected during the UltIMMA-1 and UltIMMA-2 trials was used to inform utility values
- treatment sequences, for several of the biologic drugs, were changed to ensure that subsequent treatments were from a different therapeutic class. This assumption was supported by clinical opinion to the Review Group.

Results of the Applicant's base case, and the NCPE-adjusted base case, are illustrated in Tables Table 1: Results of the Applicant's corrected base case pairwise cost-effectiveness analysis of risankizumab versus comparators. Probability of cost-effectiveness of risankizumab versus each comparator, at willingness to pay thresholds of €20,000 per QALY and €45,000 per QALY, for the Applicant base case and NCPE-adjusted base case are also illustrated in Tables Table 1: Results of the Applicant's corrected base case pairwise cost-effectiveness analysis of risankizumab versus comparators.

Table 1: Results of the Applicant's corrected base case pairwise cost-effectiveness analysis of risankizumab versus comparators.

Drug	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)	Probability of cost-effectiveness (%)	
				WTP €20,000 per QALY	WTP €45,000 per QALY
Risankizumab*	-	-	-	-	-
Biologic systemic therapies					
Adalimumab	51,954	0.85	61,414	0	0
Brodalumab	-153	0.19	Dominant	100	100
Etanercept	45,444	0.97	46,626	0	24
Guselkumab	5,954	0.19	32,151	2	97
Ixekizumab	5,154	0.22	23,050	28	100
Secukinumab	9,228	0.22	41,544	0	73
Tildrakizumab 100mg^	9,914	0.44	22,770	18	100
Tildrakizumab 200mg^	14,247	0.54	26,279	1	100
Ustekinumab	14,241	0.24	59,517	0	1
Non-biologic systemic therapies					
Acitretin	64,098	1.08	59,216	0	1
Apremilast	76,486	1.32	57,848	0	0
Ciclosporin	57,371	0.82	69,731	0	0
Dimethyl fumarate	82,119	1.48	55,593	0	0
Methotrexate	74,185	0.82	91,025	0	0

ICER=Incremental cost-effectiveness ratio; **IL-=**interleukin; **QALY=**Quality-adjusted life-year
ICERs presented are based on the list price of all medicines; however, commercial in confidence Patient Access Schemes are in place for several of the comparators (not included). Numbers are presented as rounded; calculations may not be directly replicable.
*Intervention under assessment
^The Health Technology Assessment (HTA) of tildrakizumab is ongoing. For the purpose of assessment, an assumption of price parity was made between risankizumab and tildrakizumab 100mg.

Table 2: Results of the NCPE adjusted base case pairwise cost-effectiveness analysis of risankizumab versus comparators.

Drug	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)	Probability of cost-effectiveness (%)	
				WTP €20,000 per QALY	WTP €45,000 per QALY
Risankizumab*	-	-	-		
Biologic systemic therapies					
Adalimumab	43,178	0.43	99,587	0	0
Brodalumab	-4,149	0.07	Dominant	100	100
Etanercept	36,668	0.51	72,093	0	0
Guselkumab	6,722	0.11	59,809	0	8
Ixekizumab	8,924	0.14	62,623	0	1
Secukinumab	452	0.07	6,381	77	99
Tildrakizumab 100mg^	11,491	0.26	43,598	0	59
Tildrakizumab 200mg^	16,375	0.33	49,760	0	20
Ustekinumab	5,465	0.08	67,726	0	7
Non-biologic systemic therapies					
Acitretin	64,098	0.63	101,770	0	0
Apremilast	67,710	0.71	95,202	0	0

Ciclosporin	57,371	0.48	119,816	0	0
Dimethyl fumarate	73,342	0.80	91,592	0	0
Methotrexate	74,185	0.47	156,404	0	0

ICER=Incremental cost-effectiveness ratio; **IL-=**interleukin; **QALY=**Quality-adjusted life-year
ICERs presented are based on the list price of all medicines; however, commercial in confidence Patient Access Schemes are in place for several of the comparators (not included). Numbers are presented as rounded; calculations may not be directly replicable.
*Intervention under assessment
^The HTA of tildrakizumab is ongoing. For the purpose of assessment, an assumption of price parity was made between risankizumab and tildrakizumab 100mg.

4. Budget impact of risankizumab

The price to wholesaler per pack of risankizumab is €3,107.20; each pack contains two 75mg pre-filled syringes of risankizumab. Assuming that patients continue treatment with risankizumab beyond week 16, the cost per patient for the first year of treatment is €24,279 (incorporating mark-up, 5.5% rebate, and pharmacy patient care fees) including VAT. The cost per annum from year two onwards is €17,744 including VAT.

The Applicant estimated that approximately 124 patients would be treated with risankizumab in year one, rising to 719 in year five. This was based on an assumption that approximately 14% of patients with moderate to severe plaque psoriasis, and who are receiving treatment in secondary care in Ireland, would receive biologic therapy. The Review Group noted that these figures do not align with results from cross-sectional studies of secondary care centres for psoriasis in Europe, which suggest much higher biologic uptake. The Review Group estimates that approximately 145 patients would be treated with risankizumab in year one rising to 826 in year five, but acknowledges that these figures are also uncertain.

The Review Group identified a significant limitation to the Applicant's budget impact model. From year two onwards, the Applicant only applied the costs of the first year of treatment to incident patients with psoriasis; maintenance costs (which are lower) were applied to prevalent patients. This meant that, from years two to five, the number of patients receiving maintenance treatment far exceeded the number of patients who had received year one of treatment the year before. As a result, the Review Group considered that the budget impact model lacked face-validity and the full costs of initiating treatment have not been captured by the model. Overall, due to uncertainty with respect to eligible patient numbers, and

concerns regarding budget impact model structure, the Review Group considers the budget impact estimates to be highly uncertain.

The Applicant estimated the gross budget impact for risankizumab to be €2.5 million in year one increasing to €12.9 million in year five with the five-year cumulative gross budget impact estimated to be €36 million. The introduction of risankizumab will likely result in displacement of some of the other biologic and non-biologic systemic therapies licensed for the treatment of moderate to severe plaque psoriasis. The Applicant estimated the five-year cumulative net budget impact to be €47,162. Using NCPE-adjusted eligible patient numbers, the five-year cumulative gross and net budget impacts were estimated to be €43 million and €1.1 million, respectively. Commercial in confidence Patient Access Schemes, which are not included in this summary document, are in place for a number of the biologic (both patented and biosimilar) comparators; the true net budget impact to the HSE will likely be higher than that presented here.

5. Patient submission

A patient organisation submission was received from the Irish Skin Foundation during the course of this assessment, and this will be provided to the HSE. This submission will form part of the data that the HSE considers.

6. Conclusion

The NCPE recommends that risankizumab (Skyrizi®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.