Cost-effectiveness of tildrakizumab (Ilumetri®) 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 tildrakizumab (Ilumetri®) in patients with moderate to severe plaque psoriasis who have failed non-biologic therapy and first-line biologic treatment with adalimumab; this is a subpopulation of the product licence for tildrakizumab. Following assessment of the Applicant's submission, the NCPE recommends that tildrakizumab (Ilumetri®) 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 (Almirall Ltd) Health Technology Assessment of tildrakizumab (Ilumetri®). 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 multidisciplinary team including clinicians, pharmacists, pharmacologists, epidemiologist, information specialists 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 **November 2021**

Summary

In May 2021, Almirall Ltd submitted a dossier of clinical, safety and economic evidence on tildrakizumab (Ilumetri®) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy and who have failed treatment with non-biologic therapies and first-line biologic treatment with adalimumab. This is a subpopulation of the product licence, which specifies that tildrakizumab may be prescribed for all adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy. Almirall Ltd are seeking reimbursement on the High Tech Drug Arrangement. Final data was submitted by the Applicant in August 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.

Tildrakizumab 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 tildrakizumab is 100mg (a single injection) administered by subcutaneous (SC) injection at week 0, week 4, and once every 12 weeks thereafter. In patients with certain characteristics (e.g. high disease burden [not specifically defined in the product licence] or body weight ≥90kg), a 200mg dose (2 x 100mg injections) may provide greater efficacy. Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 28 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 tildrakizumab 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. Tildrakizumab 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 risankizumab), 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 who provided opinion indicated that they would consider adalimumab for first-line biologic treatment. The licensed indication for tildrakizumab positions it such that it may be used as either a first-, second-, or third-line systemic treatment option. The Review Group considered the broader population defined by the product licence for tildrakizumab (all patients with moderate to severe plaque psoriasis who are candidates for systemic therapy) to be the relevant population to the assessment; all systemic therapies (both non-biologic and biologic) were considered to be relevant comparators. However, the Applicant chose to position tildrakizumab as a second- or subsequent biologic treatment option for patients who have failed, or are unsuitable for treatment with non-biologic therapies and first-line biologic treatment with adalimumab. In view of this positioning, the Applicant included the IL-23 inhibitors (guselkumab and risankizumab), the IL-17 inhibitors (brodalumab, ixekizumab and secukinumab) and the IL-12/23 inhibitor (ustekinumab) as relevant comparators. No non-biologic treatments were considered. All cost-effectiveness analyses and budget impact analyses presented pertain to this subpopulation of the product licence.

1. Comparative effectiveness of tildrakizumab

Clinical evidence is available from two pivotal, phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre international trials. reSURFACE1 (n=772) and reSURFACE2 (n=1,090) both compared tildrakizumab (two arms: 100mg or 200mg at week 0, week 4, and once every 12 weeks thereafter) to placebo. reSURFACE2, in addition,

compared the intervention to a fourth arm: active comparator etanercept (50mg). Co-primary endpoints for both trials were the number of patients achieving a PASI 75, and the number of patients achieving a Physician's Global Assessment (PGA) of clear (0) or almost clear (1) with at least a two grade reduction from baseline, at week 12. Tildrakizumab, at both doses, demonstrated improved outcomes in both trials, with respect to co-primary endpoints, at week 12 versus placebo and etanercept; the results were statistically significant. Evidence from an open-label extension study, following completion of reSURFACE1 and reSURFACE2 in patients who achieved at least PASI 50 response, demonstrated sustained treatment effect with tildrakizumab up to week 244.

While the pivotal trials provided direct comparative evidence for tildrakizumab versus placebo, and for etanercept (reSURFACE2 only), indirect evidence was required to compare tildrakizumab with the remaining systemic therapy comparators. The Applicant conducted a network meta-analysis (NMA), informed by 53 studies, to generate comparative clinical evidence pertaining to PASI response at two different time periods (between week 12 and week 16, and between week 24 and week 28) for tildrakizumab 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 for the first time period (between week 12 and week 16) tildrakizumab 100mg and 200mg are more effective than placebo as well as the TNF-α inhibitor, etanercept, in obtaining PASI 50, PASI 75, PASI 90, and PASI 100 responses. There was no significant difference between tildrakizumab 100mg and 200mg when compared to the IL-12/23 inhibitor, ustekinumab, and the TNF-α inhibitor, adalimumab. Tildrakizumab 100mg and 200mg was demonstrated to be less effective compared to the IL-17 inhibitors, (brodalumab, ixekizumab, and secukinumab) and the other IL-23 inhibitors (guselkumab and risankizumab). In the second time period (between week 24 and week 28), tildrakizumab 100mg and 200mg were statistically significantly more effective than etanercept, in obtaining PASI 50, PASI 75, PASI 90 and PASI 100 responses. There was no significant difference between tildrakizumab 100mg and 200mg when compared to ustekinumab, adalimumab, and in this instance the IL-17 inhibitor, ixekizumab. Tildrakizumab 100mg and 200mg was demonstrated to be less effective compared to brodalumab, secukinumab,

guselkumab and risankizumab, at both doses (however the difference was not statistically significant for brodalumab at the tildrakizumab 200mg dose).

2. Safety of tildrakizumab

Tildrakizumab was demonstrated to have a favourable safety profile when compared to placebo or etanercept in the two pivotal clinical trials. The most frequently reported adverse drug reaction (ADR) associated with tildrakizumab treatment, in the reSURFACE1 and reSURFACE2 trials, was nasopharyngitis which occurred in <20% of patients. Other reported ADRs included upper respiratory tract infection, headache, gastroenteritis, nausea, diarrhoea, injection site pain, and back pain. Overall, tildrakizumab was well tolerated with discontinuation in the pivotal clinical trials due to ADRs less than 2%. The overall safety profile of tildrakizumab is in line with other biologics for the treatment of psoriasis. There were no differences observed between the 100mg and 200mg doses observed to support favouring one dose regime over the other, neither in incidence of ADRs nor in type of ADRs. The lack of placebo arm and lack of blinding in the long term open-label extension study; together with the use of 'as observed' datasets (which exclude many of the non-responders and dropouts); must be acknowledged as limitations of the safety findings and long-term study findings for tildrakizumab.

3. Cost effectiveness of tildrakizumab

Cost effectiveness was assessed using a Markov model with a life-time horizon. Model cycle length was 14 weeks; a half-cycle correction was applied. Treatment effectiveness was determined by PASI response. The model assumed that patients receive treatment with a single biologic therapy which, upon discontinuation, is followed by best supportive care (BSC). The model consisted of four mutually exclusive treatment-related states: the primary response (induction) state, maintenance treatment state, BSC, and death. Within each state (except death) patients were categorised according to PASI response. Duration of the primary response period was assumed to be 14 weeks for comparators and 28 weeks for tildrakizumab. The assumption of a 14-week primary response period did not align with the product licence for the majority of comparators which, in reality, varies between treatments. At the end of the primary response period, patients who achieved PASI 75 response or greater 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 BSC. Patients who entered maintenance treatment were assumed to retain the same level of PASI response until discontinuation due to any cause. Patients who entered BSC 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. It was assumed that the discontinuation rate for each treatment was constant and would not vary over time.

Several limitations were identified in the model structure by the Review Group. The cycle length of 14 weeks did not allow for precise modelling of the primary response period for each biologic comparator. A shorter cycle length (one to two weeks) would more accurately capture the varying primary response periods for all included drug treatments. 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 tildrakizumab states that patients who demonstrate an initial partial response may subsequently benefit from continued treatment beyond 28 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. The Applicant's base case assumed that patients would only receive treatment with one biologic comparator before transitioning to BSC; the Review Group does not consider this to reflect Irish clinical practice. Whilst there is uncertainty in relation to how drugs will be sequenced in the treatment pathway, the Review Group considers a model structure allowing for multiple lines of treatment to be more appropriate. The Applicant provided a scenario analysis incorporating sequencing of multiple biologics. However, in some cases, the treatment sequences included drugs from the same class. The Review Group did not consider this to most accurately reflect clinical practice. Clinical opinion to the Review Group indicated a preference for switching to treatments from a different class. The Review Group also had concerns that the BSC state in the model is not representative of 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. Data from reSURFACE1 were considered most appropriate for inclusion in the base case by the Applicant. The health state utilities were applied based on the EQ-5D-3L data recorded at week 12 only of the reSURFACE1 study. EQ-5D data were also collected at weeks 28, 52 and 64 in reSURFACE1, but this was not utilised by the Applicant. The Review Group consider that trial based utility values should have been informed by data collected at all available time points.

The Review Group made a number of necessary changes to the Applicant's base case model, including adjustments to cost inputs and the inclusion of treatment sequences. It was assumed that treatments in the same class were not repeated. Clinical opinion to the NCPE indicates a preference for switching to a treatment from a different class which the patient has not already been prescribed. For consistency, the NCPE adjusted base case also uses the same sequence across all treatments in the same class.

Results of the Applicant's base case, and the NCPE-adjusted base case, are illustrated in Tables 1 and 2, respectively. Probability of cost-effectiveness of tildrakizumab 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 1 and 2.

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

Drug	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)	Probability of cost-effectiveness (%)	
				WTP €20,000 per QALY	WTP €45,000 per QALY
Tildrakizumab*	-	-	-	-	-
Biologic systemic therapies					
Brodalumab	9,366	0.43	21,634	50.8	95.0
Guselkumab	1,705	0.19	9,130	76.0	93.8
Ixekizumab	12,515	0.63	19,953	50.5	96.7
Risankizumab†	-28,003	-0.87	Less costly, less effective	Less costly, less effective¥	Less costly, less effective¥
Secukinumab	21,037	0.87	24,185	31.0	96.4
Ustekinumab	31,967	1.05	30,500	9.8	86.4

ICER: incremental cost-effectiveness ratio; **NMB:** net monetary benefit; **QALY:** quality-adjusted life-year; **WTP**: willingness to pay

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. A discount rate of 4% on costs and outcomes is applied.
*Intervention under assessment
†Tildrakizumab is less costly, but also less effective than risankizumab.
¥ The probabilistic sensitivity analysis indicates that tildrakizumab is less costly and less effective than risankizumab. The probability of cost-effectiveness is not presented because it is interpreted differently compared to drugs which are indicated to be costlier and more effective.

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

Drug	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)	Probability of cost-effectiveness (%)	
				WTP €20,000 per QALY	WTP €45,000 per QALY
Tildrakizumab*	-	-	-		
Biologic systemic therapies					
Brodalumab	2,585	0.03	80,451	17.9	69.0
Guselkumab	4,786	0.14	33,271	24.1	89.5
Ixekizumab	3,180	0.14	22,667	40.4	94.7
Risankizumab†	-12,216	-0.49	Less costly, less effective	Less costly, less effective¥	Less costly, less effective¥
Secukinumab	8,719	0.28	30,895	21.0	90.7
Ustekinumab	7,235	0.15	46,721	6.7	73.7

ICER: incremental cost-effectiveness ratio; **NMB**: net monetary benefit; **QALY:** quality-adjusted life-year; **WTP**: willingness to pay
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. A discount rate of 4% on costs and outcomes is applied.
*Intervention under assessment
†Tildrakizumab is less costly, but also less effective than risankizumab.
¥ The probabilistic sensitivity analysis indicates that tildrakizumab is less costly and less effective than risankizumab. The probability of cost-effectiveness is not presented because it is interpreted differently compared to drugs which are indicated to be costlier and more effective.

4. Budget impact of tildrakizumab

The price to wholesaler per pack of tildrakizumab is €2,905.77. Pack sizes containing one pre-filled syringe (PFS) (100mg dose) and two PFS (200mg dose) are priced the same. Assuming that patients continue treatment with tildrakizumab beyond week 28, the cost per patient for the first year of treatment is €22,784 (incorporating mark-up, 5.5% rebate, and pharmacy patient care fees) including VAT. The cost per annum from year two onwards is €16,596 including VAT.

The Applicant estimated that approximately 22 patients would be treated with tildrakizumab in year one, rising to 107 in year five. This was based on an assumption that approximately 40% of patients with moderate to severe plaque psoriasis, and who are receiving treatment in secondary care in Ireland, don't respond to first-line biologic treatment with adalimumab.

The Review Group identified several issues with the Applicant's budget impact model (BIM). Maintenance treatment costs for year one have been overestimated slightly by the Applicant for both the intervention and comparators. From year two onwards, the Applicant assumes that only incident patients commence treatment with biologic agents; consideration is not given to prevalent patients who may switch from one biologic treatment to another. The Applicant also assumes no discontinuation and no mortality; however, there may be a number of patients who discontinue treatment for a variety of reasons. Finally, the Review Group considers there to be uncertainty associated with the market share estimates. Overall, due to uncertainty with respect to eligible patient numbers, market share values, and concerns regarding budget impact model structure, the Review Group considers the budget impact estimates to be uncertain.

The Applicant estimated the gross budget impact for tildrakizumab to be €491,186 in year one increasing to €1,823,073 in year five with the five-year cumulative gross budget impact estimated to be €6,124,193. The introduction of tildrakizumab will likely result in displacement of some of other biologic therapies licensed for the treatment of moderate to severe plaque psoriasis. The Applicant estimated the five-year cumulative net budget impact to be -€82,852. 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

No patient organisation submission was received during the course of this assessment.

6. Conclusion

All recommendations here pertain to a subgroup of the licensed population. The NCPE recommends that, if reimbursed, implementation of measures to manage access to tildrakizumab should be considered.

The NCPE recommends that tildrakizumab (Ilumetri®), for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and who have failed treatment with non-biologic therapies and first-line biologic treatment with

adalimumab, 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.