NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Ruxolitinib for treating non-segmental vitiligo in people 12 years and over

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ruxolitinib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on ruxolitinib. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using ruxolitinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 21 February 2024
- Second evaluation committee meeting: 6 March 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Ruxolitinib is not recommended, within its marketing authorisation, for treating non-segmental vitiligo with facial involvement in people 12 years and over.

1.2 This recommendation is not intended to affect treatment with ruxolitinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

There are no licensed treatments for non-segmental vitiligo. Initial treatment may include topical corticosteroids and topical calcineurin inhibitors which are used on the skin. After trying these, some people have phototherapy.

Clinical trial evidence shows that ruxolitinib increases repigmentation and reduces how noticeable the vitiligo patches are compared with a type of cream called 'vehicle cream' (which is equivalent to not having any treatment because it does not contain an active ingredient). It is uncertain how well ruxolitinib works compared with phototherapy because the company provided no evidence to support this comparison.

The assumptions in the company's economic model do not reflect how vitiligo is treated in clinical practice. It was not possible to determine a reliable cost-effectiveness estimate. So, ruxolitinib is not recommended.

2 Information about ruxolitinib

Marketing authorisation indication

2.1 Ruxolitinib (Opzelura, Incyte) is indicated for 'the treatment of non-segmental vitiligo with facial involvement in adults and adolescents from 12 years of age'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for ruxolitinib.

Price

2.3 The list price of ruxolitinib is currently confidential. The company has a commercial arrangement, which would have applied if the ruxolitinib had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Incyte, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Vitiligo is a chronic autoimmune condition in which areas of the skin lose pigment. In non-segmental vitiligo (NSV), symmetrical patches can appear on both sides of the body. The committee noted submissions from stakeholders, clinical and patient experts. They described how vitiligo is often poorly understood and dismissed by healthcare professionals as being a solely cosmetic condition. They explained how vitiligo patches can affect self-esteem and lead to social rejection, identity loss, stress and humiliation, particularly if they are visible on the face and hands. They described how vitiligo can be more noticeable in brown and black skin tones and that these people may experience more discrimination because

of cultural factors. However, vitiligo can be distressing for people of all skin tones (see section 3.15). They highlighted that people with vitiligo often worry about how their appearance may change if they develop new patches. The patient expert described how vitiligo can affect social status. They said this has been intensified by social media and dating apps, where judgement is made on visual appearance. They explained that this may exacerbate the impact of vitiligo patches on self-image, particularly in young people. The clinical submissions described how living with vitiligo can be psychologically devastating and may result in avoiding the sun, or risking sunburn with minimal exposure. The committee recognised the substantial social and psychological impact that vitiligo has on people and their quality of life.

Current treatment of vitiligo

3.2 The submissions highlighted an unmet need for treatments for vitiligo, with no licensed treatments for the condition currently available in the NHS. They described how existing topical treatments including corticosteroids and calcineurin inhibitors may be prescribed in primary care. But they noted that these often have limited clinical effectiveness and long-term use can cause side effects. Some people may be referred for a specialist diagnosis in secondary care. The submissions highlighted that the waiting time for an NHS dermatology clinic appointment may be between 1 to 2 years and at this point there may be further waiting lists for phototherapy treatment. They further described how hospital-based phototherapy for vitiligo is time-consuming (usually 2 to 3 times per week for up to 12 months). So, it is often prioritised for other skin conditions which need shorter courses of treatment. The submissions described the personal and financial burden of completing a course of phototherapy around work, education and family life. For some people taking time off work for phototherapy may not be possible. The clinical experts estimated that around 50% of people seen in secondary care would be referred for phototherapy. They explained that the suitability of phototherapy would

likely depend on where the vitiligo patches are on a person's body and the body surface area affected. The clinical experts estimated that around half of people referred for phototherapy would be able to commit to a course of it. They explained that if phototherapy is not suitable, after first-line topical treatments have been tried there are no other active treatments. The committee understood that there is an unmet need for people with vitiligo and that ruxolitinib is the first licensed treatment for NSV with facial involvement in people 12 years and over. The committee concluded that people with the condition and clinicians would welcome ruxolitinib as a treatment option.

Positioning of ruxolitinib

3.3 First-line treatments for vitiligo usually include topical corticosteroids and topical calcineurin inhibitors. Second-line treatments may include phototherapy (narrow-band ultraviolet B therapy) with or without topical first-line treatments for vitiligo which is not rapidly progressive. For vitiligo which is rapidly progressive, oral betamethasone may be used with phototherapy. The committee understood that no active treatments are routinely used in the third-line setting. It discussed the company's positioning of ruxolitinib between existing first and second-line treatments. The target population included people 12 years and over with NSV with facial involvement that has not responded to topical first-line treatments or when these treatments are not suitable. The committee understood that the company's positioning of ruxolitinib was narrower than its marketing authorisation, which would allow use in the first-line setting. It noted that the company had in effect created an extra step in the treatment pathway, in which ruxolitinib would be used after topical corticosteroids or topical calcineurin inhibitors, but before phototherapy. The clinical experts confirmed that the company's positioning of ruxolitinib was appropriate and reflected its expected use in clinical practice. They explained that because ruxolitinib is a topical treatment, it would be preferred to phototherapy, which is more burdensome for people with vitiligo (see

section 3.2), is not targeted to only vitiligo patches and is difficult to access given current capacity constraints in the NHS. The committee discussed the setting in which ruxolitinib could be prescribed, noting that the summary of product characteristics (SmPC) states that ruxolitinib 'should be initiated and supervised by physicians with experience in the diagnosis and treatment of non-segmental vitiligo'. The clinical experts stated that given the company's positioning it may be appropriate and would be preferable if ruxolitinib was prescribed in primary care, after a specialist diagnosis. The committee understood that the company had offered a patient access scheme for ruxolitinib but such schemes are only applicable to secondary care. It noted that the NHS England budget impact analysis submission stated that the prescribing, supply and monitoring of ruxolitinib would be managed by secondary care. The committee concluded that the company's positioning of ruxolitinib was appropriate but noted concerns about the treatment setting and its implications for the current commercial arrangement.

Comparators

3.4 The final scope for the appraisal included established clinical management without ruxolitinib as the comparator. The company considered vehicle cream (no active treatment) to be the most suitable comparator. This was because it considered that at its proposed positioning of ruxolitinib, most people would not be having any active vitiligo treatment. The company also considered that oral betamethasone was not a relevant comparator because most people in the key clinical trials had a stable condition, rather than a rapidly progressive condition (see section 3.5). The EAG considered that the relevant comparators would be existing second-line treatments that ruxolitinib would displace if it was recommended. This would largely be phototherapy with or without topical first-line treatments. The committee noted that the clinical experts considered that ruxolitinib would be used before phototherapy and agreed not all people would be subsequently eligible for or have phototherapy.

But it considered that the cost-effectiveness estimates should take into account the clinical benefits of phototherapy. The committee agreed that the appraisal should consider any displacement of phototherapy if ruxolitinib was available in clinical practice. It further agreed that it was also relevant to consider a comparison with no active treatment because a proportion of people would not have active treatments after first-line topical treatments in clinical practice. The committee concluded that if ruxolitinib was to be prescribed in primary care, the relevant comparator would be no active treatment, followed by phototherapy (with or without topical treatments) for people who are eligible for it. It further concluded that if ruxolitinib was to be prescribed in secondary care, the relevant comparators would include phototherapy (with or without topical treatments) for people who are eligible for it and no active treatment for people who are not eligible for phototherapy.

Clinical effectiveness

Clinical effectiveness evidence

3.5 The key clinical evidence came from TRuE-V1 (n=330) and TRuE-V2 (n=344), which were phase 3, double-blind, randomised controlled trials. Both trials were multinational with no UK sites. The trials included a double-blind phase (24 weeks) in which people were randomised to either ruxolitinib or vehicle cream (no active treatment) twice a day. This was followed by an open-label extension (28 weeks) in which all people had ruxolitinib. The population was people 12 years and over with NSV affecting at least 0.5% body surface area on the face, and at least 3% body surface area on non-facial areas. The total body vitiligo area (facial and non-facial) could not exceed 10% body surface area. Assessment of the extent of the condition in the trials was measured using the Vitiligo Area Scoring Index (VASI). People in the trials had a facial VASI (F-VASI) score of at least 0.5 and a total body VASI (T-VASI) score of at least 3. The primary outcome from the TRuE-V trials was repigmentation, defined as the proportion of people with an improvement of at least 75% from

baseline in the F-VASI score (F-VASI 75) at week 24. The company presented pooled results from TRuE-V1 and TRuE-V2 because the trial designs were identical. In the intention-to-treat population, the proportion of people with F-VASI 75 at week 24 was statistically significantly higher in the ruxolitinib group compared with the vehicle cream group (odds ratio 4.17, 95% confidence interval 2.43 to 7.14, p<0.0001). The clinical experts considered that the vitiligo noticeability scale score is clinically relevant and may be a more accurate measure of the efficacy of treatment because it is a patient reported outcome. In the intention-to-treat population, the proportion of people with a vitiligo noticeability scale score of 4 or 5 (which indicates that a person's vitiligo is a lot less noticeable or no longer noticeable) was significantly higher in the ruxolitinib group compared with the vehicle cream group (odds ratio 6.52, 95% confidence interval 3.11 to 13.67, p<0.0001) at week 24. The committee concluded that ruxolitinib increases repigmentation and reduces the noticeability of vitiligo patches compared with vehicle cream. It recalled that it had considered phototherapy (with or without topical treatments) to be a relevant comparator if ruxolitinib was prescribed in secondary care (see section 3.4). The committee noted that it had not been presented with any clinical evidence for this comparison. It understood that the company had explored the feasibility of an indirect treatment comparison but considered that there was insufficient evidence to robustly compare the efficacy of ruxolitinib with phototherapy. The committee acknowledged that there may be limitations in doing this comparison. But it concluded that the company should provide comparative evidence for ruxolitinib with all relevant comparators, including phototherapy.

Prior therapy subgroups

3.6 The clinical effectiveness evidence presented in the company submission was based on the pooled full trial populations from TRuE-V1 and TRuE-V2. The EAG considered that the clinical evidence was not consistent with the target population (people who have had topical first-

line treatments or when these treatments are unsuitable) or the prior therapy subgroup used in the model (people who have had any previous treatment). The committee noted that the company had submitted evidence for the prior therapy subgroup in response to clarification. But the EAG considered that this was not submitted in a format that could be fully appraised. The committee understood there was a slightly higher response rate to ruxolitinib for people who had previous treatment compared with the full trial population. It noted the EAG's critique that without complete data for the prior therapy subgroup, it was not possible to determine whether this was evidence of a true difference in treatment effect between treatment lines. The committee considered that it was unclear how generalisable the full trial populations from the TRuE-V trials were to the target population who would be eligible for ruxolitinib. It concluded that the company should submit a full submission of evidence for the prior therapy and target population subgroups which can be appraised by the EAG. The committee considered that subgroup evidence should include a comparison of ruxolitinib to the relevant comparators (see sections 3.4 and 3.5).

Economic model

Markov model

3.7 The company presented a Markov state-transition model with 7 mutually exclusive health states: initial period, maintenance period, stable, retreated, stable retreated, non-response and death. The maintenance period health state was split into 2 states (F-VASI 75 to 89 or F-VASI 90 and more [a 75% to 89%, or 90% or more improvement in F-VASI score from baseline]) to assign differential utility values. In the model, all people enter the initial period health state and have either ruxolitinib or vehicle cream. People in the initial period health state who met F-VASI 75 were classified as having response and can move to other health states in the model. People who met F-VASI 90 or more could move to the stable health state where they have no treatment. The model included a cycle

length of 4 weeks with a half-cycle correction applied to costs and outcomes over a lifetime time horizon. The committee noted that the company had modelled a comparison of ruxolitinib to vehicle cream (modelled as sunscreen) to represent no active treatment. It considered that people would continue to use sunscreen regardless of treatment, so it was not appropriate to include the costs of vehicle cream to represent no active treatment in the model. The committee noted that the company's model only included a comparison of ruxolitinib with vehicle cream. It concluded that the company should revise the model to enable a comparison of ruxolitinib with phototherapy (see section 3.4).

Inappropriate company modelling assumptions and clinical data use

3.8 The committee agreed with the EAG that there were flaws in the company's model. It considered that model was not suitable for decision making and was disappointed that the company had submitted a model that did not reflect the condition or treatment pathway. The committee agreed that the following issues should be resolved by the company:

- The definition of who would continue treatment with ruxolitinib did not reflect expected clinical practice. The company's model assumed that people who reach F-VASI 50 to 75 (a 50% to 75% improvement in F-VASI score from baseline) at week 24 have not had response. The EAG considered that this did not align with current NHS clinical practice because VASI measures are not routinely used to assess response to treatment in clinical practice. The EAG's clinical expert suggested that they would assess response every 3 to 4 months and look for around 20% improvement in repigmentation to justify continuing treatment. The committee noted that the company's continuation rule did not align with the TRuE-V trials in which people could continue with ruxolitinib after week 24 in the open-label extension period (see section 3.5). It further noted that the SmPC for ruxolitinib states that satisfactory repigmentation may require treatment beyond 24 weeks and that stopping should be considered if there is less than 25% repigmentation

in treated areas at week 52. The committee considered that the company's continuation rule underestimated the proportion of people who would continue ruxolitinib after 24 weeks. The model should reflect anticipated continuation of ruxolitinib in clinical practice.

- People in the non-response health state could not have any improvement in their vitiligo. The committee considered that this structural assumption did not reflect clinical practice, in which another treatment option would usually be offered after a trial of topical treatment. The company model assumed that a proportion of people would have phototherapy with costs being accrued without any accompanying benefit, which the committee considered to be implausible. Costs in the non-response state were applied for 10 years, which the EAG stated were unsubstantiated, preferring for costs to be applied over the modelled time horizon. The committee stated that the model should allow people to transition from the non-response state if they have an improvement of their vitiligo on subsequent treatments. The company should present and apply in the model data for the clinical benefit of phototherapy for treating NSV and the costs in the non-response state should not be capped at 10 years.
- The maintenance period health state in the model included people who had an F-VASI 75 at week 24. These people continued taking ruxolitinib or vehicle cream. The EAG stated that it was structurally impossible for people reaching F-VASI 75 to 89 in the maintenance period health state to transition to the stable health state, in which they stopped treatment. The committee concluded that this structural error should be corrected.
- People who had an F-VASI 90 response and stopped treatment had the same topical treatment used previously (either ruxolitinib or vehicle cream) if their vitiligo subsequently relapsed (defined as response dropping below F-VASI 75). The committee agreed with the EAG that retreatment with vehicle cream did not reflect NHS clinical practice. The

committee concluded that the modelled treatment sequence should reflect clinical practice.

The committee considered that the company's inappropriate modelling assumptions and use of clinical data from the TRuE-V trials significantly biased the cost-effectiveness results in favour of ruxolitinib. It noted that the EAG had little confidence in the results of the model so could only present tentative base-case results. The committee concluded that the company's model did not reflect clinical practice and was not suitable for decision-making. It further concluded that it was necessary for the company to provide a revised model, which corrects the current structural flaws and uses clinical data and assumptions that reflect the treatment pathway for vitiligo.

Dosing assumptions

3.9 The SmPC for ruxolitinib recommends a thin layer of cream to be applied twice daily to the depigmented skin areas up to a maximum of 10% of body surface area. No more than 2 individual tubes (100 g each) of ruxolitinib should be used per month. The committee understood that the dose of ruxolitinib is likely to vary for each person depending on the size of the area of vitiligo and will depend on a person's adherence to the SmPC. The patient expert explained that healthcare professionals would need to provide detailed information to support people in managing how much cream they apply to their vitiligo patches. The company stated that the patient information leaflet would provide information on how much people should apply. The company's model assumed that the pooled median daily dose of treatment in the TRuE-V trials (across ruxolitinib and vehicle cream arms, week 1 to week 24) reflected the expected daily dose of ruxolitinib in NHS clinical practice. This was a lower amount than the 200 g per month limit in the SmPC. The EAG considered that it was more appropriate to use the mean dose of ruxolitinib alone, rather than the median dose across arms. It noted that the mean dose of ruxolitinib in the

pooled TRuE-V trials was larger than both the median and the dose limit of ruxolitinib as specified in the SmPC. The committee noted that this implied that some people in the TRuE-V trials used significantly more ruxolitinib than recommended. The company outlined how it had assessed individual patient-level body surface area and dosing data from the TRuE-V trials stratified by trial and treatment arm. It explained that the treatment duration for a small number of people in the trials had been miscalculated as lasting 1 day, because the treatment duration for these people had not been recorded in the trials. The company explained that excluding the results for these outliers reduced the mean dose of ruxolitinib to a value similar to the median. The committee noted that the EAG had presented 2 alternative base cases using either the mean dose of ruxolitinib from the TRuE-V trials (week 1 to week 52) or the maximum recommended dose in the SmPC. It understood that changing the ruxolitinib dosing assumptions had a large impact on the incremental cost-effectiveness ratio (ICER). The committee concluded that mean dose of ruxolitinib alone from the pooled TRuE-V trials should be used in the model, using appropriate methods to account for any missing data. It considered that the company should provide the individual patient-level body surface area and dosing data from the TRuE-V trials.

Costs and resource use

Phototherapy

3.10 The non-response health state included phototherapy costs as part of best supportive care, every 4-week cycle for 10 years from baseline. The company assumed that a large proportion of people in the non-response health state (the company considers the exact figure to be confidential so it cannot be reported here) have a course of hospital-based phototherapy for 9 months every year. The EAG considered that the company had overestimated the proportion of people who have phototherapy and the expected costs of such treatment in the non-response health state. It considered that the company's assumption of near continuous

phototherapy was not plausible given current NHS dermatology capacity constraints. The committee noted that the company's estimate of the proportion of people who would have phototherapy was much higher than the estimate provided by clinical experts, who considered that around 25% of people would proceed to have phototherapy (see section 3.2). The clinical expert explained that a course of hospital-based phototherapy for vitiligo would be for no longer than 12 months, because it would not be realistic to expect people to attend hospital appointments beyond this period. They explained that a person could potentially have another course of phototherapy in their lifetime, but it would not be possible to have continuous phototherapy each year. The committee considered that the company's assumptions around the use of phototherapy in the non-response health state likely biased the cost-effectiveness results in favour of ruxolitinib. It concluded that the company should revise its phototherapy treatment duration assumptions and the proportion of people who have phototherapy in line with clinical practice for people with vitiligo.

Psychological support and NHS dermatology attendance

3.11 In the model, the number of appointments for NHS psychological support varied depending on the health state. The EAG considered that the company had overestimated the proportion of people having psychological support in its base-case analysis. The EAG noted that in the TRuE-V trials at baseline, the mean scores on the Hospital Anxiety and Depression Scale (HADS) were within normal range. It considered that there was no difference in HADS score between those having ruxolitinib and vehicle cream at 24 weeks. The committee considered that this suggested that a lower proportion of people would be expected to have psychological support than modelled by the company and that this would not largely differ based on response to treatment. The EAG reduced the proportion of people having psychological support and applied this value to all health states in its base-case analyses. This was based on clinical advice to the EAG, which suggested that around 15% of people with

vitiligo are directed towards psychological support resources. The committee noted the company's model also assumed that people in the non-response health state would have NHS dermatology appointments around every 2 months for 10 years post baseline. The clinical experts explained that this did not reflect clinical practice given current NHS dermatology resource constraints. The committee considered that the company's dermatology attendance and psychological support assumptions overestimated resource use, which likely biased the cost-effectiveness results in favour of ruxolitinib. It noted that changing these assumptions had a large impact on the ICER. The committee concluded that it preferred the EAG's approach for modelling the proportion of people having psychological support. It further concluded that the company should revise its assumptions on NHS dermatology attendance in line with expected clinical practice for people with vitiligo.

Utility values

3.12 EQ-5D data was not collected in TRuE-V1 and TRuE-V2 trials. So, the company derived EQ-5D-3L values largely from F-VASI scores collected in the TRuE-V trials. This needed an assumption that F-VASI is proxy for repigmentation score, allowing the application of a mapping algorithm developed by Begum et al. (2023). Both F-VASI and repigmentation score are measures of change in pigmentation from baseline, so baseline utility estimates were derived by applying baseline vitiligo-specific quality-of-life instrument (VitiQoL) scores collected in the TRuE-V trials to the mapping algorithm. The utilities used to inform health states in the model were estimated using outputs from a regression analysis which included the covariates: baseline, no response, F-VASI 50 to 74, F-VASI 75 to 89 and F-VASI 90. Regression analyses were performed to estimate changes in utility from baseline to 24 weeks. The committee noted that the EAG had concerns with the company's approach and the validity of the utility values generated. This included that the utility values for the maintenance period, stable and stable retreated health states were higher than the age-

equivalent general population estimates. In its base-case analyses, the EAG capped the utility values for these health states to not exceed the general population utility estimates. The EAG noted that for F-VASI 50 to 74, the company's approach generated a utility value of 0.890, but in the model these people were classified as not having response and assigned a utility value of 0.797. The committee noted that the EAG preferred to set the non-response health state utility to a weighted average of no response (0.797) and F-VASI 50 to 74 (0.890) values, using the proportion of people in the ruxolitinib arm in each category measured at 24 weeks. The committee noted that the EAG's preferred utility assumptions had a moderate impact on the ICER. It concluded that the company's overall approach to derive health state utility values was reasonable so no capping of utilities to general population estimates was needed. The committee further concluded that the EAG's revision to estimate the utility for the non-response health state was appropriate.

Adverse events

3.13 The company's model included the costs of treatment-arm specific adverse events occurring in at least 4% of people having ruxolitinib or vehicle cream across the TRuE-V trials (week 1 to week 24). Treatment-related adverse events affected 47.7% of people having ruxolitinib in the pooled TRuE-V population. The committee noted that ruxolitinib was associated with a small increase in the rate of serious adverse events but that none of these events were considered to be related to treatment. The committee understood that the company's analysis did not include any disutility related to adverse events, because the company considered that most of the events in the TRuE-V trials were unlikely to significantly affect health-related quality of life (HRQoL). The EAG considered that the company's approach to modelling adverse events may introduce bias in favour of ruxolitinib. This was because it considered 4% to be an arbitrary and high cut-off for common adverse events and some people in the

TRuE-V trials used more ruxolitinib than indicated in the product licence (see section 3.9). It considered this may result in safety issues unanticipated with the intended use of ruxolitinib. The committee understood that the because the incremental quality-adjusted life year (QALY) gains for ruxolitinib are small, accounting for the HRQoL implications of adverse events appropriately could meaningfully affect cost-effectiveness results. The committee further noted that the SmPC stated that non-melanoma skin cancers had been reported in people having topical ruxolitinib. The SmPC states that most of these people had risk factors such as previous non-melanoma skin cancer or previous phototherapy. A causal relationship to topical ruxolitinib has not been established. The committee noted that the SmPC recommends periodic skin examination for all people, particularly those with risk factors for skin cancer. The committee recognised that adverse events with prolonged ruxolitinib use were unclear, and that it would not be possible to quantify this uncertainty in the cost-effectiveness estimates. It concluded that the company should incorporate utility and cost implications for adverse event data (occurring in 1% or more of people in any treatment group) into its analyses, as requested by the EAG at clarification. It further concluded that utility and cost implications for adverse events relating to phototherapy use should be included in the model.

Cost-effectiveness estimates

Uncertainty in cost-effectiveness estimates and further analyses needed

3.14 NICE's health technology evaluations manual notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Including the confidential patient access scheme for ruxolitinib, the company's probabilistic base-case ICER compared with vehicle cream was £14,676 per QALY gained. The EAG presented analyses which included minor corrections to the

company base case and its preferred modelling assumptions. These included:

- removing vehicle cream and phototherapy costs and assuming no dermatology visits in the non-response health state
- assuming 15% of people would have psychological support in each health state
- capping the utility values at general population values, and using a weighted average in the non-response health state of the values presented by the company for no response and having F-VASI 50 to 74
- applying costs in the non-response health state for a person's lifetime
- assuming missing data from the trials implied non-response when estimating the transition probability for people who have retreatment after relapse and do not regain response
- assuming either the dose of ruxolitinib was the mean value from the trials or people used the maximum amount of ruxolitinib per month as stated in the SmPC.

Including the confidential patient access scheme for ruxolitinib, the EAG's tentative probabilistic base-case results compared with vehicle cream were above £250,000 per QALY gained. The committee recalled that the patient access scheme for ruxolitinib would only be applicable to secondary care (see section 3.3). It understood that the cost-effectiveness estimates would be higher if ruxolitinib was prescribed in primary care. The committee noted that the EAG's base-case results were based on ruxolitinib being positioned as a third-line treatment, but that it had considered the company's proposed positioning of ruxolitinib between first- and second-line treatments to be appropriate (see section 3.3). Despite this difference, the committee agreed with the EAG's preferred assumptions on:

- removing vehicle cream costs

- the proportion of people having psychological support
- utility values in the non-response state
- using the mean dose of ruxolitinib in the model
- duration of costs in the non-response state
- accounting for missing data in calculating response rates on retreatment with ruxolitinib.

These all increased the ICER to be higher than £30,000 per QALY gained. The committee acknowledged that it was beyond the scope of the EAG's exploratory analyses to correct the inappropriate modelling assumptions (outlined in section 3.8). The committee discussed that correcting the model to reflect the condition and treatment pathway would likely increase the ICER further when ruxolitinib was compared with no active treatment and there was no plausible estimate under £30,000 per QALY gained. So, it could not recommend ruxolitinib for treating NSV with facial involvement in people 12 years and over. The committee considered that it would like to see:

- a revised model which includes corrections as outlined in sections 3.7 and 3.8 and incorporates utility and cost implications for adverse event data as outlined in section 3.13
- analyses including the committee's preferred assumptions as described in this section
- analyses which reflect expected phototherapy use (see section 3.10) and number of dermatology visits (see section 3.11) in NHS clinical practice for people whose vitiligo does not respond to treatment
- a full data package for the prior therapy and target population subgroups (see section 3.6)
- individual patient-level body surface area and dosing data from the TRuE-V trials (see section 3.9)
- clinical data on clinical effectiveness, adverse effects and the costs of phototherapy reflective of NHS use to inform a comparison between ruxolitinib and phototherapy (for people who would have phototherapy

in clinical practice, see sections 3.4 to 3.6, section 3.10 and section 3.13).

Other factors

Equality

3.15 The committee noted that several potential equality issues were raised at scoping and in the stakeholder and expert submissions. This included that vitiligo is more noticeable in brown and black skin tones, but that the psychological impact and risk of sunburn is apparent for all skin tones. The submissions described that there may be an additional cultural burden in people with brown and black skin tones, which may lead them to experience more discrimination (see section 3.1). The committee noted comments which highlighted that there is a risk of depression and anxiety with vitiligo and this may be greatest in Black and minority ethnic populations. It discussed comments that if ruxolitinib was recommended, it should be offered to all people with vitiligo irrespective of their ethnicity or any other protected characteristic. The company described how the TRuE-V trials included a small proportion of people with brown or black skin tones (defined as having a Fitzpatrick scale skin type of 4 to 6). It explained that there was no significant difference in repigmentation (assessed using F-VASI 75) between people with brown and black skin tones and those with white skin tones (defined as having a Fitzpatrick scale skin type of 1 to 2). The clinical and patient experts explained that the impact of vitiligo patches varies individually and does not necessarily depend on a person's skin colour or Fitzpatrick scale skin type. They described how a vitiligo patch on the face could be equally distressing for a person with a Fitzpatrick scale skin type of 1 or 6. The committee noted comments highlighting how vitiligo is more common in younger people, and that if ruxolitinib was recommended it should be available to people 12 years and over. The committee was mindful of its obligations in relation to the Equality Act 2010. It considered that it could only recommend ruxolitinib within its marketing authorisation. The committee understood

that some quality-of-life measures may discriminate against people with English as a second language but that it was unclear whether this was relevant to the measures used in the TRuE-V trials. It noted a stakeholder comment explaining that access to phototherapy may vary depending on where a person lives. The committee considered that this was a healthcare implementation issue that could not be addressed in a technology appraisal. It recalled comments from the stakeholder and expert submissions highlighting the personal and financial burden associated with a course of phototherapy, which may mean that it is not suitable for some people who are eligible for treatment (see section 3.2). The committee considered that if ruxolitinib was recommended it may provide another option that does not have the associated barriers to access that phototherapy has. It concluded that there were no equality issues relevant to the recommendations.

Innovation

3.16 The committee recalled that ruxolitinib is the first licensed treatment for NSV with facial involvement in people 12 years and over (see section 3.2). It recognised that because ruxolitinib is a topical treatment it may be less burdensome than phototherapy, which needs multiple hospital visits to complete a course (see section 3.2). The committee noted that the company considered that the utility estimates derived from condition-specific outcome measures mapped to EQ-5D (see section 3.12) may not fully capture the HRQoL impairment of living with vitiligo. It considered these factors when deciding if ruxolitinib was innovative. The committee did not identify additional benefits of ruxolitinib not captured in the economic modelling. So, it concluded that all additional benefits of ruxolitinib had already been considered.

Conclusion

Recommendation

3.17 The committee concluded that it had not been presented with a cost-effectiveness estimate that was suitable for decision making, so it could not recommend ruxolitinib.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John
Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Anita Sangha
Technical lead

Mary Hughes
Technical adviser

Kate Moore

Project manager

ISBN: [to be added at publication]