NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendations

1.1 Ruxolitinib cream 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 cream 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 healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, 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. There are unlicensed treatments used with the aim of restoring the skin's colour (repigmentation). These are corticosteroids and calcineurin inhibitors that are used on the skin. After trying these, some people have treatment with light (phototherapy). Ruxolitinib cream is a licensed treatment for non-segmental vitiligo that affects the face.

Clinical-trial evidence shows that ruxolitinib cream increases repigmentation and reduces how noticeable vitiligo patches are compared with placebo (a cream that does not contain any of the drug). An indirect comparison is too uncertain to show how well ruxolitinib cream works compared with phototherapy.

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The cost-effectiveness estimates are very uncertain because of limitations in the economic model, which does not reflect how vitiligo is treated in the NHS. It is also uncertain whether treatment with ruxolitinib cream would improve people's quality of life. The most likely cost-effectiveness estimate is higher than what NICE considers an acceptable use of NHS resources. So, ruxolitinib cream is not recommended.

2 Information about ruxolitinib

Marketing authorisation indication

2.1 Ruxolitinib cream (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 cream.

Price

2.3 The list price of ruxolitinib cream is £657.00 for a 100 g tube (Incyte website, accessed June 2024). The company has a commercial arrangement, which would have applied if ruxolitinib cream 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, symmetrical patches can appear on both sides of the body. The committee noted submissions from

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stakeholders, healthcare professionals and patients. The patient expert described how vitiligo is often poorly understood and dismissed by healthcare professionals as being a solely cosmetic condition. They explained that this dismissal diminishes the profound psychological distress and social anxiety caused by vitiligo, which often leads to reduced participation in external activities and family life. It can create an increased pressure to appear 'normal'. They explained how vitiligo patches can affect self-esteem and lead to social rejection, identity loss, stress and humiliation. The effect on self-esteem can be impacted by the location of vitiligo patches, with people with vitiligo explaining that they feel more self-conscious if the patches are easily visible or difficult to cover up with clothing. They also explained that people in public-facing jobs such as hospitality, retail, teaching and care will often experience a greater social impact from their vitiligo. They described how vitiligo can be more noticeable in brown and black skin tones, which may cause people to experience more discrimination because of cultural factors. But vitiligo can be distressing for people of all skin tones (see section 3.20). They explained 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 and this is intensified by social media and dating apps, because people may make judgements about visual appearance. 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 explained 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

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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 explained that waiting time for an NHS dermatology clinic appointment may be between 1 to 2 years, then there may be a further waiting list for phototherapy treatment. They 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 that 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 depend on where the vitiligo patches are on a person's body and the body surface area affected. The clinical experts estimated that about 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 there is an unmet need for people with vitiligo and that ruxolitinib cream is the first licensed treatment for non-segmental vitiligo with facial involvement in people 12 years and over. The committee concluded that people with the condition and clinicians would welcome ruxolitinib cream as a treatment option.

Positioning of ruxolitinib cream

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 that is not rapidly progressive. For vitiligo which is rapidly progressive, oral betamethasone may be used with

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phototherapy. The committee understood there are no routinely used active third-line treatments. It discussed the company's positioning of ruxolitinib cream between existing first and second-line treatments. The target population includes people 12 years and over with non-segmental vitiligo with facial involvement that has not responded to topical first-line treatments or when these treatments are not suitable. The committee understood the company's positioning of ruxolitinib cream is narrower than its marketing authorisation, which would allow first-line use. It noted the company had in effect created an extra step in the treatment pathway, in which ruxolitinib cream would be used after topical corticosteroids or topical calcineurin inhibitors, but before phototherapy. The clinical experts confirmed the company's positioning of ruxolitinib cream is appropriate and reflects its expected use in clinical practice. They explained that because ruxolitinib cream 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 cream could be prescribed, noting that the summary of product characteristics (SmPC) states that ruxolitinib cream '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 preferable if ruxolitinib cream is prescribed in primary care, after a specialist diagnosis. The committee understood that the company has offered a patient access scheme for ruxolitinib cream, but such schemes are only applicable to secondary care. At consultation, the company clarified that ruxolitinib cream is being positioned as a secondary-care treatment option. So, the committee anticipates that ruxolitinib cream will be prescribed, supplied and monitored in secondary care.

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Comparators

3.4 The final scope for this appraisal included established clinical management without ruxolitinib cream as the comparator. The company considered vehicle cream (a proxy for no active treatment) to be the most suitable comparator because, at its proposed positioning of ruxolitinib cream, most people would not be having any active vitiligo treatment. The company also considered that oral betamethasone is not a relevant comparator because most people in the key clinical trials had stable vitiligo, rather than rapidly progressive vitiligo (see section 3.5). The EAG advised the relevant comparators are existing second-line treatments that ruxolitinib cream would displace if it was recommended. This would usually be phototherapy with or without topical first-line treatments. The EAG noted that some people seeking treatment would be having no active treatment, so this could be considered an appropriate comparator. The clinical experts advised that ruxolitinib cream would be used before phototherapy and agreed not all people would subsequently be eligible for or have phototherapy. The committee agreed that the appraisal should consider the clinical effectiveness of phototherapy and if ruxolitinib cream would displace the treatment or move it further down the pathway if it was available in clinical practice. It concluded that, because ruxolitinib cream is proposed to be prescribed in secondary care and likely to be more effective than phototherapy (see section 3.6), ruxolitinib cream would effectively create a new position in the specialist treatment pathway before phototherapy. So, a comparison with no active treatment followed by some people having phototherapy would be most reflective of what ruxolitinib cream would displace in clinical practice.

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. They included a double-

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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 everyone had ruxolitinib cream. The population was people 12 years and over with non-segmental vitiligo affecting at least 0.5% of body surface area on the face, and at least 3% of body surface area on non-facial areas. The total body vitiligo area (facial and non-facial) could not exceed 10% of 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. Most people (74%) had 'stable vitiligo' at baseline and generally represented people that had vitiligo for a long time (mean 14.8 years since diagnosis). 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. People in the TruE-V open-label extension were assigned to one of 2 cohorts (A or B) based on their F-VASI responses at the time of enrolment. Cohort A had complete or almost complete facial repigmentation by year 1 of TruE-V (F-VASI 90 or more), but cohort B did not have F-VASI 90 by year 1. 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 committee noted that the company had positioned ruxolitinib cream for use for non-segmental vitiligo with facial involvement, but the primary repigmentation outcome focused on improvements in vitiligo on the face only. It considered that improvements in F-VASI did not necessarily correspond directly to the quality of life of people with vitiligo, because changes in F-VASI did not always correlate with changes to T-VASI. The clinical experts considered that the Vitiligo Noticeability Scale score is clinically relevant and may be a more accurate

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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 cream increases repigmentation and reduces the noticeability of vitiligo patches compared with vehicle cream. It considered phototherapy (with or without topical treatments) to be a relevant comparator (see section 3.4) and noted it had not been presented with any clinical evidence for this comparison. It understood 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 cream with phototherapy. The committee acknowledged there may be limitations in doing this comparison. But it concluded that the company should provide comparative evidence for ruxolitinib cream with all relevant comparators, including phototherapy. This was provided at consultation by the company (see section 3.6).

Indirect treatment comparison

3.6 After consultation, the company provided an indirect treatment comparison with phototherapy, with or without topical corticosteroids. Both a naive and matching-adjusted indirect comparison were provided. Data from HI-Light trial (a randomised, pragmatic, 3-arm placebo-controlled trial) informed the clinical effectiveness of phototherapy. The population was people aged 5 years and over, with non-segmental vitiligo affecting less than 10% of body surface area. Assessment of the extent of the condition was measured using repigmentation scores according to the Vitiligo Noticeability Scale. Data from the pooled TruE-V trials informed the clinical effectiveness of ruxolitinib cream. Results of the indirect treatment comparison showed that people who had ruxolitinib cream were

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statistically significantly more likely to experience an overall response (25% to 100% repigmentation) compared with people having phototherapy, after 9 months of treatment. The EAG concluded that neither approach taken by the company would provide reliable effect estimates of the comparison with ruxolitinib cream and phototherapy, and it had no confidence in the results of the comparison. It had concerns about variation in baseline characteristics between HI-Light and the TruE-V trials, and between the arms of the HI-Light trial. It also noted discrepancies between baseline characteristics reported for each trial that could be used in matching and meaningful differences in the outcomes measured in each trial. The EAG acknowledged that the company had made significant effort to produce the analyses, and that the limitations in the comparability of evidence for ruxolitinib cream and phototherapy was beyond the control of the company at this stage of the appraisal. The committee considered that the analysis justified the clinical opinion that ruxolitinib cream would be used before phototherapy because of the increased clinical efficacy, but did not provide a robust enough comparison to inform cost utility analyses. This confirmed that the comparison of no active treatment followed by phototherapy is most representative of the positioning of ruxolitinib cream.

Prior-therapy subgroups

3.7 The clinical-effectiveness evidence in the company's submission was based on the pooled full trial populations from TRuE-V1 and TRuE-V2. The EAG advised 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 submitted evidence for the prior-therapy subgroup in response to clarification. But the EAG advised that this was not submitted in a format that could be fully appraised. The committee understood there was a slightly higher response rate to

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ruxolitinib cream 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 decided 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 cream. It concluded that the company should submit a full submission of evidence for the prior-therapy and target population subgroups that can be appraised by the EAG. At consultation, the company provided all available evidence from the pooled TRuE-V trials relating to the efficacy of ruxolitinib cream in the overall population and prior-therapy populations. The prior-therapy population from the pooled TRuE-V trials had a slightly higher response rate with ruxolitinib cream compared with the overall trial population (odds ratio 4.6 [$p<0.0001$] compared with 4.17 [$p<0.0001$]). The EAG explained that although the results indicated ruxolitinib cream is highly effective in reducing vitiligo, it was unable to determine if the effects were comparable between the overall population and subgroup populations because no statistical comparison was provided by the company. The committee concluded it was unable to consider the prior-therapy subgroup separately and so did not review clinical and cost-effectiveness evidence for this subgroup.

Economic model

Markov model structure

3.8 The company initially presented a Markov state-transition model comparing ruxolitinib cream with vehicle cream. This used 7 mutually exclusive health states based on response status and including the opportunity for retreatment. At the first committee meeting the committee concluded that the company's model did not reflect clinical practice, significantly biased the cost-effectiveness results in favour of ruxolitinib cream and was not suitable for decision making. The committee decided

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the company should provide a revised model to correct the structural flaws, including:

- The definition of who would continue treatment with ruxolitinib cream 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 committee considered that the company's continuation rule underestimated the proportion of people who would continue ruxolitinib cream after 24 weeks. The model should reflect anticipated continuation of ruxolitinib cream 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.
- The maintenance period health state in the model included people who had an F-VASI 75 at week 24. These people continued using 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.
- 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.

3.9 After consultation the company made substantial changes to the structure, input parameters and assumptions underlying its original model as follows:

- People with an initial response of F-VASI 90 by year 1 transition straight into the stable health state.

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- People with an initial response of less than F-VASI 25 by year 1 transition directly to the non-response health state.
- People with an initial response between F-VASI 25 and F-VASI 89 transition to the maintenance/retreatment health state for an upper limit of 1 year. Response is reassessed at year 2 and is linked to the response achieved at year 1. If F-VASI 90 is reached by year 2, people transition to the stable health state. If not, they transition to the non-response health state.
- Everyone is eligible to transition to the stable health state, correcting the structural error relating to people reaching F-VASI 75 to 89 in the maintenance period health state.

3.10 The company applied the updated model structure to 4 comparisons, with no active treatment (either followed by phototherapy or not) and phototherapy (either as monotherapy or in combination with topical corticosteroid). The committee decided the most appropriate comparison was no active treatment followed by phototherapy, but noted that the efficacy of phototherapy was not included in this analysis. The EAG considered the company's revised model to be an improvement on its previous model and more closely matched how it would expect ruxolitinib cream to be used in clinical practice. The model also had more realistic expectations of assessing and monitoring response from the available clinical data. But the EAG still had concerns about the revised model, including:

- uncertainty and reliability of assumptions about retreatment after loss of response (see section 3.13)
- validity relating to the proportion of people reaching F-VASI 90 (see section 3.14)
- discrepancy between baseline and 'no response' health state utility values and other concerns with these values (see section 3.17).

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The committee concluded that the updated model more closely matched the expected use of ruxolitinib cream in clinical practice. But some issues had not been resolved, particularly how the model is based around a response from a baseline for facial vitiligo only. This may not reflect distinct health states representing the course of the disease and how it affects people's quality of life and resource uses. The committee concluded that there remained some structural uncertainty, but it did not consider it would likely be resolved with any further changes to the model. So, it agreed the model structure was adequate for decision making. But it paid close attention to the structural limitations of the model and any potential biases these created.

Dosing assumptions

3.11 The SmPC for ruxolitinib cream recommends applying a thin layer of cream 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 cream should be used per month. The committee understood that the dose of ruxolitinib cream 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 the ruxolitinib and vehicle cream arms, week 1 to week 24) reflected the expected daily dose of ruxolitinib cream in NHS clinical practice. This was a lower amount than the 200 g per month limit in the SmPC. The EAG advised it is more appropriate to use the mean dose of topical ruxolitinib alone, rather than the median dose across trial arms. It noted that the mean dose of ruxolitinib cream in the pooled TRuE-V trials was larger than both the median and the dose limit of ruxolitinib cream

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specified in the SmPC. The committee noted this implied that some people in the TRuE-V trials used significantly more ruxolitinib cream 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 cream 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 cream from the TRuE-V trials (week 1 to week 52) or the maximum recommended dose in the SmPC. It understood that changing the ruxolitinib cream dosing assumptions had a large impact on the incremental cost-effectiveness ratio (ICER). The committee concluded that the mean dose of topical ruxolitinib alone from the pooled TRuE-V trials should be used in the model, using appropriate methods to account for any missing data.

3.12 At consultation, the company updated its base-case dosing assumption with an estimated mean daily dose of ruxolitinib cream. This was calculated by applying a lognormal distribution to the entire TruE-V trial dosing data. It also provided an alternative scenario in which the mean daily dose was estimated by excluding the outliers that had missing treatment-duration data. The EAG noted that it had not received any numerical or graphical validation for the lognormal distribution, or any assessment of statistical goodness-of-fit. So, it could not validate the appropriateness of the company's analysis. It advised that the only evidence-based approach was to use the revised estimate that excluded the outliers. The company noted that real-world evidence from Europe and the US suggested that the mean use of ruxolitinib cream in clinical practice is expected to range between values lower than those seen in TruE-V. It suggested that the difference seen between TruE-V and real-

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world evidence could be related to the body surface area restriction within TruE-V's exclusion criteria. So, the trial population had a higher mean body surface area (7.4%) compared with those in real-world studies (1.4% to 3.8%). The EAG explained that determining the true cost of ruxolitinib cream to the NHS would be difficult because several factors influence this, including dispensing practices, overall intended use and retreatment**.** The committee noted the uncertainty inherent in the trial design because the primary outcome of facial VASI score only may not be explicitly linked to dose used, which would be linked to the entire body surface area affected. The patient expert noted that dose would likely be significantly reduced with higher responses to maintain response on smaller patches. The committee concluded it was most appropriate to use the dosing estimate from TruE-V that excluded the outliers rather than the estimate calculated using the lognormal distribution.

Modelling retreatment

3.13 The economic model structure contains an optional retreatment component for people who have had a stable (F-VASI above 90 from baseline) response to treatment, containing the retreated and stable retreated health states. People can enter these states after relapse from the stable state, defined as a loss of response equivalent to less than F-VASI 75 from trial baseline. The EAG noted that the response required to enter the retreated state differs markedly from the initial treatment period, where people with a response between F-VASI 25 and F-VASI 89 transition to the maintenance/retreatment state. It explained that people who enter the retreated state would instantly leave according to their F-VASI response; people with a response less than F-VASI 90 would transition to the non-response state, and those with a response of F-VASI 90 would enter the stable retreated state. In reality, people in the retreated state would have treatment for a given period of time, followed by an assessment of their vitiligo's response to treatment. The EAG explained that once people experience a reduction in F-VASI response to

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below F-VASI 75 from baseline, they transition to the non-response health state. People entering this state remain there for the lifetime of the model and are unable to return to any previous states within the model. This issue was also present in the company's initial model. As a result of this, people were only permitted to have one course of retreatment with ruxolitinib cream. The EAG considered this did not reflect expected use in clinical practice because people may have multiple rounds of ruxolitinib cream if their vitiligo responds to it. The patient expert explained that people would not necessarily continue to apply ruxolitinib cream continuously once repigmentation had occurred, and the frequency of application would be expected to reduce after an initial period of treatment. The clinical experts agreed it would be unusual for people to continuously apply creams for multiple years, and they would likely have maintenance treatment rather than stopping treatment completely. The committee was disappointed that the company did not revise the model to address these issues with retreatment and the permanency of the non-response state (see section 3.8). It agreed with the clinical and patient experts that people with a high response to treatment would likely have maintenance treatment (or a reduced dose) rather than the highly controlled stopping and reinitiation rules in the economic model. So, the committee concluded that the model likely underestimated both the costs and benefits of treatment in this section of the model structure. The EAG noted concerns with the benefits accrued in the ruxolitinib retreatment phase in proportion to the costs when compared with the same ratio in the initiation phase. The committee agreed with concerns about the costs and benefits associated with retreatment, because the costs were approximately equivalent to 1 month of treatment (at the initiation phase), but benefits were modelled to potentially last for multiple years. It concluded that the model did not accurately capture the likely reality of retreatment in clinical practice or ultimate disease course. It considered this structure likely biased in favour of ruxolitinib cream because of the

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minimal costs, but this was unclear because the clinical evidence of an appropriate maintenance dose is not available.

Validation of F-VASI 90

3.14 When assessing the revised model, the EAG noted that the average additional time people spent with a response of F-VASI 90 had approximately doubled in comparison to the initial version. It provided Markov model traces from both versions of the model. It attempted to validate the proportions of people with a response of F-VASI 90 at year 1 and 2 by comparing them to time spent at F-VASI 90 seen in the TruE-V trials (30.3% [106/350] at year 1 and 18.7% [61.8% of 30.3%] at year 2). Analysis done by the EAG indicated that proportion of people achieving F-VASI 90 at year 2 was not consistent between models and was higher than seen in the TruE-V trials. The EAG also noted that in the revised model, the proportion of people achieving F-VASI 90 increased between years 1 and 2. This implied that more people who did not achieved F-VASI 90 by year 1, did so by year 2; while a smaller proportion of people who achieved F-VASI 90 at year 1 had lost their response by year 2. The company disagreed with the premise of the EAG's validation exercise because the proportion of people reaching F-VASI 90 at year 2 only included those that initially had an F-VASI 90 response at year 1 from the TruE-V trials (cohort A). Also, it did not include people with a potentially slower response to treatment that resulted in an F-VASI 90 response by year 2 (cohort B). The committee considered the proportion of people having a F-VASI 90 response or higher was a key driver in the economic model and should be informed and validated against results from the trial using an intention-to-treat style analysis of everyone randomised at the start of treatment, because this level of response could take more than 1 year to realise. It recognised that this analysis was complicated in using the available evidence because of the trials' 6-month open-label extension and crossover, re-randomisation at 1 year of each of the cohorts and analysis of attrition. The company considered the total

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number who reached a F-VASI 90 response was greater than what the model predicted, which validated the model outcomes. The EAG commented that it was unable to validate the proportion of people who would have this response quoted by the company and it was unclear how this was derived. The committee agreed with the company that more people may have an F-VASI 90 response with further treatment after 1 year, and the revised model structure allows for this. So, it did not question the validity of the output on this basis. But it agreed that for the purposes of validation of the trial outcomes in the appropriate population, it was unclear what proportion of people in the TruE-V trials had a F-VASI 90 response to ruxolitinib cream at each time point. This is because the design of the studies did not allow for this to easily be established and there was a lack of clear reporting from the company on how the estimates from the trials were derived. The committee considered that the company's estimate of the proportion of people achieving F-VASI 90 at year 2 was plausible, but it was uncertain how this estimate was derived. It concluded that the uncertainty behind this key driver of the model interacts with the issue of retreatment (see section 3.13), because it describes the proportion of people who would potentially benefit from retreatment/maintenance of treatment.

Costs and resource use

Phototherapy

3.15 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 advised that the company overestimated the proportion of people who have phototherapy and the expected costs of such treatment in the non-response health state. It considered the company's assumption of near continuous phototherapy

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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 about 25% of people would 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 decided that the company's assumptions about the use of phototherapy in the non-response health state likely biased the cost-effectiveness results in favour of ruxolitinib cream. 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. At consultation, the company updated its cost-effectiveness analyses to align with the committee's preferences on phototherapy in the non-response state. When comparing ruxolitinib cream with phototherapy (with or without topical corticosteroids) or no active treatment only, people in the non-response health state do not have phototherapy. When comparing ruxolitinib cream with no active treatment followed by phototherapy, 25% of people are assumed to have phototherapy in the non-response health state in line with the clinical opinion received at the first committee meeting. The committee concluded that the company's updated assumptions on phototherapy were reflective of clinical practice for people with vitiligo.

Psychological support and NHS dermatology attendance

3.16 In the model, the number of appointments for NHS psychological support varied depending on the health state. The EAG advised that the company overestimated the proportion of people having psychological support in its base-case analysis. The EAG noted that in the TRuE-V trials at baseline,

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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 about 15% of people with vitiligo are referred to 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 about every 2 months for 10 years after baseline. The clinical experts explained that this did not reflect clinical practice given current NHS dermatology resource constraints. The committee decided that the company's dermatology attendance and psychological support assumptions overestimated resource use, which likely biased the cost-effectiveness results in favour of ruxolitinib cream. It noted that changing these assumptions had a large impact on the ICER. The committee preferred the EAG's approach for modelling the proportion of people having psychological support. It concluded that the company should revise its assumptions on NHS dermatology attendance in line with expected clinical practice for people with vitiligo. At consultation, the company updated its disease management assumptions in line with the committee's preferences. Monitoring in secondary care by a dermatologist for people with vitiligo that did not respond to treatment was reduced to 15%, and all health states included 15% of people accessing psychological support services. The committee concluded that these disease management assumptions were more aligned with expected clinical practice for people with vitiligo.

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Utility values

3.17 EQ-5D data was not collected in TRuE-V1 and TRuE-V2. So, the company derived EQ-5D-3L values largely from F-VASI scores collected in both 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 response 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 that included the proposed response states as covariates. Regression analyses were done to estimate changes in utility from baseline to 24 weeks. The committee noted the EAG's concerns about the company's approach and the validity of the utility values generated, including:

- The number and strength of assumptions needed to do this mapping and regression analysis meant the EAG questioned the reliability of the results.
- The clinical evidence submission did not show a treatment effect on patients' health-related quality of life, including domains expected to be affected by ruxolitinib cream such as anxiety and depression.
- The value for F-VASI 25 to 49 was higher than F-VASI 50 to 74. The company stated this may be because of the inability to discriminate the difference in quality of life between these 2 response categories. As a result, the EAG set the utility value for F-VASI 25 to 49 to equal that of F-VASI 50 to 74.
- The utility values associated with F-VASI 75 and over 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.

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- The reason for the large difference between the utility values for non-response and baseline states was unclear. The EAG provided scenario analyses exploring the impact of setting 'no response' equal to baseline, or using an average of the 2 current values.

The committee discussed its concerns about the model structure and whether it accurately reflected clinical practice. The EAG and the committee were concerned about the discrepancy between the utility values for non-response and baseline, with baseline values being considerably higher than people in the 'no response' state. The committee considered that this health state was highly heterogeneous, incorporating people who had experienced minimal increases in F-VASI response, stable disease and increased depigmentation (progression). It noted that most people in the trial had stable vitiligo and a mean of 14 years since diagnosis at baseline (see section 3.5), which may have indicated the baseline level was also reflective of no response. The company stated that people in TRuE-V could have adapted to the chronic condition, but some of the decreased utility for non-responders may be associated with the expectation of treatment benefit. It stated that people who had been affected by vitiligo for longer, or had spent a long time on treatment, would experience poorer quality of life if treatment did not work. The EAG advised this discrepancy could be greater than what would be expected and provided scenario analyses using the baseline value for no response and a scenario half-way between the current no response and the baseline value. The committee questioned the validity of the non-response utility value, because the utility decrement seen when there was no response to treatment was much larger than the utility increment seen when reaching a high F-VASI response. So, it noted that quality-of-life benefits were driven more by avoiding the 'no response' state than by realising quality-of-life benefits associated with response. The EAG also preferred to cap utility values to the general population utility estimates from the age and sex adjusted trial population, in line with NICE's methods manual, which effectively reduced the range of potential benefit.

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The committee decided the key drivers for establishing utility value inputs in the model should rely on evidence of a relative benefit of treatment, and it did not consider the model structure accurately captured this transition. It also considered the potential that people with newly diagnosed vitiligo may have different quality-of-life considerations than the population in the TRuE-V trials. For capping at the general population utility levels, it recognised that this affected the absolute values but because of the uncertainty, it may also be important to consider how it affects relative utility benefit. So, it considered a range of scenarios. It preferred the EAG's scenario analysis changing the value of the 'no response' state and exploring with and without capping of utility values to general population levels. It concluded that the evidence of benefit of responding to treatment was highly uncertain. So, it could not make a decision on its preferred assumptions. But it noted that scenarios that reduced the range of utility values substantially increased the cost-effectiveness estimates.

Adverse events

3.18 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 cream in the pooled TRuE-V population. The committee noted that ruxolitinib cream 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. The EAG considered that the company's approach to modelling adverse events may introduce bias in favour of ruxolitinib cream. 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 cream than indicated in the

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product licence (see section 3.11). It considered this may result in safety issues unanticipated with the intended use of ruxolitinib cream. The committee understood that because the incremental quality-adjusted life year (QALY) gains for ruxolitinib cream are small, accounting for the health-related quality of life implications of adverse events appropriately could affect the cost-effectiveness results. The committee noted the SmPC states that non-melanoma skin cancers have 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 everyone, particularly those with risk factors for skin cancer. The committee recognised that adverse events with prolonged topical ruxolitinib use were unclear, and 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. The committee considered this important because the positioning of ruxolitinib cream in the pathway meant that it was being compared to no intervention. Any adverse events experienced by people are therefore likely to have a perceivable impact on quality of life, and so are relevant to informing cost effectiveness. This was not provided by the company at consultation. So, the committee concluded that the impact of incorporating utility and cost implications for adverse event data was uncertain, but the cost-effectiveness analysis may be more sensitive to any disutility associated with adverse events.

Cost-effectiveness estimates

Uncertainty in cost-effectiveness estimates

3.19 NICE's health technology evaluations manual notes that judgements about the acceptability of a technology as an effective use of NHS

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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. The committee considered the most appropriate comparison was with no active treatment followed by phototherapy. Including the confidential patient access scheme for ruxolitinib cream, the company's deterministic base-case ICER for this comparison was £18,103 per QALY gained. The EAG presented analyses that included minor corrections to the company's base case and its preferred modelling assumptions. These included:

- capping the utility values at general population values, and setting the F-VASI 25 to 49 value equal to the F-VASI 50 to 74 value
- assuming the dose of ruxolitinib cream was the mean value from the trials, excluding the outliers whose duration of treatment was imputed as 1 day.

Including the confidential patient access scheme for ruxolitinib cream, the EAG's probabilistic base-case results for this comparison was £25,856 per QALY gained. The committee decided that neither of these estimates captured the underlying structural uncertainty inherent in the model and key inputs. The committee noted that the ICER was sensitive to applying a different modelling approach to the 'no-response' utility state and capping the utility values to that of the general population as proposed by the EAG. Applying these approaches in the model and considering a number of plausible scenarios resulted in ICERs that ranged from £33,065 per QALY gained to £167,585 per QALY gained. The committee decided this likely captured the range of uncertainty in the quality-of-life estimates. But it still had concerns about how retreatment was operationalised and whether it reflects how ruxolitinib cream would be used in clinical practice, which it concluded could not be captured in the ICER calculation.

Other factors

Equality

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3.20 The committee noted potential equality issues raised at scoping and in the stakeholder and expert submissions. These 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 the risk of depression and anxiety with vitiligo, which may be greatest in Black and minority ethnic populations. It discussed comments that if ruxolitinib cream were 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 cream were recommended it should be available to people 12 years and over. The committee understood its obligations in relation to the Equality Act 2010 and that it could only recommend ruxolitinib cream within its marketing authorisation. It noted the stigma associated with vitiligo. It understood that some quality-of-life measures may discriminate against people with English as a second language, but 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

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that could not be addressed in a technology appraisal. It noted comments from the stakeholder and expert submissions highlighting the personal and financial burden associated with a course of phototherapy, which may mean it is not suitable for some people who are eligible for treatment (see section 3.2). The committee considered that if ruxolitinib cream 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

3.21 The committee noted that ruxolitinib cream is the first licensed treatment for non-segmental vitiligo with facial involvement in people 12 years and over (see section 3.2). It recognised that because ruxolitinib cream is a topical treatment it may have an advantage over phototherapy that requires sequential hospital visits to complete a course (see section 3.2). The committee noted the company's statement that the utility estimates derived from condition-specific outcome measures mapped to EQ-5D (see section 3.17) may not fully capture the health-related quality of life impairment of living with vitiligo. It considered these factors when deciding if ruxolitinib cream was innovative. Otherwise, the committee did not identify additional benefits of ruxolitinib cream not captured in the economic modelling. So, it concluded that all additional benefits of ruxolitinib cream had already been considered.

Conclusion

Recommendation

3.22 The committee concluded that the cost-effectiveness modelling using its preferred assumptions resulted in cost-effectiveness estimates that were higher than what NICE considers an acceptable use of NHS resources. This was despite considering the impact of potential uncaptured benefits in the model. The committee therefore concluded that ruxolitinib cream

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would not be an acceptable use of NHS resources. 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.

Emily Leckenby and Anita Sangha
Technical leads

Adam Brooke and Mary Hughes
Technical advisers

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Kate Moore

Project manager

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