NICE National Institute for Health and Care Excellence

NICE guidance

Birch bark extract for treating epidermolysis bullosa

Highly specialised technologies guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Birch bark extract is recommended, within its marketing authorisation, as an option for treating partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa in people aged 6 months and over. It is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Dystrophic and junctional epidermolysis bullosa have a substantial impact on quality of life, and there are no licensed treatments. Usual treatment includes wound management, pain management and repeated surgery.

In a clinical trial, birch bark extract led to quicker wound healing than a control gel. The results also suggest that it may lead to a reduced amount of affected skin.

The results of the trial were used to estimate the numbers of people with different disease severities in the economic model. But some people did not finish the trial, and a higher proportion of people with severe epidermolysis bullosa dropped out than those with less severe epidermolysis bullosa. This means there was uncertainty around cost-effectiveness estimates.

Taking into account the evidence and the uncertainties, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, birch bark extract is recommended.

2 Information about birch bark extract

Marketing authorisation indication

2.1 Birch bark extract (Filsuvez, Amryt Pharmaceuticals) is indicated for the 'treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months or older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for birch bark extract.

Price

2.3 The list price for birch bark extract is £275.33 per 23.4-g tube.

2.4 The company has a commercial arrangement. This makes birch bark extract available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Amryt Pharmaceuticals, 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

Epidermolysis bullosa

3.1 Epidermolysis bullosa (EB) is a condition caused by gene mutations that mean certain skin anchoring proteins are not expressed correctly or are disrupted. This results in very fragile skin that blisters and breaks frequently, particularly in response to minor trauma or friction. Many of the wounds that happen in EB are partial thickness wounds, meaning they extend through multiple different layers of the skin surface. There are various types of EB, but birch bark extract is only indicated for dystrophic and junctional EB. Junctional EB affects a part of the skin called the lamina lucida between the epidermis and the dermis. Dystrophic EB can be more severe than junctional EB and affects a part of the skin called the sublamina densa, below the lamina lucida. There are 2 types of dystrophic EB, defined by whether 1 or 2 copies of the relevant gene are affected. In dominant dystrophic EB, only 1 copy is affected, and in recessive dystrophic EB, which is often more serious, both copies are affected. Severe forms of EB such as dystrophic or junctional are likely to present from birth and so are often diagnosed in babies or children. The body surface area percentage (BSAP) score is 1 way of measuring EB disease severity. But this only describes the amount of the skin surface covered in wounds; it does not capture the impact or location of wounds, and does not describe other aspects of the condition, such as damage to the gastrointestinal tract. The clinical experts explained that, in addition to the direct symptoms of EB, there was an increased risk of infections and squamous cell carcinoma, and of nutritional issues linked to effects on the mucosal surfaces of the gastrointestinal tract.

Effects on quality of life

3.2 EB can have substantial effects on quality of life, and this is particularly true for the more severe types such as dystrophic and junctional. It can cause constant itching of the skin, blistering and pain. Substantial segments of skin may fall off, and skin wounds stay open for prolonged periods of time, increasing the risk of infection. The patient expert explained that the pain from skin wounds was constant, severe and made all aspects of life very difficult. The patient expert's advocate also explained that itch was a constant problem and could be as bad as, or even worse in some ways, than the pain. This was because it was not possible to get any relief from the itching. Itching often causes people to scratch the skin in their sleep, leading to more skin wounds and restarting the cycle. The patient organisation submission noted the substantial treatment requirements to manage the symptoms of EB, including daily cleaning of wounds and dressing changes, which take between 2 and 5 hours a day. The patient expert explained that on some days there could be over 6 hours of dressing changes, often totalling 37 hours a week. Also, the dressing changes themselves cause substantial pain. The patient organisation submission stated that the treatment requirements and pain affect mental health and can include feelings of isolation from personal, professional and educational life. The patient expert confirmed that their professional career had been heavily curtailed and their social life was severely limited by EB. The patient expert's advocate noted how any kind of travelling or social activities done by the patient had a cost in terms of skin damage and pain, and their life had essentially been restricted to their home. EB also affects mucosal surfaces and can lead to damage to the eye, mouth and oesophagus, which can make eating challenging. Repeated skin breakdown and healing can cause extensive scarring and this may cause fusion of fingers or obstruction of the oesophagus by scar tissue. These symptoms may need repeated surgery. Many people with EB have 1 or more informal carers whose quality of life can be affected because they spend substantial amounts of their time caring for family or loved ones with EB. The patient organisation expert noted that families had reported difficulties accessing the specialist care needed and noted that the need to visit specialist centres interfered with carers' professional lives and brought a risk to job security. The patient organisation expert also noted the substantial indirect effect on siblings of those with EB because of the extensive care need that parents have to attend to. The committee concluded that EB has extensive and severe effects on quality of life.

Clinical management

Existing treatment

3.3 The clinical experts explained that there were no licensed disease-modifying treatments for EB, and current treatment options aim only to manage symptoms. Symptom management has 3 broad categories. First, wound management including bathing to wash wounds, lancing and draining blisters and using non-adhesive dressings and bandages to manage open wounds. Topically applied steroid creams and antimicrobial creams (in the event of infections) are also used off label. Second, surgical procedures are used to manage complications of EB such as fusion of fingers and oesophageal structures. Third, pain management, which includes pharmacological and non-pharmacological interventions to manage the pain from EB and from surgical and wound management procedures. The patient expert's advocate explained that they relied on pain relief medication such as ketamine and strong opioids to manage the pain associated with EB wounds. They also stated that they had been offered methotrexate and antihistamines to try to manage itching, but these did not improve the itching very well. The clinical experts explained that care for EB was managed from 1 of 4 specialist centres in the UK, where multidisciplinary teams help people control symptoms of EB. People generally visited these specialist centres every 3 to 6 months (although visits may be more frequent for children). Day-to-day care for people with EB was done at home with the help of carers, and there may be support from local dermatologists in between visits to specialist centres. But, given the complex and wide-ranging nature of EB, specialist care was essential to manage the condition. The committee considered that there were no satisfactory treatments available for EB and that there was an unmet need for treatments that would improve quality of life for people with EB. The committee concluded that current clinical management without birch bark extract was the appropriate comparator for this appraisal.

Clinically significant benefit

3.4 The clinical expert submission stated that a clinically significant benefit for people 10 years and older would be for a wound to heal and to remain healed for

3 months. It was more difficult to define a clinically significant benefit for people under 10 years. The clinical expert explained that there was no broadly accepted definition of a clinically meaningful difference and stated that, because of the severity of the disease and the pain caused by each open wound, people with EB would value any incremental benefit. The patient expert noted that for them to lead a more normal life, they may need to see a more than 50% improvement in wound burden. But they also noted that because some chronic wounds are particularly painful, and each wound that remains open causes additional pain, healing of any wounds would improve their quality of life. They also noted that there would be greater gains in quality of life associated with healing wounds in particular sites on the body. The patient organisation expert explained that by reducing wound burden in any way, the time needed to clean and redress wounds would be reduced, thereby improving quality of life for people with EB and their carers by reducing the total amount of pain associated with dressing changes each day and freeing up time for other activities. The committee concluded that although improvements in skin damage and wound healing would have to be very high to transform quality of life, people with EB would value any improvement in the speed at which wounds heal.

Clinical effectiveness

Data sources and results

3.5 Clinical-effectiveness data for birch bark extract came from the EASE trial, which was a phase 3 randomised double-blind trial. The trial recruited people with junctional EB and both subtypes of dystrophic EB who had a target wound of between 10 cm^2 and 50 cm^2. A target wound was a single wound used to assess outcomes such as speed of wound healing. People were randomised to have either birch bark extract gel or a control gel. The randomisation was stratified by EB subtype and target wound size to try to equally represent these characteristics in both arms. The double-blind period of the trial lasted for 90 days, after which people still in the trial had birch bark extract for up to 24 months. The trial's primary outcome was the proportion of people with a first complete target wound closure within 45 days. Statistically significantly more people experienced this outcome in the birch bark extract arm than in the control

arm (odds ratio [OR] 1.84, 95% confidence interval [CI] 1.02 to 3.30). For the secondary outcomes of the proportion of people with first complete target wound closure within 90 days, and the incidence of target wound infection up to day 90, there were no statistically significant differences between the trial arms. Two other outcomes were the change from baseline in BSAP score (mean difference −1.3; 95% CI −2.9 to 0.3) and Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) score (mean difference 0.1; 95% CI −1.6 to 1.8). The committee noted that the mean change in EBDASI and BSAP scores numerically favoured birch bark extract over current clinical management, but that this difference was small and not statistically significant. The committee considered the primary outcome of the trial and concluded that birch bark extract was a clinically effective treatment for treating skin wounds associated with junctional and dystrophic epidermolysis bullosa.

Economic model

Company's modelling approach

3.6 The company constructed a state transition model with 7 health states to model the disease course of EB for current clinical management and birch bark extract. Health states 1 to 6 were defined by taking the BSAP score range reported in the EASE trial and dividing it up equally between 6 states. The higher health states represented more severe disease and a seventh health state represented death. In each of the 30-day cycles, people in the modelled cohort could move between any of the health states and to the absorbing death state. Movement between the health states was determined by transition probabilities (see section 3.8), which were derived from the EASE trial. For the current clinical management arm, transition probabilities were applied until 90 days before a steady state assumption (no further movement between health states) was applied. In the birch bark extract arm, transition probabilities were applied for 12 months and from that point onwards a steady state assumption was applied. There was no stopping rule in the model and people were assumed to continue treatment with birch bark extract until either stopping treatment due to patient choice or the patient died. The committee concluded that the model structure was appropriate for decision making.

Stopping treatment in the model

3.7 The company applied a 1% annual treatment stopping rate in the model after 90 days. This was lower than the stopping rate recorded in the EASE trial, which is considered confidential and cannot be reported here. The company explained that the higher stopping rate in the trial was because of the trial procedures and people stopping for breaches of trial protocol, for example, incidence of squamous cell carcinoma. The committee recalled the severity of EB and how the condition can make travel difficult. It understood that aspects of the trial, such as travelling to follow-up visits every 30 days or attending clinics during the COVID-19 pandemic, could be challenging for those with EB. The company stated that these issues would not occur in clinical practice and so were not included in the cost-effectiveness model. The committee also recalled that usual care for EB meant applying topical treatments, such that continuing birch bark extract was no additional burden. It concluded that the stopping rate seen in the trial was not generalisable to clinical practice and accepted the company's modelled 1% annual stopping rate.

Calculating transition probabilities

3.8 The company used an approximation method to calculate transition probabilities for the birch bark extract and current clinical management arms of the model. This method used the mean change in BSAP score and its standard deviation from the entire trial period to calculate the transitions between the various health states for each cycle. This method meant assuming that change in BSAP score was normally distributed (a probability distribution that is symmetrical around the mean). The company provided a graph of change in BSAP score from the entire trial period to support the assumption of a normal distribution. The company acknowledged that there was uncertainty around how best to calculate transition probabilities. It explained that in EB, unexpected events such as trauma or infection could result in substantial worsening of health states. It considered that the approximation method was designed to reduce the undue influence of such events and help capture the overall effect of birch bark extract. It also provided a scenario in which the transition probabilities up to 90 days were derived directly from the EASE trial and the approximation method was used to estimate transition probabilities from 90 days to 12 months (see section 3.9). The EAG was

concerned that the approximation approach gave more favourable transition probabilities to birch bark extract and less favourable transition probabilities to current clinical management than if the transition probabilities were calculated directly from the EASE trial data. It noted that under the approximation method, most people in the birch bark extract arm of the model either stayed in the same health state or improved, which it considered implausible. The EAG also considered that although the change in BSAP score from the overall trial period may be normally distributed, this may in fact represent several separate distributions that may or may not be normal. The EAG preferred to use the data directly from the EASE trial to calculate transition probabilities for both arms of the model. It noted that this produced a wider range of transitions, with people in both arms both improving and worsening between cycles. The EAG acknowledged the company's scenario that used 90 days of transition probabilities from the EASE trial followed by the approximation approach until 12 months. But it considered that if transition probabilities were applied beyond 90 days, then they should be calculated using data from the EASE trial, not using the approximation method. The committee considered the company's justification for using the approximation method and it noted that, if the unexpected events that drove the substantial health state changes were part of the natural disease course of EB and would be seen in clinical practice, then they should not be removed by using an approximation, and should be included in the model. It considered that there was direct comparative evidence for birch bark extract from a relatively well sized clinical trial, which showed that people sometimes moved more than 1 health state between visits. It concluded that calculating transition probabilities directly from the EASE trial was preferable to the approximation method for modelling health state occupancy.

Applying transition probabilities

3.9 The company had applied the approximated transition probabilities to the current clinical management arm for 90 days and to the birch bark extract arm for 12 months before applying a steady state assumption. The steady state assumption meant that the average cohort health state occupancy did not change. The EAG preferred to use the transition probabilities observed from the EASE trial (see section 3.8) and to apply them to both treatment arms until 90 days, after which the steady state assumption was applied to both arms. The

company considered that the full effect of birch bark extract was only seen after 12 months and provided a real-world evidence study to support this assumption. It did also acknowledge the uncertainty around the transition probabilities for birch bark extract and accepted that the EAG's assumption was plausible. The committee examined data on change in BSAP score from the 2 years of the EASE trial and noted that it was plausible that a steady state was achieved somewhere between 90 days and 2 years, but that this was uncertain. It considered that as the trial had reported 27 months of follow up for birch bark extract, the full data from the trial should be used to inform the model. The committee agreed that it would like to see an analysis where the transition probabilities in the model were informed by the full dataset from the trial from randomisation to 810 days. After the committee meeting the company provided updated analyses using the EASE trial data to directly calculate transition probabilities up to day 810. But the EAG explained that, at later time points in the EASE trial, proportionally more people were lost to follow up from severe health states (states 5 and 6) than the less severe states, and that this could be because of informative censoring. Informative censoring occurs when people leave a clinical trial for reasons that are related to the trial itself (for example, they can no longer take part because of the severity of their condition). The committee understood that informative censoring in the company's new analyses could bias the cost-effectiveness estimates in favour of birch bark extract. This is because it would underestimate the numbers of people in the most severe health states, which are responsible for the highest costs and lowest utilities. The EAG produced 2 scenarios that attempted to control for the effects of informative censoring by estimating what health states the missing people would have been in at day 810, had they not left the trial. One of these scenarios assumed that for people missing at a given time point, their disease severity was not measured again in the trial, and the second scenario assumed that some of the people who were missing had their disease severity measured again later in the trial. The committee considered that the risk of informative censoring meant that the company's analysis that did not account for informative censoring was not appropriate for decision making. It felt that both of the EAG scenarios were plausible but that it was more appropriate to assume that people lost to follow up at a given time point would not be seen again later in the trial. The committee concluded that the first EAG scenario, which attempted to control for informative censoring while assuming that people who were lost to follow up did not reappear later in the EASE trial, was the most appropriate for decision making.

Applying continuity corrections

3.10 There were health state transitions that, although clinically plausible, did not occur in the EASE trial. This could have been because the trial's sample size was too small for all possible transitions to be seen at each visit. This would have meant that some transitions that are possible in clinical practice would not be represented in the model. Continuity corrections can be applied in such situations to allow clinically plausible transitions not seen in the clinical trial to occur in the model. The EAG considered 2 types of continuity corrections that could be applied, but did not apply either to its base case. It noted that this meant the base case likely underestimated the incremental cost-effectiveness ratio (ICER) because many of the plausible transitions that were not observed were to more severe health states. The EAG also explained that it was unclear whether it was appropriate to apply the continuity correction to the company analyses using the approximation method, because this method already allowed transitions between any health state. The committee considered that it was plausible that all health state transitions were possible and that the trial size and potentially unobserved transitions resulted in uncertainty for the analyses. The committee considered that applying an equal likelihood to all possible health state transitions was not appropriate in this evaluation. This was because the trial data suggested that, for example, moving from health state 1 to health state 2 was more likely than moving from health state 1 to health state 6. This would not be reflected in the proposed continuity corrections, which assigned an equal fraction of an observation to all possible transitions. The committee concluded that it preferred not to apply a continuity correction. Although this would leave unresolved uncertainty in the model because it would not reflect the transitions between health states that would occur in reality. The committee concluded that this could underestimate the ICER if transitions to more severe health states were underrepresented in the model, but that it would take this uncertainty into account in its decision making.

Utility values

Modelling carer disutility

3.11 Carer quality-of-life data was not collected in the EASE trial, so the company did a time-trade-off study to estimate carer disutility. A time-trade-off study presents people with a vignette describing a situation and asks them to decide how much life expectancy with full health they would be willing to trade to avoid a specific amount of time in the described situation, which then generates a utility estimate for that situation. The EAG noted that this study used vignettes that described the individual as 'the main caregiver'. But the company modelled carers based on health state severity, with people in health states 5 and 6 having 1.78 carers. The EAG considered that applying a utility value based on a main caregiver to more than 1 caregiver lacked face validity. The company submitted a survey it did with DEBRA (a patient organisation for EB). In this, respondents considered that a secondary caregiver would experience 77% of the quality-adjusted life year (QALY) loss of the primary caregiver. The company included a modifier in the model so that any additional carers modelled for people in health states 5 and 6 had 77% of the quality-of-life reduction of the primary carer. The committee considered the evidence submitted by the company in support of its modelling of carer disutility and concluded that this approach was appropriate for decision making.

Cost-effectiveness estimates

Acceptable ICER

3.12 The committee considered the evidence on birch bark extract for treating junctional and dystrophic EB. It noted:

- the unresolved uncertainty around informative censoring when the EASE 810-day data was used (see section 3.9)
- the unresolved uncertainty associated with the clinically plausible yet unobserved transitions (see section 3.10)

- that the undiscounted QALYs for birch bark extract did not qualify for any QALY weighting to be applied.

  The committee considered these points and concluded that the maximum acceptable ICER for this appraisal would be £100,000 per QALY gained.

Committee-preferred cost-effectiveness estimates

3.13 The committee's preferred assumptions included:

- the company's 1% annual discontinuation rate in the model (see section 3.7)
- to use the maximum amount of data available from the EASE trial (810 days) to directly inform health state occupancy in the model before applying a steady state assumption (see sections 3.8 and 3.9)
- to use the first EAG scenario to account for informative censoring, which assumed people lost to follow up left the trial completely (see section 3.9)
- to model carer disutility using the company time-trade-off study results and the 'subsequent carer' modifier (see section 3.11).

  The committee's preferred base case resulted in an ICER below £100,000 per QALY gained compared with current clinical management (see section 3.12).

Other factors

Equality issues

3.14 The committee considered comments from stakeholders that some people with EB may have lower socioeconomic status than others. These people may be particularly impacted by EB because of the high costs imposed by modifications to everyday life and in travelling to 1 of the 4 treatment centres, which are found only in London and Birmingham. In addition, some people may have difficulties accessing specialist care because of cultural issues such as language barriers, or

lack of familiarity with the healthcare system or support available from charities. The patient organisation expert also explained that people may not want to be seen in public with a condition such as EB that has very visible symptoms. The committee considered the relatively small improvements that birch bark extract had on BSAP score as reported in the trial (see section 3.5). The clinical experts stated that it was unlikely that such improvements would change the frequency with which people had to attend the specialist treatment centres because of the size of the improvements and because the care provided in the treatment centres addressed health problems other than those associated with the skin alone. The committee concluded that the recommendation of birch bark extract was not likely to impact the reported health inequalities.

Conclusion

Recommendation

3.15 The committee considered its preferred assumptions (see section 3.13) and the uncertainty that remained in the economic model (see section 3.12). It noted that the most plausible ICER was under £100,000 per QALY gained compared with current clinical management. So, it considered birch bark extract a cost-effective use of NHS resources. Therefore, it recommended birch bark extract for routine use in the NHS for treating junctional and dystrophic EB in people aged 6 months and over, only if the company provides birch bark extract according to the commercial arrangement.

4 Implementation

4.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has junctional or dystrophic epidermolysis and the doctor responsible for their care thinks that birch bark extract is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

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

Paul Arundel
Vice chair, highly specialised technologies evaluation committee

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.

Samuel Slayen
Technical lead

Christian Griffiths
Technical adviser

Celia Mayers
Project manager

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