NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

IN.PACT drug-coated balloon for peripheral arterial disease

The National Institute for Health and Care Excellence (NICE) is producing guidance on using **the IN.PACT drug-coated balloon for peripheral arterial disease** in the NHS in England. The medical technologies advisory committee has considered the evidence submitted and the views of expert advisers.

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical effectiveness and resource savings reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?
- Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?

Note that this document is not NICE's final guidance on the IN.PACT drug-coated balloon for peripheral arterial disease. The recommendations in section 1 may change after consultation. After consultation the committee will meet again to consider the evidence, this document and comments from public consultation. After considering these comments, the committee will prepare its final recommendations which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the medical technologies evaluation programme process guide and medical technologies evaluation programme methods guide.

Key dates:

- Closing time and date for comments: 17:00 Monday 21 June 2018

- Second medical technologies advisory committee meeting: Friday 20 July 2018

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice. If the case for adopting the technology is supported, then the technology has been found to offer advantages to patients and the NHS. The specific recommendations on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages.

1 Draft recommendations

1.1 The case for adopting the IN.PACT drug-coated balloon for the treatment of intermittent claudication in people with peripheral arterial disease is supported by the evidence. Using IN.PACT improves medium-term vessel patency and reduces the need for repeat interventions compared with percutaneous transluminal angioplasty alone.

1.2 IN.PACT should be used in people with intermittent claudication, when percutaneous transluminal angioplasty is recommended (see section 1.5 of the NICE clinical guideline on peripheral arterial disease).

1.3 Cost modelling indicates that, assuming a target lesion revascularisation rate over 1 year of 30%, IN.PACT is cost saving after 5 years when the acquisition cost is no more than £519.

2 The technology

Description of the technology

2.1 The IN.PACT drug-coated balloon (Medtronic) is an over-the-wire angioplasty catheter and drug delivery system for treating peripheral arterial disease. IN.PACT has a dual-lumen shaft: 1 lumen for the passage of the guidewire, and the other to allow the balloon to be inflated and deflated using a contrast medium diluted with saline. Two radiopaque markers show the working length of the balloon, so that X-ray fluoroscopy can be used to properly position the device. IN.PACT is introduced using standard percutaneous transluminal angioplasty (PTA). When inflated, the balloon widens the narrowed vessel, leading to an increase in blood flow. The outer surface of the polyamide balloon is coated with paclitaxel (3.5 micrograms per mm^2), combined with a urea carrier which is delivered into the vessel wall when the balloon is inflated. Paclitaxel reduces the extent of intimal smooth muscle cell proliferation that may lead to recurring narrowed vessels (restenosis). IN.PACT is designed for a single inflation only, after which it is deflated and withdrawn. More than 1 IN.PACT device may be used in the same patient for long or multiple lesions.

2.2 IN.PACT is available in a variety of balloon sizes and in 2 versions, depending on the diameter of the guidewire used: the IN.PACT Admiral is compatible with a 0.035 inch guidewire and the IN.PACT Pacific is compatible with a 0.018 inch guidewire. The list price of both the Pacific and Admiral versions as stated in the company's submission is £910. Purchase prices vary depending on local arrangements. An average price of £603, based on IN.PACT sales data in the UK over a rolling 12-month period, was used in the cost modelling base case.

2.3 The claimed benefits of IN.PACT in the case for adoption presented by the company are:

- improved primary patency
- decreased rates of repeat interventions
- improved target lesion revascularisation rates
- reduced claudication symptoms and scores
- improved quality of life and function
- fewer hospitalisations for vascular treatment of the target limb.

Current management

2.4 The NICE guideline on peripheral arterial disease recommends that initial management should focus on preventative treatments and lifestyle changes. People with intermittent claudication should be offered a supervised exercise programme. PTA should only be offered when exercise has not shown improvement, lifestyle changes have been reinforced and when suitability has been confirmed by imaging. Bypass surgery should only be offered to people with severe lifestyle-limiting intermittent claudication when PTA has been unsuccessful or is unsuitable, and in the presence of appropriate patterns of vascular disease.

3 Evidence

Summary of clinical evidence

3.1 The external assessment centre (EAC) considered 11 studies to be relevant to the scope of the decision problem (7 published and 4 unpublished), including 7 of the 23 identified by the company. In 7 of the 11, the control arm was PTA with or without stenting. The remaining 4 studies were single-arm studies. All studies were multicentre and done prospectively, with patient outcomes reported up to 3 years. In 7 of the studies, patients were randomised to

treatment modality. For full details of the clinical evidence, see section 3 of the assessment report.

EAC's analysis of the clinical evidence

3.2 The EAC considered that the IN.PACT SFA randomised trial (Laird et al. 2015, Krishan et al. 2016) provided the most relevant evidence. Although the EAC considered that the trial was subject to potential bias, specifically an unclear risk of attrition bias and unclear risk of performance bias, it acknowledged that IN.PACT SFA was the largest comparative trial with the longest follow-up and was fully relevant to the scope. The study reported a statistically significant reduction in restenosis and clinically driven target lesion revascularisation (defined as re-intervention at the target lesion because of symptoms or a decrease in ankle-brachial index [of at least 20% or more than 0.5] compared with baseline) compared with PTA alone. IN.PACT and PTA alone were equally effective in terms of functional outcomes and the need for target limb major amputations. There was a statistically significant lower mortality rate in patients having PTA alone compared with those having IN.PACT. The EAC was unable to conduct a meta-analysis on the studies because there were no common outcome measures with which to synthesise results.

3.3 The EAC noted that the reduction in target lesion revascularisation seen in IN.PACT SFA was broadly supported by evidence from the single-arm studies. Although none of the included studies was done in the UK, the EAC considered that the results should nonetheless be relevant to a UK clinical setting as the diagnosis of intermittent claudication, procedure, and patient characteristics were comparable.

Summary of economic evidence

3.4 The company submitted a decision-tree model with:

- PTA alone as the control
- IN.PACT (including PTA) as the intervention
- target lesion revascularisation as the endpoint
- a 3-year time horizon.

Based on clinical practice and the results of IN.PACT, the model assumes that some patients will need implantation of a bare metal stent ('bail-out stenting'), either because of inadequate distal flow after treatment or because of the presence of a large dissection. In these cases the model includes the cost of bail-out stenting, and also allows the option of a variable target lesion revascularisation rate.

EAC's analysis of the economic evidence

3.5 The EAC considered the company's model to be appropriate: it revised the value for the probability of a target lesion revascularisation, but otherwise made no changes to the model inputs. For full details of the company's parameters and EAC changes see section 4.2 of the assessment report.

3.6 The company's base case showed that, at 3 years, IN.PACT is slightly cost incurring compared with PTA alone. However, it becomes cost saving at 4 years (by £95 per patient). With the EAC's updated value for the probability of a target lesion revascularisation, IN.PACT becomes cost incurring at 3 years by £106 per patient and at 4 years by £36 per patient.

3.7 The EAC did a number of sensitivity analyses by varying several model parameters. In most instances, IN.PACT remained cost incurring at 3 years. However, using the lower bounds of the

sensitivity analyses, IN.PACT is cost saving in each case at 4 years. Because of this, the EAC considered that cost savings using IN.PACT were likely to be realised after 4 years. Furthermore, the model did not include potential clinical benefits other than target lesion revascularisation, such as avoiding critical limb ischaemia or the need for lower limb amputations. As a result, the model may underestimate the cost benefits associated with adopting IN.PACT. For full details see sections 4.5 to 5.2 of the assessment report.

4 Committee discussion

Clinical effectiveness

4.1 The committee agreed that the results of IN.PACT SFA, including recently published 3-year follow-up patient outcomes data (Schneider 2018), provided the most relevant clinical-effectiveness evidence. It concluded that IN.PACT is equally as effective as PTA alone in terms of functional outcomes, while also improving primary patency rates and reducing target lesion revascularisation rates.

4.2 The committee noted the statistically significant difference in mortality rates between the IN.PACT and PTA groups in IN.PACT SFA. It considered the causes of the deaths reported in the trial and the conclusions of the trial data safety monitoring board and clinical events committee. It also heard expert advice about the expected mortality rates for patients with peripheral arterial disease and intermittent claudication, and asked the EAC to explore mortality rates in other studies on this patient group. Having reviewed this information, the committee concluded that the reported mortality rates in patients having IN.PACT in the trial were reflective of expected mortality rates in these patients regardless of their treatment. The committee also considered that the difference in mortality rates observed between the treatment arms in the trial

was a consequence of an unusually low mortality rate in the PTA control arm. It considered further analyses by the EAC in an attempt to understand this unusually low rate of mortality. The committee noted that there was no evidence to suggest that the low rate could be explained by unusual clinical or demographic characteristics of the patients in the study. It concluded that this outcome remained an unexplained anomaly.

4.3 The committee considered the significance of clinically driven target lesion revascularisation as an outcome measure. The clinical expert advisers explained that repeat revascularisation procedures are done based on many different factors. In the context of clinical studies, they may be prompted by patient follow-up that detects symptomatic recurrence or imaging evidence of restenosis. The experts explained that in UK practice, such follow-up arrangements are unusual and it is more common for patients to be discharged to primary care after revascularisation. Consequently, restenosis may go undetected; the experts explained that best practice should ideally include rigorous follow-up to identify when target lesion revascularisation is indicated. The committee concluded that measuring clinically driven target lesion revascularisation is an appropriate outcome measure that is relevant to best NHS practice.

Pathway positioning

4.4 The committee discussed the recommendations for patients with intermittent claudication described in the NICE guideline on peripheral arterial disease, and noted that they do not refer to the use of drug-coated balloons. However, the February 2017 guideline review refers to emerging evidence of the possible benefits of drug-coated balloon and drug-eluting stent technologies. The experts agreed that drug-coated balloons have been widely adopted in

Europe and the US to treat peripheral arterial disease, but there was no consensus about the extent of adoption in the UK.

4.5 The committee discussed whether IN.PACT may offer particular benefits in treating stenosis that has recurred after previous balloon or stent treatment. The committee noted that the published evidence in this subgroup of patients is limited; the clinical experts added that there is some evidence of benefit at 1 year, but this does not appear to be sustained in the long term. The committee noted that further research in this subgroup of patients with a difficult to manage condition would be helpful.

Cost modelling

4.6 The committee agreed with the EAC's change to the company's cost model. It noted that the main parameters that influenced the cost outcomes were the target lesion revascularisation rate and the purchase price of IN.PACT.

4.7 The committee noted that the original model assumed a constant target lesion revascularisation rate. For its updated model, the EAC reviewed the evidence of variable and diminishing target lesion revascularisation rates with time after PTA. The most pertinent studies were considered to be Tepe (2015) and Dake (2016), which both reported falling target lesion revascularisation rates up to 5 years. It was noted that both of these studies were limited in terms of their relevance to the evaluation: neither was done in the UK, and both included a large number of patients with critical limb ischaemia. Nonetheless, the experts agreed that the changing pattern of target lesion revascularisation rates in these studies is more consistent with their own clinical experience than a constant level over time. They also explained that a typical UK cohort of patients having percutaneous intervention for intermittent

claudication may well have more advanced and complex disease than those included in the published studies, which would increase the chance of their needing target lesion revascularisation. Although there is uncertainty about target lesion revascularisation rates in typical UK clinical practice, the experts agreed that a 1-year rate of 30% and a 2-year rate of 50% were reasonable estimates. The committee noted that in IN.PACT SFA and Dake et al., the target lesion revascularisation rates at years 1 to 3 were extremely similar (Dake et al. also reports clinical outcomes data up to 5 years after the intervention, but these data are not yet available for IN.PACT SFA). Because the rates were so similar, the committee concluded that it was reasonable to use the Dake et al. data to estimate later clinical outcomes (years 4 and 5) for inclusion in the cost model. The EAC did further analyses which estimated break-even purchase prices for IN.PACT, assuming different target lesion revascularisation rates over 1 year and that all rates fell over 5 years (following the same patterns as those seen in the IN.PACT SFA and Dake et al. studies).

- Assuming a 1-year target lesion revascularisation rate of 20.6% (from IN.PACT SFA) and that the rate falls over 3 years as in IN.PACT SFA, IN.PACT is cost saving at 3 years when the acquisition cost is £376 or less.
- Assuming a 1-year target lesion revascularisation rate of 20.6% (from IN.PACT SFA) and that the rate falls over 5 years as in IN.PACT SFA - Dake et al. (2016), IN.PACT is cost saving at 5 years when the acquisition cost is £396 or less.
- Assuming a 1-year target lesion revascularisation rate of 30.0% (as proposed by the clinical experts), IN-PACT is cost-saving at 3 and 5 years when the acquisition cost is no more than £498 and £519 respectively. The committee accepted this as the most relevant scenario for the NHS.

4.8 The experts explained that the average number of balloons used per patient in the model (1.4) was an accurate reflection of their own clinical practice. The company representative stated that a longer, 200 mm balloon is being designed. Assuming that this balloon is not sold at an increased price, this development is likely to reduce the cost of using IN.PACT in the future.

4.9 The committee considered that the cost model may underestimate the cost benefits of IN.PACT because it did not include potential clinical benefits other than target lesion revascularisation (section 3.7). The experts considered that these additional benefits are plausible, but the committee concluded that there is insufficient evidence to substantiate this.

7 Committee members and NICE project team

Committee members

This topic was considered by the medical technology advisory committee which is a standing advisory committee of NICE.

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

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

NICE project team

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

Neil Hewitt
Technical analyst

Bernice Dillon
Technical adviser

Jae Long
Project manager

ISBN:

