Lutonix drug-coated balloon for peripheral arterial disease

Medtech innovation briefing
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Summary

- **The technology** described in this briefing is the Lutonix drug-coated balloon (DCB; also known as the Lutonix 035). It is a paclitaxel-coated percutaneous transluminal angioplasty (PTA) catheter. It is indicated for treating peripheral arterial disease (PAD).

- **The innovative aspects** are that Lutonix DCB has a lower paclitaxel concentration than alternative devices and a drug delivery mechanism that is claimed to be novel.

- **The intended place in therapy** would be as an alternative to other reconstructive options for PAD such as standard or plain balloon PTA, or bypass grafting.

- **The key points from the evidence** summarised in this briefing are from 2 randomised trials (LEVANT studies I and II; n=101 and 476) comparing the Lutonix DCB with standard angioplasty using non-coated balloons in patients with symptomatic femoropopliteal PAD. The Lutonix DCB showed significantly lower late lumen loss rates at 6 months post-procedure with a similar complication rate to standard balloon angioplasty. Two non-comparative, retrospective case series (Steiner et al. 2016 and Micari et al. 2016) indicate that the Lutonix DCB is a potentially viable treatment for below-the-knee PAD, with acceptable outcomes and safety rates.

- **Key uncertainties** around the evidence are that the primary outcome of the 2 randomised studies is late lumen loss. This is considered to be a technical outcome so its clinical impact is unclear. The additional clinical evidence comprises retrospective non-comparative case series (n=246 and n=55).
The cost of Lutonix DCB is £580 per unit (exclusive of VAT). The resource impact, other than the device cost, should be similar to standard angioplasty balloon procedures.

The technology

The Lutonix DCB is a drug-coated balloon percutaneous transluminal angioplasty (PTA) catheter for the treatment of peripheral arterial disease (PAD), caused by atherosclerotic plaques on the vessel wall. Angioplasty is a technique used to stretch or widen narrowed peripheral arteries, by inflating a small balloon inside the vessel. The balloon compresses the plaque lesion to allow blood to flow through the artery more freely. The Lutonix technology consists of an angioplasty balloon coated with paclitaxel plus a polysorbate/sorbitol carrier. Paclitaxel acts as an antiproliferative agent to prevent restenosis (recurrence of the vessel narrowing).

After pre-dilatation of the narrowed artery using a non-drug-coated balloon, Lutonix DCB is inserted into the vessel and positioned within or at the target lesion. The balloon is inflated to allow the paclitaxel to reach the vessel wall. The balloon is then deflated and removed.

The innovation

The coating of the Lutonix DCB has a lower concentration of paclitaxel than competitor DCB devices (2 micrograms per mm$^2$ compared to a standard 3.5 micrograms per mm$^2$). This lower level of paclitaxel in the balloon coating is claimed to result in less paclitaxel entering the blood stream, which minimises systemic effects while keeping an effective dose of the drug at the site of the target lesion. The polysorbate/sorbitol drug carrier is also claimed to be novel. It is described as having been optimised to carry the paclitaxel to the arterial wall while minimising drug loss during insertion of the balloon. This device is also smaller, measuring 1.65 mm in diameter compared to 1.98 mm for standard drug-coated balloon catheters.

The device is designed to be an alternative to standard balloon angioplasty with or without stenting, or to other DCBs. The manufacturer claims that the Lutonix DCB offers an improvement in vessel patency without leaving metal implants in the vessel, which happens with current stenting technology. According to the manufacturer, this allows for more flexibility if re-intervention is needed in the future.

Current NHS options

Currently there is no cure for PAD. Initial management focuses on preventative treatments and lifestyle changes to reduce symptoms and to reduce the risk of developing other types of cardiovascular disease such as a stroke or heart attack. The NICE guideline on peripheral arterial
disease recommends providing patients with information on lifestyle changes such as smoking cessation, diet and exercise and treatment options including management of existing conditions such as diabetes, statin or antiplatelet therapy.

Additionally, the guideline recommends a supervised exercise programme and naftidrofuryl oxalate to treat intermittent claudication (PAD-related leg pain while exercising) for people with PAD.

People with disabling claudication (pain while exercising due to PAD) and critical limb ischaemia (resting pain, ulcers, gangrene) may be offered angioplasty or surgical procedures such as bypass grafts. These procedures aim to restore the flow of blood through the arteries of the legs. As part of an angioplasty procedure, a stent (a small wire mesh tube) may sometimes be left in place to keep the artery open.

After balloon angioplasty the vessel may open satisfactorily as planned, the stenosis in the vessel may immediately recoil back, or the vessel may dissect in which case a stent is needed. Over time, restenosis may happen to the opened vessel, causing it to become narrowed again.

Plain (non-drug-coated) angioplasty balloons are used to pre-dilate the blood vessel before DCB or stent application. DCBs and stents are then used individually or together to prevent or delay restenosis. They may also be used some time later, in the secondary treatment of lesions which have restenosed.

Bypass surgery may be offered to people with severe lifestyle-limiting intermittent claudication when angioplasty has been unsuccessful or is unsuitable, and where imaging has confirmed that it is appropriate. It may also be used in people with critical limb ischaemia needing revascularisation. The PAD guideline recommends that an autologous vein should be used whenever possible. A range of synthetic grafts is currently available to the NHS and current practice varies in the choice of graft.

NICE has also issued guidance on percutaneous laser atherectomy as an adjunct to balloon angioplasty (with or without stenting) for peripheral arterial disease.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function to the Lutonix DCB:

- In.Pact Admiral (Medtronic), which uses a urea-based delivery system.
- Stellarex (Spectranetics), which has a polyethylene glycol-based delivery system.
- Ranger (BostonScientific), which has a citrate ester-based delivery system.
- Passeo 18 Lux (BIOTRONIK), which has a butyryl-tri-hexyl citrate-based delivery system.
- Legflow (Cardionovum), which has Shellolic Ammonium salt-based delivery system.
- Freeway (Eurocor Endovascular), which has a shellolic and alleuritic acid-based delivery system.
- Advance 18 PTX (Cook Medical), which has a proprietary coating, using no polymers or excipients.

**Population, setting and likely place in therapy**

The Lutonix DCB would be used in secondary care by interventional radiologists or vascular surgeons and should need very little additional training over standard balloon angioplasty. It is intended to be used for people with PAD requiring intervention such as a balloon angioplasty or stenting. No significant changes to current NHS practice would be needed to adopt this technology.

The manufacturer has stated that the Lutonix DCB is currently in use in 51 UK NHS Trusts.

**Costs**

**Device costs**

Table 1 shows the prices of the Lutonix DCB and additional components.

<table>
<thead>
<tr>
<th>Component</th>
<th>Price per unit</th>
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<tbody>
<tr>
<td>Lutonix DCB</td>
<td>£580</td>
</tr>
<tr>
<td>Guidewire</td>
<td>£5</td>
</tr>
<tr>
<td>Needle introducer</td>
<td>£15</td>
</tr>
<tr>
<td>Radiopaque contrast medium</td>
<td>£1.50</td>
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</tbody>
</table>

The cost of staff, overheads and supplementary medical equipment such as the guidewire, needle introducer and radiopaque contrast medium should be the same for Lutonix DCB procedures as for standard percutaneous transluminal angioplasty procedures.
Drug-eluting peripheral angioplasty balloons are included in the 2015/16 NHS England Enhanced Tariff Option as a high cost device which can be paid for through a separate price negotiation, in addition to the national tariff set for the standard plain balloon PTA procedure.

Prices for standard non-drug-coated balloons range from £59.83 per unit (Advance 35LP, Cook Medical) to £138.56 per unit (Peripheral Balloon Catheter Evercross 0.035, Covidien UK).

Costs of standard care

NHS costs (with HRG codes) are available for standard balloon angioplasty:


The NHS costs for combined day case or ordinary elective spells (Payment by Results 2014/15) are:

- YQ13B bypasses to tibial arteries CC score 0–6: £8,028
- YQ13A bypasses to tibial arteries CC score 7+: £9,790
- YQ22B amputation of single limb with CC score 0–9: £7,493
- YQ22A amputation of single limb with CC score 10+: £11,861

Resource consequences

The resource consequences of adopting this technology should be minimal. Compared with standard balloon angioplasty, the only additional costs for using this technology would be the cost of the Lutonix DCB and the extra procedure time needed to apply it. The procedure is performed by the same clinical staff using the same additional equipment as standard balloon angioplasty, including pre-dilation with a plain balloon.

One cost-related study was identified (Delatore 2015). This US-based study aimed to estimate the potential cost impact of the Lutonix DCB compared to standard care. This study reported that the Lutonix DCB was predicted to be cost-saving in the majority of analyses e.g. Lutonix compared with covered stents: $2,202 to $2,967 (£1,547 to £2,085) saving per patient.
Regulatory information

The Lutonix 035 drug-coated balloon PTA catheter was CE-marked as a class III device in December 2011.

A search of the Medicines and Healthcare Products Regulatory Agency website revealed that no manufacturer Field Safety Notices or Medical Device Alerts have been issued for this technology.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Peripheral arterial disease (PAD) is more common in people over the age of 60 years and affects more men than women. People with diabetes have an increased risk of developing PAD, and diabetes is recognised as a long-term health condition that may cause disability. People with PAD may also be considered to be disabled if the symptoms become severe enough to affect the activities of daily living. Age, sex and disability are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published interim process and methods statement. This briefing includes the most relevant/best publicly available evidence relating to the clinical and cost effectiveness of the technology. The literature search strategy, evidence selection methods and detailed data extraction tables are available on request by contacting medtech@nice.org.uk.

Published evidence

The published evidence for the Lutonix DCB summarised in this briefing comprises 2 randomised controlled trials (LEVANT I and LEVANT II) and 2 retrospective case series where the Lutonix DCB...
was used for below-the-knee indications (Steiner et al. 2016, Micari et al. 2016). A conference abstract of an economic study with a US perspective has also been included.

The LEVANT I study was a single-blind, 9-centre, 1:1 randomised, controlled trial with 101 patients (49 randomised to the Lutonix DCB compared with 52 to uncoated balloon intervention). Patients were stratified according to whether balloon-only intervention (n=75) or stenting (n=26) was intended. This study aimed to evaluate the safety and efficacy of the Lutonix DCB’s lower 2 micrograms per mm$^2$ coating for treatment of femoropopliteal lesions. The primary end point was angiographic late lumen loss at 6 months. Secondary outcomes included adjudicated major adverse events (death, amputation, target lesion thrombosis, reintervention), functional outcomes, and pharmacokinetics. At 6 months, late lumen loss was lower for the Lutonix DCB group than for the control group. Composite 24-month major adverse events were lower in the Lutonix DCB group than in the control group.

The LEVANT II study was a single-blind, 54-site, 2:1 randomised trial with 476 patients (316 randomised to the Lutonix DCB, 160 to the uncoated balloon intervention). The primary efficacy end point was primary patency of the target lesion at 12 months. The primary safety end point was a composite of freedom from perioperative death from any cause and freedom at 12 months from limb-related death. At 12 months, the rate of primary patency was superior with the Lutonix DCB than with the standard uncoated angioplasty balloon. The Lutonix DCB was statistically non-inferior to uncoated balloons in terms of freedom from primary safety events. There were no significant between-group differences in functional outcomes or in the rates of death, amputation, thrombosis, or re-intervention.

The Steiner et al. (2016) study is a retrospective chart review of 248 patients who were treated with the Lutonix DCB for below-the-knee peripheral PAD. Evaluable follow-up data were available for analysis from 208 patients. Procedural success was defined as restoration of at least 1 below-the-knee artery with less than 30% residual stenosis in the final angiogram. Outcomes in follow-up retrieved from the charts included death, major and minor amputations, Rutherford category, need for ipsilateral below-the-knee reintervention, and target lesion revascularisation.

The Micari et al. (2016) study is a retrospective chart review of 55 patients who were treated with the Lutonix DCB for critical limb ischaemia (advanced below-the-knee PAD). All patients had evaluable follow-up data for analysis. Data on target lesion revascularizations, amputation and death rates were followed up to 12 months.
The Steiner et al. and Micari et al. studies demonstrate technical success when Lutonix DCB is offered as a treatment option for below-the-knee indications, with acceptable safety outcomes, although neither study compared outcomes with standard practice.

The Delatore et al. (2015) conference abstract describes an economic study comparing the Lutonix DCB with plain balloon percutaneous transluminal angioplasty, bare metal stents, drug-eluting stents, covered stents, and atherectomy. The study was set in the US healthcare system and employed a one-year time horizon. The authors concluded that the Lutonix DCB was potentially cost-saving compared to the alternative treatments.

Table 2 summarises the clinical evidence and its strengths and weaknesses.

**Table 2 Included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Details of intervention</th>
<th>Outcomes</th>
<th>Strengths and limitations</th>
</tr>
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| **Scheinert 2014**  
(LEVANT I)  
101 subjects. Multicentre (n=9); Germany (n=8); Belgium (n=1). Prospective, randomised, single-blinded (to patient). | **Lutonix DCB**  
(n=49) and uncoated percutaneous balloon angioplasty  
(n=52). Patient stratified according to treatment intention – balloon only (n=75), stenting (n=26). Mean age (years): 67 Lutonix DCB. 70 Uncoated percutaneous balloon angioplasty. | **The study results**  
favoured Lutonix DCB for lower late lumen loss and did not favour either treatment for complication rates. | **Strengths:**  
prospective, multicentre randomised, 1:1.  
**Limitations:**  
Single blind (to patient) – could lead to operator bias post-randomisation, although by the nature of the procedure it would not be possible to blind the clinicians to the intervention. Only limited balloon sizes were available, and the protocol-mandated angiograms at 6 months may have confounded clinical follow-up. The study was limited by small sample size for evaluating binary outcomes such as clinical events or patency.  
Sponsored by Lutonix. |
| **Rosenfield 2015**  
**(LEVANT II)**  
476 patients.  
Multicentre (n=54);  
USA (n=42);  
Europe (n=12).  
Prospective, randomised 2:1. | **Lutonix DCB**  
(n=316) and percutaneous balloon angioplasty  
(n=160).  
Mean age (years):  
67.8 Lutonix DCB.  
69 percutaneous balloon angioplasty. | The study results favour Lutonix DCB for primary patency at 12 months. Neither treatment was favoured for safety outcomes or event-free survival at 12 months post-procedure. | **Strengths:**  
multicentre randomised, 2:1.  
**Limitations:**  
Treating clinicians were not blinded to the treatment allocation but patients, investigators completing follow-up, vascular-laboratory personnel, core laboratory evaluators, and members of the clinical-events committee were. Sponsored by Lutonix. |
|---|---|---|---|
| **Delatore 2015**  
Economic modelling. | Economic modelling comparing the Lutonix DCB, balloon angioplasty, bare metal stents, drug-eluting stents, covered stents and atherectomy. | Economic modelling results show that Lutonix may be cost saving compared to most alternative treatments. | **Strengths:**  
Modelled a range of comparisons with different PAD treatments.  
Used real-world data inputs.  
**Limitations:**  
Conference abstract only  
USA/Medicare analysis may not be applicable to NHS.  
1st author was employed by the manufacturer at the time of publication. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Patients</th>
<th>Results</th>
<th>Strengths</th>
<th>Limitations</th>
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<td><strong>Micari 2016</strong></td>
<td>Retrospective case series, single centre. Non-comparative. 55 patients.</td>
<td>All patients treated with the Lutonix DCB for below-the-knee critical limb ischaemia (CLI). Follow-up completed for 55 patients. Mean age 76±4.3 years.</td>
<td>Results indicated the Lutonix DCB as a viable treatment option for CLI PAD, with an acceptable safety profile.</td>
<td>Strengths: study on below-the-knee PAD indication, specifically CLI. Limitations: retrospective, non-comparative study.</td>
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**Strengths and limitations of the evidence**

The LEVANT I and II trials were both single-blinded randomised trials of generally good quality, comparing the Lutonix DCB to uncoated balloon percutaneous transluminal angioplasty (PTA). The LEVANT II study in particular had a large number of participants. Both of the LEVANT studies were sponsored by the device manufacturer, and the first author of the LEVANT I paper was employed by the manufacturer at the time of publication.

The study by Steiner et al. (2016) was a retrospective, non-comparative case series of patients. It showed procedural success and acceptable safety using Lutonix DCB for below-the-knee PAD, but lacked any comparative element with standard treatment, and should be considered as low-quality evidence. A similar retrospective case series by Micari et al. (2016) was smaller in size (n=55) and also lacked any comparison with standard care. Both of these retrospective case studies simply showed the potential for Lutonix DCB as a treatment in below-the-knee PAD (including chronic
limb ischaemia). They provide preliminary data to indicate that the device can be used safely for this indication.

The Delatore (2015) conference abstract is the only economic data available. The study suggested that the Lutonix DCB would be potentially cost-saving when compared to most alternative PAD treatments. However, the study lacked methodological details and full results, for example describing one comparison as Lutonix DCB compared with covered stents. This economic study was set in the USA which means the results may not transfer to a UK NHS setting. The study notes that the author has an affiliation to the manufacturer (Bard), and as such this may represent some bias in this study.

**Recent and ongoing studies**

A search on clinicaltrials.gov for "Lutonix" found 15 results:


• **Drug eluting balloon in peripheral intervention for below-the-knee arteries with freeway and Lutonix.** Status: Recruiting, no results available. Indications: Peripheral artery disease. Device: Freeway PTA versus Lutonix PTA.

• **LEVANT 2 Safety Registry.** Status: Active, not recruiting, no results available. Indications: Peripheral artery disease. Device: Lutonix drug-coated balloon.


• **LEVANT 2 continued access registry.** Status: Active, not recruiting, no results available. Indications: Peripheral artery disease. Device: Lutonix drug-coated balloon.


• **Orbital vessel Preparation to Maximize Dcb efficacy in calcified below the knee (BTK) lesions — a pilot study.** Status: Recruiting, no results available. Indications: PAD/Vascular calcification. Device: Peripheral orbital atherectomy system versus 014 drug-coated balloon.

**Specialist commentator comments**

One of the specialist commentators highlighted that it is still not clear what combination of drug-coated balloons (DCBs), stenting and atherectomy offers the best long-term outcomes for patients. They felt that the current evidence is not strong enough to inform a recommendation.
about whether DCBs should replace the use of plain balloon angioplasty. They noted that currently DCBs are being used in selected patients only.

Two of the specialist commentators remarked that further research would need to be done to confirm any clinical benefit from using DCBs in general. They noted that without this information it is difficult to draw any conclusions on the cost effectiveness of this technology.

Two commentators reflected that the carrier substance used to bind and release the paclitaxel is an important factor in the design of DCBs. The carrier is important to achieving the concentration of paclitaxel at the target site. The commentators agreed that variations in carrier may determine the amount of paclitaxel needed to achieve similar biological effects.

In terms of the costs, one specialist commentator noted that at present, angioplasty using DCBs has the same tariff as plain balloon angioplasty. This may be limiting the uptake to this technology, as the acquisition cost of DCBs can be significantly higher than that for plain balloons.

One specialist commentator was concerned that the LEVANT I trial’s use of 15% late lumen loss as a primary end point may too low to be clinically significant. They noted that this is a technical measurement, and may not be an appropriate measure of patient outcome. This was echoed by another specialist, who stated that target lesion patency or restenosis is a poor surrogate end point for true clinical benefit.

Another specialist commentator noted that the LEVANT trials involved treating the femoropopliteal segment, and advised caution in extrapolating the outcomes of these trials to treatment of PAD in other areas. They also reflected that LEVANT II aimed to achieve quality of life improvement, but found no benefit in patient-reported health related quality of life. Similarly, another commentator noted that the LEVANT trials enrolled people with claudication, and so this may not reflect the outcomes of people with critical limb ischaemia. They also highlighted that a high proportion of patients were current smokers at the time of treatment and that smoking is a key factor in restenosis. Good practice would be to achieve smoking cessation prior to intervention, and as a result, restenosis rates would be lower following plain balloon angioplasty. In this case, the benefits of DCB treatment may be lost. The commentator noted that the trials do not comment on the use of exercise therapy, which should be part of the treatment package, and may have a similar impact as smoking cessation.
Specialist commentators

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

The following clinicians contributed to this briefing:

- Professor Alun Davies, Professor of Vascular Surgery, Imperial College London. Professor Davies has received funding for a PhD studentship from Acergy and has received grants from Urgo Laboratoire and Vascular Insights.

- Professor Julie Brittenden, Professor of Vascular Surgery, University of Glasgow. No conflicts of interest declared.

- Mr Peter Holt, Consultant Vascular Surgeon, St. George's University Hospitals NHS Foundation Trust. No conflicts of interest declared.

- Mr Dan Carradice, Honorary Senior Lecturer, Hull York Medical School. No conflicts of interest declared.

- Mr David McLain, Consultant Vascular Surgeon, Aneurin Bevan University Health Board. Mr McLain is a proctor for aortic aneurysm interventions for Cook Medical and has had fees for lectures and hospitality from Cook Medical, Covidien and LeMaitre Vascular. None of these areas relate to the product being reviewed or any of its direct or indirect competitors.

- Miss Janice Tsui, Senior Lecturer/Consultant Vascular Surgeon, UCL Division of Surgery and Interventional Science, Vascular Unit, Royal Free London NHS Foundation Trust. No conflicts of interest declared.

- Dr Arun Sebastian, Consultant Interventional Radiologist, Colchester University Hospital NHS Foundation Trust. Dr Sebastian has given advice to the NICE IPAC Committee previously.

Development of this briefing

This briefing was developed for NICE by Cedar. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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