NICE advice

Aptiva for painful diabetic neuropathy

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is Aptiva. It uses a frequency rhythmic electrical modulation system (FREMS) to treat painful diabetic neuropathy.
- The **innovative aspect** of the technology is that it is designed to be a non-drug option for treating painful diabetic neuropathy, with a novel mechanism of action.
- The intended **place in therapy** is uncertain. It could be used in addition to, or in place of, current drug treatment options.
- The **main points from the evidence** summarised in this briefing are from 4 non-UK-based studies, consisting of 1 randomised controlled trial, 2 randomised double-blind crossover studies and 1 case–control study. The studies include 151 adult patients in an ambulatory care setting. They show that Aptiva can reduce pain and improve quality of life and neurovascular measures compared with placebo in patients with painful diabetic neuropathy.
- **Key uncertainties** around the evidence or technology are that there are no studies

comparing Aptiva with other available treatment options, and the current evidence is limited in quality and quantity.

- The **cost** of Aptiva is £28,750 per unit with an additional cost of £5.46 for consumable electrodes per treatment session (excluding VAT). Additional staff costs associated with administering Aptiva would range between £437.50 and £770 per patient per year. The **resource impact** would be that it would increase costs compared with standard care in terms of capital cost, consumables and staff time.

The technology

Aptiva (Fremslife) is a non-invasive frequency rhythmic electrical modulated system (FREMS) for treating diabetic neuropathy.

The device consists of the FREMS unit including a liquid crystal display with touchscreen, 1 power supply unit and power cable, 1 remote control, electrode connection cables for neuromodulation, electrodes, 1 user treatment card and 1 connection protection cover.

During a treatment session, a series of monophase-compensated negative potential electrical pulses are delivered through disposable electrode pads applied to the skin along the pathway of the nerve involved in the neuropathy. The pulses are characterised by:

- a sharp spike and an asymmetrical shape with a peak amplitude variable from 0 V to 255 V
- pulse frequency variable within a range of 0 Hz to 50 Hz
- pulse duration variable within the range of 10 μs to 40 μs.

For diabetic neuropathy, 8 electrode pads (2 per connection cable) are applied to the calf, shinbone, ankle and midfoot of each leg. At the beginning of each treatment session, the electrical dose is set by the clinician, based on the sensation felt by the patient: the electrical stimulation should be felt but should not be painful. The duration of a treatment session is 35 minutes with a treatment cycle comprising 10 daily sessions. The company's suggested treatment frequency is 3 cycles per year, depending on the response to treatment.

The device was formerly known as PhysioFlog ETS 501.

Innovations

Aptiva is designed to provide a non-drug approach for treating painful diabetic neuropathy. It uses modulated electrical pulses, which differ from those used in percutaneous electrical nerve stimulation (PENS), and it is intended to improve the supply of oxygen to nerve cells with the aim of reducing pain.

Current NHS pathway or current care pathway

An estimated 9% of adults in the UK have a diagnosis of type 1 or type 2 diabetes (Diabetes UK) with about 21–25% of these diagnosed with painful diabetic neuropathy (Abbot et al. 2011; Tesfaye et al. 2010). The NICE guideline on neuropathic pain in adults: pharmacological management in non-specialist settings recommends a stepped approach to managing neuropathy. A choice of amitriptyline, duloxetine, gabapentin or pregabalin should be offered as an initial treatment for neuropathic pain (including diabetic neuropathy). If the first choice of drug is not effective, the remaining drugs should be tried in turn depending on response and tolerance. Tramadol should be considered if acute rescue therapy is needed and capsaicin cream should be considered for people with localised neuropathic pain who do not want, or who cannot tolerate, oral treatments.

NICE interventional procedures guidance on percutaneous electrical nerve stimulation (PENS) for refractory neuropathic pain states that PENS can be used with normal arrangements for clinical governance, consent and audit for patients selected by teams specialising in pain management. With PENS, one or more individual nerves are stimulated using needle probes with low voltage electrical currents. Each session lasts between 15 and 60 minutes with the duration of treatment varying between patients.

Aptiva would be used in addition to, or as a replacement for, pharmacological treatments if they fail to adequately manage pain or are poorly tolerated.

Population, setting and intended user

The Aptiva device would be offered to adults with painful neuropathy caused by type 1 or type 2 diabetes. It may be used by diabetes specialist nurses but also by any member of a diabetes or podiatry multidisciplinary team. In some hospitals it may also be administered by healthcare assistants. Treatment would be administered either in secondary care or in a community setting. Minimal training is needed and this is provided by the manufacturer at

no additional cost.

Costs

Technology costs

Table 1 Costs of Aptiva device (excluding VAT)

Description	Cost	Additional information
Device cost	£28,750	Multiple use
Electrodes and treatment cards (consumables)	£3,500	This includes 10,240 single-use electrodes, equivalent to 640 treatment sessions

Table 1 shows the device and consumable costs for Aptiva. Each treatment uses 16 electrodes costing £5.46. Ten treatments are needed per cycle, and there are up to 3 cycles of treatment each year. In the case that the full 3 cycles are completed, it would cost £163.80 per year in consumables.

Costs of standard care

Table 2 shows the costs of standard pharmacological treatments recommended for the treatment of diabetic neuropathy.

Table 2 Cost of pharmacological treatments (NHS Electronic Drug Tariff 2017)

Description	Cost per 28 days	Cost per 1 year	Additional information
Duloxetine	£2.17 to £4.34	£28.21 to £56.42	Based on dosage of 60 mg to 120 mg per day
Amitriptyline	£0.83 to £3.57	£10.79 to £46.41	Based on dosage of 10 mg to 75 mg per day
Gabapentin	£2.65 to £10.60	£34.45 to £137.80	Based on dosage of 900 mg to 3.6 g per day
Pregabalin	£32.20 to £64.40	£418.60 to £837.20	Based on dosage of 150 mg to 600 mg per day
Tramadol	£3.13 to £6.26	£40.69 to £81.38	Based on dosage of 200 mg to 400 mg per day

The cost of a multi-use Biowave PENS machine is £2,000 (excluding VAT) and the cost of the single-use PENS electrodes is £100 per treatment.

Resource consequences

Aptiva would generate additional costs to the NHS compared with standard care: for the cost of the device itself, consumables and additional staff time. For example, if it were administered by a band 3 healthcare assistant it would cost an extra £437.50 per patient per year. That figure rises to £770 if administered by a band 6 diabetes specialist nurse (PSSRU 2016).

The overall resource consequences are uncertain and depend on whether Aptiva were used in addition to, or in place of, current drug treatments. Among people using Aptiva in a randomised controlled trial (Bosi et al. 2013), none of those already on medication stopped it in the course of the study; no information was given on whether using Aptiva reduced dosage. Aptiva could be cost effective if it were shown to significantly improve quality of life compared with current drug therapies, but there is no evidence available to determine this.

Aptiva could lead to significant changes in the current care pathway, mainly from the time needed for treatment. Each cycle involves 10 35-minute sessions and up to 3 cycles are recommended per year. Additional clinic space is needed for each treatment.

Aptiva is currently used in 1 NHS Trust.

Regulatory information

Aptiva was CE marked as a class IIa device in October 2016.

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).

People of South Asian, African or Caribbean family origin are at higher risk of developing type 2 diabetes. Type 1 diabetes is most commonly diagnosed in people aged under 20; type 2 is most commonly diagnosed in people aged over 45. Race and age 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 interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Four studies are summarised in this briefing with a total of 151 participants. Two of these studies are randomised double-blind crossover studies, 1 is a randomised controlled trial and 1 is a case/control study. All studies were conducted in Europe.

The overall assessment of the evidence summarises the clinical evidence and its strengths and limitations.

Overall assessment of the evidence

The evidence base is very limited in quality and quantity. Two studies used the same sample but reported different outcomes. Three studies had small sample sizes which could affect the reliability of the results. None of the studies used a comparator device, 3 used a placebo or sham condition as their comparator and 1 had no comparator. Two studies used the predecessor device, the PhysioFlog ETS 501. Because the devices are

functionally similar, the results seem likely to be generalisable to the Aptiva device. All of the studies showed benefits of using the Aptiva device, including reduced pain and improved quality of life.

Although the studies included were not conducted in the UK, the outcomes reported are relevant to the NHS care pathway. It would be beneficial to have evidence directly comparing Aptiva with current NHS treatment options, including evidence from patients in whom treatment has failed. Longer follow-up periods would also show if the Aptiva device provides sustained benefits to patients.

Bocchi et al. (2010)

Study size, design and location

10 adult healthy controls and 10 adult patients with type 2 diabetes and diagnosed polyneuropathy. Case–control design. Italy.

Intervention and comparator(s)

Aptiva FREMS; no comparator.

Key outcomes

Blood flow improved in both groups after FREMS treatment.

Mean difference in blood flow in healthy participants was 10% higher compared to those with diabetes after treatment.

During treatment, there was a statistically significant increase in vasomotion power spectra in the diabetes group only. There was a non-significant increase in the healthy control group.

After treatment, relative energy values around the 0.1 Hz peak of the power spectra remained significantly higher in the diabetes group.

Strengths and limitations

- Within-patient control design.
- Small sample sizes.
- No comparator.
- Vasomotion power spectra results may not be a relevant clinical outcome.

Bosi et al. (2005)

Study size, design and location

31 adult patients with type 1 or type 2 diabetes and painful neuropathy. Randomised, double-blind crossover design. Italy.

Intervention and comparator(s)

PhysioFlog ETS 501 FREMS and placebo (sham treatment using the same device with no electrical stimulation) in 2 cycles of 10 treatments with each intervention in random sequence, with each series lasting no more than 3 weeks.

Key outcomes

After FREMS treatment there was a significant decrease in daytime and night-time pain scores and a significant increase in vibration perception across all recruited patients. Motor nerve conduction velocity and sensitivity to the Semmes-Weinstein monofilament pressure test were recorded for 26 and 12 patients respectively and a significant increase was observed after FREMS therapy in those tested.

These improvements persisted up to the final follow-up at 4 months.

No significant differences were observed after placebo treatment.

At 4-month follow-up, there were significant improvements in quality of life (SF-36).

Strengths and limitations

Randomised double-blind design. Funded in part by a research grant from Lorenz Biotech (the original manufacturer).

Bosi et al. (2013)

Study size, design and location

110 adult patients with a diagnosis of type 1 or 2 diabetes with symptomatic neuropathy. Randomised controlled trial. Six sites across Italy, Germany and France.

Intervention and comparator(s)

Aptiva FREMS and placebo (sham treatment using the same device with no electrical stimulation).

Key outcomes

There was no significant difference in the change in nerve conductance velocity (NCV) between groups.

Night-time and daytime pain was significantly reduced in the intervention group up to 37 weeks after initial treatment. Total follow-up was 51 weeks.

The difference in pain between groups was not significant 3 months after the last treatment.

There was no significant difference in the change in tactile sensation between groups.

There was a significant increase in cold sensation threshold in the intervention group compared with the placebo group.

Strengths and limitations

- Long follow-up.
- Randomised double-blind design.

- Large sample size.
- Focused on mild neuropathy only.
- Funded by Lorenz Lifetech.
- Patients were already medicated at baseline.

Conti et al. (2009)

Study size, design and location

Same sample used by Bosi et al. (2005). Randomised, double-blind crossover design. Italy.

Intervention and comparator(s)

PhysioFlog ETS 501 FREMS and placebo (sham treatment using the same device with no electrical stimulation).

Key outcomes

Within the 3-week treatment timeframe, there were no changes in skin cutaneous blood flow after FREMS or placebo treatment.

$TcPO_2$ appeared significantly reduced after FREMS treatment during rest.

There were no significant changes in $TcPCO_2$.

At 4-month follow-up, there was a significant increase in cutaneous blood flow during rest compared with baseline.

Strengths and limitations

Funded in part by a research grant from Lorenz Biotech. Randomised double-blind design.

Recent and ongoing studies

No ongoing or in-development trials were identified.

Specialist commentator comments

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.

One out of 4 specialist commentators was familiar with or had used this technology before.

Level of innovation

All commentators agreed that this device was innovative with 2 stating that it was a minor innovation and 1 classing it as a novel device.

Potential patient impact

All commentators agreed that the main patient impact would be a reduction in pain or improvement in quality of life. Two commentators noted that these effects may only be short-term. Three commentators stated that this treatment may be best for patients whose condition has failed to respond to standard pharmacological treatment.

One commentator stated that this treatment could lead to a reduction in medication use, and 2 commentators stated that there was a possibility that it could lead to improved clinical outcomes. One commentator noted that this treatment might lead to increased hospital visits for the patient. Another commentator noted that this patient cohort has many comorbidities, which may make it difficult for them to attend all their appointments and complete a therapy cycle. One commentator felt that only a small proportion of people with diabetes might be eligible for this treatment; another stated that this could be up to 50% of those with painful diabetic neuropathy, but that this would depend on how the target population was defined. One noted that many patients with painful diabetic neuropathy can be managed successfully with medication, but this has an element of trial and error with several different medications.

Potential system impact

All commentators agreed that this device would most likely be an addition to standard care, and would therefore need additional resources including staff time, appointment

rooms and equipment. One commentator stated that the improvement in clinical outcomes could lead to a reduced burden on other areas of the NHS and care services. One noted that it would most likely cause an increase in outpatient appointments. However, another commentator stated that this device may cost less than some current medications without the burden of associated side effects. Three commentators agreed that specialist training is needed in order to introduce this device to the care pathway, but one stated that staff had found the device easy to use after the training. A fourth commentator noted that additional personnel would be needed to manage each patient.

General comments

One commentator stated that painful neuropathy is difficult to treat and the level of pain is considerable, so felt that all possible therapies should be examined. Three commentators agreed that larger studies are needed to address uncertainties in the evidence base.

Specialist commentators

The following clinicians contributed to this briefing:

- Theresa Torrance, diabetes specialist nurse, Tayside NHS Trust. No conflicts declared.
- Vanessa Goulding, highly specialist podiatrist, Cardiff and Vale University Health Board. On the study management group for the Parafricta study.
- Dr Abd Tahrani, honorary consultant in diabetes and endocrinology, Heart of England NHS Foundation Trust. He is supported by the NIHR in the UK and has received honoraria for lectures and advisory work from Boehringer Ingelheim, Bristol–Myers Squibb, Eli Lilly, Novo Nordisk and Sanofi-Aventis. Has also had investigator-led grant support from the Novo Nordisk Research Foundation.
- Professor Michael Edmond, consultant in diabetes, King's College Hospital. On advisory board of Urgo and Limflow and previously Klox technologies and Crawford.

Patient organisations

Representatives from the following patient organisations were asked to comment:

- Diabetes UK
- Diabetes Research & Wellness Foundation
- Foot in Diabetes UK
- InDependent Diabetes Trust
- INPUT Patient Advocacy.

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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