

## Health Technology Briefing January 2022

### Nicardipine for treating aneurysmal subarachnoid haemorrhage

Company/Developer

BIT Pharma GmbH

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 29189

NICE ID: 10593

UKPS ID: Not Available

#### Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

#### Summary

Nicardipine is in clinical development for adult patients who have an aneurysmal subarachnoid haemorrhage (aSAH) and are undergoing aneurysm clipping. A subarachnoid haemorrhage is an uncommon type of stroke caused by bleeding into the compartment surrounding the brain, known as subarachnoid space. aSAH is a severe medical emergency and can lead to death or severe disability even when recognised and treated immediately. Up to half of all cases of subarachnoid haemorrhage (SAH) are fatal and 10–15% of casualties die before reaching a hospital. It is unclear why brain aneurysms develop in some people, although certain risk factors have been identified, such as smoking and alcohol consumption. Treatment aims to close the ruptured aneurysm (by clipping) and prevent re-bleeding. Unfortunately, even after successful closure of the ruptured aneurysm severe complications can occur. The current treatments for aSAH provide less than optimal effectiveness and can cause severe side effects in a substantial number of patients.

Nicardipine is a medicine incorporated into an implant to relax and widen blood vessels, reducing blood pressure and improving the flow of blood. When this is implanted in the brain during surgery to repair the bleeding blood vessel, it supplies nicardipine over 21 days just to the area where it is needed, relaxing the surrounding blood vessels and preventing them from narrowing. If licensed, nicardipine would provide a targeted treatment option for patients who have an aSAH who are undergoing aneurysm clipping.

## Proposed Indication

Adult patients aged 18 – 75 years who have an aneurysmal subarachnoid haemorrhage (aSAH) and are undergoing aneurysm clipping.<sup>1</sup>

## Technology

### Description

Nicardipine (NicaPlant) is a dihydropyridine calcium-channel blocker which inhibits the influx of extra cellular calcium across the myocardial and vascular smooth muscle cell membranes possibly by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.<sup>2</sup>

Nicardipine is currently in clinical development for adult patients who have an aSAH and are undergoing aneurysm clipping. In the ongoing phase IIb clinical trial (NCT04269408), patients will be given 10 nicardipine implants (releasing 4 mg nicardipine each; total 40 mg nicardipine) which will be placed after clip ligation into the basal cisterns in direct contact with the exposed cerebral blood vessel walls. In addition, patients will receive standard of care for aSAH patients according to the treatment guidelines.<sup>1</sup>

### Key Innovation

The management of patients with aSAH remains a highly demanding challenge in critical care medicine. Despite all efforts, the calcium channel antagonist nimodipine remains the only drug approved for improving outcomes after aSAH. However, in its current form of application, it provides less than optimal efficacy and causes dose-limiting hypotension in a substantial number of patients. *In vitro* and *in vivo* observations of nicardipine show promising results in terms of confirmed vasoactivity and lack of toxicity. The local application of nicardipine delivery system to the subarachnoid space improves patient outcomes while avoiding systemic side effects.<sup>3</sup>

Nicardipine is placed in close contact to the wall of cerebral arteries at the time of aneurysm clipping, in this way circumventing the blood brain barrier and obtaining sufficient drug concentration at the site of action.<sup>4</sup> The surgical procedure is only extended by a couple of minutes hence the administration is perceived to be very convenient for the neurosurgeon.<sup>a</sup>

In a phase IIa clinical trial (BIT-001; EudraCT number 2016-004521-17) safety and tolerability of increased doses of nicardipine, number of implants were tested. There were no notable differences with regard to laboratory values and vital signs. Overall, nicardipine implants were safe and generally well tolerated by the patients. The overall incidence of cerebral vasospasm was lower in the groups of patients treated with nicardipine implants compared to the patients in the control group who received oral nimodipine (standard of care).<sup>b</sup>

## Regulatory & Development Status

<sup>a</sup> Information provided by BIT Pharma GmbH

<sup>b</sup> Information provided by BIT Pharma GmbH

Nicardipine is not licensed as a modified release formulation implant for any indication in the EU/UK. However, it is licensed in the UK as a solution for injection for the treatment of acute life-threatening hypertension, particularly in the event of:<sup>5</sup>

- Malignant arterial hypertension/hypertensive encephalopathy
- Aortic dissection, when short acting beta-blocker therapy is not suitable, or in combination with a betablocker when beta-blockade alone is not effective
- Severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated
- As a treatment of postoperative hypertension

Nicardipine is also licensed in the UK as an oral medication for the following indications:<sup>6</sup>

- Prophylaxis of chronic stable angina in adult patients
- Mild to moderate hypertension in adult patients

Nicardipine is in phase III/II clinical development for:<sup>7</sup>

- Acute stroke
- Endovascular thrombectomy
- Cell carcinoma
- Covid-19

Nicardipine was granted orphan designation in the EU in 2020 for the treatment of non-traumatic subarachnoid haemorrhage.<sup>8</sup>

## Patient Group

### Disease Area and Clinical Need

A subarachnoid haemorrhage is most often caused by a burst blood vessel in the brain (a ruptured brain aneurysm). A brain aneurysm is a bulge in a blood vessel caused by a weakness in the blood vessel wall, usually at a point where the vessel branches off. As blood passes through the weakened vessel, the pressure causes a small area to bulge outwards like a balloon. Occasionally, this bulge can burst (rupture), causing bleeding around the brain. Around 8 out of every 10 subarachnoid haemorrhages happen in this way. A brain aneurysm does not usually cause any symptoms unless it ruptures. However, some people with unruptured aneurysms experience symptoms such as sight problems, pain on one side of the face or around the eye and persistent headaches. It is not known exactly why brain aneurysms develop in some people, although certain risk factors have been identified. These include: smoking, high blood pressure, excessive alcohol consumption, a family history of the condition, severe head injury and autosomal dominant polycystic kidney disease.<sup>9</sup>

The annual incidence of aSAH in the UK is in the order of 8-12/100,000 and at least 800-900 patients undergo either endovascular coiling or surgical clipping each year in England alone. In contrast to more common types of stroke, aSAH often occurs at a relatively young age: half the patients are younger than 60 years.<sup>10</sup> The 2020-2021 Hospital Episode Statistics (HES) for England recorded a total of 10,098 finished consultant episodes (FCEs) for SAH (i.e. stroke caused by bleeding on the surface of the brain) (ICD-10 I60), resulting in 5,883 hospital admissions, 90,697 FCE bed days and 35 day cases.<sup>11</sup> In 2020-21, HES for procedures or interventions recorded 430 FCEs for clipping of aneurysm of cerebral artery (OPCS-4 L33.2).<sup>11</sup>

### Recommended Treatment Options

For managing confirmed aneurysmal subarachnoid haemorrhage, NICE recommends:<sup>12</sup>

- Nimodipine
- Short-course tranexamic acid
- Reducing the risk of venous thromboembolism
- Fluid therapy
- Managing the culprit aneurysm

### Clinical Trial Information

<b>Trial</b>	<a href="#">NCT04269408</a> ; <a href="#">EudraCT-2017-005159-10</a> ; A Phase IIb: Randomised, Single-Blind, Safety, Tolerability, Efficacy and Pharmacokinetic Study of NicaPlant® in Aneurysmal Subarachnoid Haemorrhage Patients Undergoing Aneurysm Clipping <b>Phase II:</b> recruiting <b>Location(s):</b> 2 EU countries <b>Primary completion date:</b> May 2022 <sup>c</sup>
<b>Trial Design</b>	Randomised, parallel assignment, single-blinded
<b>Population</b>	N=40 (estimated); patients aged 18 to 75 years who have ruptured saccular aneurysm with aSAH clinical symptoms and undergoing aneurysm clipping
<b>Intervention(s)</b>	<ul style="list-style-type: none"> <li>• 10 nicardipine implants releasing 4 mg nicardipine each (total 40mg nicardipine)</li> <li>• Standard of care</li> </ul>
<b>Comparator(s)</b>	Standard of care
<b>Outcome(s)</b>	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> <li>• Incidence of moderate to severe cerebral angiographic vasospasm assessed by digital subtraction angiography [Time frame: day 8 ± 1 after aneurysm rupture]</li> <li>• Safety by adverse event recording [Time frame: through study completion, an average of 2 years]</li> </ul> <p>See trial record for full list of other outcomes.</p>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

### Estimated Cost

The cost of nicardipine implant is not yet known.

### Relevant Guidance

<sup>c</sup> Information provided by BIT Pharma GmbH

#### NICE Guidance

- NICE technology appraisal in development. Subarachnoid haemorrhage due to ruptured aneurysms (GID-NG10097). Expected date of issue to be confirmed.

#### NHS England (Policy/Commissioning) Guidance

- NHS England. Neurointerventional Services for Acute Ischaemic & Haemorrhagic Stroke. March 2018.
- NHS England. 2013 NHS Standard contract for Neurosurgery (Adult). D03/S/a.

#### Other Guidance

- Steiner et al. European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Haemorrhage. 2013.<sup>13</sup>
- American Heart Association/American Stroke Association. Guidelines for the Management of Aneurysmal Subarachnoid Haemorrhage. 2012.<sup>14</sup>

### Additional Information

BIT Pharma GmbH did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

### References

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