

**NIHR Innovation Observatory
Evidence Briefing: January 2018****Nefecon (targeted-release budesonide formulation)
for IgA nephropathy (Berger's disease)**

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LAY SUMMARY

IgA nephropathy (IgAN) also known as Berger's disease is one of the most common kidney diseases, aside from those caused by high blood pressure or diabetes. It is an autoimmune (where the immune cells attack the body) disease affecting the kidneys. IgA antibodies are molecules made by immune cells which help stop intruders from attacking the body. IgAN is caused when faulty IgA molecules get trapped in the kidneys, stopping them from working properly. The trapped IgA also causes inflammation and damage to kidneys, which may build up over years and result in kidney failure. Symptoms of IgAN are not obvious and are usually identified following blood tests. Signs of IgAN include blood and protein in the urine and high blood pressure.

Budesonide is a steroid drug which reduces inflammation. Nefecon is a new oral formulation of budesonide that is designed to specifically deliver the drug to a place in the intestine where most of the immune cells producing IgA are located. This has the potential advantage of targeting the underlying process that causes IgAN with significantly fewer side effects when compared to the generally used systemic steroids such as prednisone, (which is delivered throughout the whole body). If licenced, Nefecon has the potential to become the first disease-specific treatment for IgAN.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Primary IgA nephropathy (Berger's disease)

TECHNOLOGY

DESCRIPTION

Nefecon (PL-56) is a proprietary oral formulation designed to release the steroid drug, budesonide, in the ileum, which has a high density of Peyer's patches. This is where the majority of immunoglobulin A (IgA) antibody producing B-cells are located. Local delivery of budesonide directly to this site of action reduces the amount of side effects usually observed with systemic high dose corticosteroids.¹ Budesonide, the active drug in Nefecon, works in an immunosuppressive manner by suppressing the formation of immune complexes in patients with IgA nephropathy.²

In the completed phase IIb clinical trial (NCT01738035), Nefecon was administered to IgA nephropathy patients, as a capsule in two doses: 8mg per day (as 2x 4mg capsules) and 16mg per day (as 4x 4mg capsules) per day for 9 months.³

Nefecon does not currently have Marketing Authorisation in the EU for any indication.

The active component of Nefecon, budesonide, is licenced for use in the EU for a range of indications including asthma, Crohn's disease and ulcerative colitis.^{4, 5, 6, 7} Some examples of common adverse effects that have been reported include reduced glucose tolerance, diabetes mellitus, hypertension, sodium retention with oedema, increased potassium excretion, inactivity or atrophy of the adrenal cortex, dry mouth, dyspepsia, insomnia, fatigue, myalgia, blood cortisol decreased, palpitations.^{4, 5, 6}

INNOVATION and/or ADVANTAGES

If licensed, Nefecon has the potential to become the first disease-specific treatment for IgA nephropathy.⁸ Nefecon has the potential, through its unique delivery formulation and mechanism of action, to become the first disease-specific treatment for IgA nephropathy with the potential to delay disease progression and therefore reduce the need for dialysis or kidney transplantation.⁹ Nefecon also has the potential to provide advantages to IgA nephropathy patients by reducing the burden of systemic side effects of corticosteroids while still providing effective treatment to the localised region where most IgA producing B cells are located.¹

DEVELOPER

Calliditas Therapeutics AB (formerly Pharmalink AB)

AVAILABILITY, LAUNCH or MARKETING

Nefecon was designated Orphan Drug Status in the EU by the EMA for the treatment of primary IgA nephropathy on 18 November 2016.¹⁰

Nefecon was designated Orphan Drug Status in the USA by the FDA to slow the progression of immunoglobulin A nephropathy & delay kidney failure in patients affected by the disease on 17 May 2010.¹¹

PATIENT GROUP

BACKGROUND

IgA nephropathy (IgAN or Berger's disease) is an autoimmune kidney disease caused by the accumulation of IgA in the glomeruli of the kidneys. IgAN is thought to occur because patients have increased levels of IgA in the blood which contain less galactose than usual, resulting in these IgA being recognised as foreign bodies. Other types of antibody then attach to the faulty IgA causing the formation of an immune complex which then become stuck in the kidneys.¹² These immune complexes also attach to receptors on the surface of mesangial cells in the glomeruli of the kidneys causing the cells to grow and generate proteins, therefore reducing the kidneys capacity to function normally and filter the blood.¹³ The accumulation of these immune complexes causes inflammation and damage, which causes blood and proteins to be leaked into the urine and scar the kidneys which progresses over time. This eventually leads to end stage kidney disease where the kidneys fail, resulting in a need for kidney transplant or dialysis.¹²

Symptoms of IgAN include haematuria proteinuria, hypertension and reduced kidney function evidenced by raised creatinine levels. As IgAN does not cause any obvious symptoms, it can remain undetected for many years and the diagnosis can only be carried out through a kidney biopsy. The progression of IgAN can be highly variable between patients, resulting in a number of possible outcomes including total disease resolution, slow disease progression, slow loss of kidney function, complete kidney failure and IgAN which reoccurs after kidney transplantation.¹³ There are several complications associated with IgAN, including acute kidney failure, chronic kidney failure), nephrotic syndrome cardiovascular problems and Henoch-Schonlein purpura¹²

CLINICAL NEED and BURDEN OF DISEASE

Prevalence of IgAN is difficult to estimate as diagnosis can only be made with a kidney biopsy and many cases may go undetected.

IgA nephropathy affects males two or three times more often than females. It usually occurs in adolescents or young adults between the ages of 15-35 years. In the USA, it affects approximately 130,000 people annually.¹⁴ In Europe the prevalence is 4 patients in 10 000.¹⁰

The worldwide incidence of IgA nephropathy is estimated at 2.5 per 100,000¹⁵ and prevalence of IgA nephropathy worldwide is approximately 1.3%. IgAN is the most common cause of glomerulonephritis in the world, accounting for 25-50% of renal biopsy diagnosis.¹⁶

Approximately 20–50% of patients with IgA nephropathy progress to end-stage renal disease, and will therefore require dialysis or kidney transplant for survival, within 10–20 years of diagnosis.^{13 8, 17}

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Clinical Guideline. Chronic kidney disease in adults: assessment and management (CG182). January 2015.

- NICE Evidence Summary. Minimal change disease and focal segmental glomerulosclerosis in adults: rituximab (ES1). November 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Rituximab for the treatment of relapsing steroid sensitive nephrotic syndrome. NHS England E03/P/b. July 2015.

OTHER GUIDANCE

Kidney Disease Improving Global Outcomes. KDIGO Clinical Practice Guideline for Glomerulonephritis. June 2012

CURRENT TREATMENT OPTIONS

There is no curative therapy for IgAN and once the kidneys have been damaged, they cannot be repaired. Therefore the main aim of treatments for IgAN is to slow the progression of the disease and prevent or delay end stage kidney disease.

A consortium of kidney disease experts, Kidney Disease: Improving Global Outcomes (KDIGO), has published guidelines for the treatment of IgA nephropathy. However, none of the drugs included in the guidelines have been approved by the Regulatory Authorities specifically for the treatment of IgA nephropathy.¹⁸

There are different treatments currently used to reduce symptoms and delay disease progression:^{12, 13}

- Drugs to control blood pressure – controlling blood pressure slows the progression of kidney disease for symptomatic treatment. A combination of drugs (usually two or more medications) are usually used, including:
 - angiotensin-converting enzyme (ACE) inhibitors
 - Angiotensin receptor blockers (ARBs)
 - Beta blockers
 - Calcium channel blockers
- Diuretic medications – to help the kidneys remove extra fluid from the blood. Often taken in combination with drugs to reduce blood pressure.
- Immunosuppressive medications – to control the immune response and suppress inflammation in the kidneys, including:
 - Corticosteroids e.g. prednisone
 - Cyclophosphamide
- Cholesterol lowering medication, e.g. statins

If damage to the kidneys progresses to end stage kidney disease (ESRD) and the kidney's fail, patients will require dialysis or a kidney transplant.¹²

EFFICACY and SAFETY

Trial	NEFIGAN, NCT01738035 , EudraCT-2012-001923-11, 2012-001923-11, DRKS00006496; budesonide targeted-release (Nefecon) vs placebo; phase II trial
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Sponsor	Calliditas Therapeutics AB.
Status	Published
Source of Information	Publication ⁸ , trial registry ³
Location	10 EU countries, including the UK
Design	Randomised, double-blind, placebo-controlled
Participants	n=150; aged 18 years and older; biopsy verified primary IgA nephropathy
Schedule	<p>Participants randomised to one of three treatment arms:</p> <ol style="list-style-type: none"> 1. Nefecon 8mg/day (administered as two 4mg capsules of Nefecon per/day) plus two placebo capsules/day 2. Nefecon 16mg/day (administered as four 4mg capsules of Nefecon per/day) 3. Placebo group: four placebo capsules per day. <p>All treatment arms receive treatment for 9 months followed by a 3-month follow-up phase of which the first 2 weeks will be used to taper the dose of those patients that received 16 mg/day dosing to 8 mg/day, with the placebo and 8 mg/day groups receiving placebo to retain blinding.</p> <p>All patients will receive a maximum recommended daily dose of an ACE Inhibitor and/or ARB (angiotensin receptor blocker) (or maximum tolerated dose not exceeding the maximum recommended daily dose) for the duration of the treatment and follow-up phases.</p>
Follow-up	9 months active treatment and 3 month follow up
Primary Outcomes	Change from baseline to 9 months in urine protein creatinine ratio (UPCR)
Secondary Outcomes	<p>Change from baseline to 9 months in urine albumin creatinine ratio</p> <p>Change from baseline to 9 months in 24 hour albuminuria</p> <p>Change from baseline to 9 months in estimated GFR</p>
Key Results	Abstract stated primary endpoint was met at the pre-specified interim analysis; mean UPCR decreased by 24% (budesonide targeted release 8+16 mg/d) vs 3% increase (placebo) at 9 months (p=0.007). At final analysis, mean change in eGFR was -4.7 mL/min/1.73m ² for placebo compared with 0.32 and 1.95 mL/min/1.73m ² for budesonide targeted release 8 and 16 mg/d, respectively; difference in mean percentage change in eGFR achieved statistical significance for 8 mg/d (p=0.006) and 16 mg/d (p=0.003).
Adverse effects (AEs)	Higher adverse event rates were found in the budesonide targeted release groups (88–94%) compared to placebo (84%). Two serious adverse events were assessed as possibly related to budesonide targeted release; deteriorated renal function (in follow-up) and deep vein thrombosis.
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of Nefecon is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|---|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input checked="" type="checkbox"/> Other: <i>this drug has the potential to reduce side effects associated with high dose corticosteroid use</i> | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services: potentially reduced need to treat side effects of corticosteroids |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs: <i>company have indicated the cost of this drug may be substantial</i> | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input checked="" type="checkbox"/> Other reduction in costs: <i>Potentially reduced costs for dialysis and transplantation due to slower disease progression</i> |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

OTHER ISSUES

Clinical uncertainty or other research question identified

None identified

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