New and Emerging Technology Briefing

Fibrillex (Eprodisate disodium) for secondary amyloidosis

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Horizon Scanning Review

Early assessments of new or emerging technologies contain time-limited information and should be used with due caution.
Fibrillex (Eprodisate disodium) for secondary amyloidosis

Summary
Fibrillex (NC-503, Eprodisate disodium, sodium1,3-propanedisulfonate, 1,3-propane-disulphonic acid, 1,3-PDS), an orally active amyloid precursor protein antagonist that inhibits amyloid deposition, is in development as a new treatment for amyloid A amyloidosis in patients with underlying chronic inflammation and infection. A pivotal phase II/III randomised, placebo-controlled trial in 183 patients reported that 13.4% more of the treated group had stable or improved kidney function as compared to the placebo group (although this did not meet the primary endpoint). Secondary outcomes indicated that the progression of renal disease is delayed (5-month delay to dialysis). A three-year open-label extension to the trial is ongoing.

Developer – Neurochem.


Unit cost – To be determined.


Relevant existing UK guidance – None.

Burden of disease – AA amyloidosis is a rare but serious and potentially life-threatening condition that is a late consequence of chronic inflammatory disease (particularly rheumatoid arthritis) or infection, and for which there is currently no specific treatment. Diagnosis is often delayed and the prognosis is poor, often progressing to end-stage renal failure and death. There are an estimated 125-600 new patients diagnosed each year.

Potential clinical benefit – Research evidence suggests that fibrillex delays the progression of renal disease in adults with AA amyloidosis – thereby potentially reducing morbidity and improving quality of life. No specific alternative treatment is available.

NHS or societal resource impact – Without full results of the phase II/III trial and cost information, it is difficult to predict the potential impact of fibrillex. Evidence from the trial suggests that fibrillex may slow the progression of kidney disease and therefore may offer potential savings in delaying the need for dialysis in a small group of patients.

The technology
Fibrillex (NC-503, Eprodisate disodium, sodium1,3-propanedisulfonate, 1,3-propane-disulphonic acid, 1,3PDS) – Neurochem, is an orally active precursor protein antagonist that inhibits amyloid deposition. It is in phase II/III trials as a new treatment for amyloid A (AA) amyloidosis in patients with underlying chronic inflammation and infection, administered at
400-1,200mg twice a day. Fibrillex is a designated orphan drug in the EU and USA, and is currently preregistration in the USA.

**Burden of disease and patient group**

Reactive systemic AA amyloidosis is a metabolic disorder in which a starch-like substance called amyloid accumulates in the kidneys, liver, spleen and other tissues; progressively impairing function. AA amyloidosis can cause a diffuse range of non-specific symptoms (often delaying diagnosis), but typically presents as the progressive impairment of renal and/or gastrointestinal functions as a late complication of chronic inflammatory conditions such as rheumatoid arthritis and chronic infections such as tuberculosis.

AA amyloidosis is a rare condition, with estimates of incidence ranging from 125 to over 600 new patients per year.\(^1\) It is one of the most severe complications of rheumatoid arthritis (RA), occurring in around 5% of adults with RA in Europe,\(^2\) with a delay of around 19 years from the onset of RA.\(^3\) The prognosis is poor, with patients frequently (but gradually) progressing to end-stage renal disease and death. There was an estimated mortality from AA amyloidosis in England and Wales of 33 in 1998.\(^4\) Median survival time from diagnosis is 2-10 years\(^5\) (50% survival >4 years; 25% >10 years\(^6\)).

The National Amyloidosis Centre (at the Royal Free Hospital in London) has seen 400 patients over the last 12 years, with about 30-40 new patients seen per year.

**Current treatment and alternatives**

In the absence of a specific treatment for AA amyloidosis, clinical management relies on the treatment of the underlying inflammatory disease or infection. There is some evidence that the early control of the underlying inflammatory condition may effectively slow or even halt the progression of AA amyloidosis.\(^7,8\) A growing understanding of genetic factors which predispose to the formation of amyloid may help in the future, to identify those particularly at-risk.\(^9\)

Amyloidosis is a specialist service designated by the National Specialist Commissioning Advisory Group (NSCAG). The National Amyloidosis Centre at the Royal Free Hospital in London provides diagnostic imaging, histology and DNA analysis, genetic counselling, and clinical monitoring; and makes recommendations for treatment and evaluation of existing and new therapies for 1,000 patients per year (a doubling of activity since 1999).

**Cost**

The cost of fibrillex is yet to be determined.

**Current research evidence**
Effectiveness
A pivotal phase II/III, double-blind, placebo-controlled, multicentre (27 sites in 13 countries including the US and UK) parallel-design therapeutic trial randomised 183 adults with AA amyloidosis and renal impairment to either fibrillex (400mg, 800mg or 1,200mg twice daily) or placebo for 24 months. Renal impairment was categorised as persistent proteinuria (urinary protein excretion of >1g/24h or creatinine clearance 20-60ml/min, and serum creatinine >3mg/dl). Sixty-six per cent of the patients had rheumatological diseases. The trial results have been reported in abstract, with final analysis and formal publication planned for mid 2006.

The primary outcome was a composite assessment of renal and gastrointestinal functions defined as:

**Improved** - the occurrence of any of: the remission of nephrotic syndrome; increase in creatinine clearance (>50%); remission of chronic diarrhoea; or increase in body weight (>10%).

**Worse** - the occurrence of any of: the progression of nephrotic syndrome; reduction in creatinine clearance (>50%); progression to dialysis-dependence; development of chronic diarrhoea; decrease in body weight (>10%); or the use of rescue medication.

**Stable** - none of the above milestones met.

Secondary outcomes were (i) visceral amyloid content, (ii) amyloid content in abdominal fat tissue, and (iii) change in urinary protein excretion, serum creatinine, serum albumin, alkaline phosphatase, body weight, hepatomegaly or splenomegaly.

There were 13.4% fewer patients classified as worse in the fibrillex group compared to placebo (p=0.063), although this did not achieve the specified primary endpoint of a 20% difference (p=0.01). Fibrillex reduced by 54% the relative risk of patients doubling their creatinine clearance (p=0.027); reduced by 50% the relative risk of a 50% decrease in creatinine clearance (p=0.011); reduced the relative risk of occurrence of a first event of renal decline by 44% (p=0.021); and reduced by 46% the relative risk of progression to end-stage renal disease/dialysis (p=0.20), all compared to the placebo group. Furthermore, there was a 42% reduced risk of renal decline or all-cause mortality; a 3.6 month delay in the time required to reach double serum creatinine; a 4.4 month delay in reaching a 50% decrease in creatinine clearance; and a 5.3 month delay in progression to dialysis.

**Update:** Further analyses have been submitted by the company using the Cox proportional hazards regression model, which they consider to be more powerful for evaluating results concerning a delay to the time of an event (the primary efficacy results given above were based on analysis using the Cochran-Mantel-Haenszel test). The Cox model estimates the risk of any worse event (renal decline or death) in the treated group to be reduced to 42% of the risk for the placebo group (p=0.025). Analysis using the Kaplan-Meier method shows that the time to a first worse event was significantly longer in the treated group compared to the placebo group (p=0.016). Cox model analysis of the individual renal components of the primary composite endpoints indicates that fibrillex has a protective effect on function, as measured by a doubling of serum creatinine (relative risk 59%, p=0.019), and a ≥50% decrease in creatinine clearance (relative risk 52%, p=0.008). The delay in progression to dialysis/end-stage renal disease in the treatment group was not statistically significant (relative risk 46%; p=0.20). Secondary outcomes indicated that fibrillex slowed the rate of decline in the slope of creatinine clearance by 4.7mL/min/1.73m²/year (p=0.025).
Cost-effectiveness
No cost-effectiveness evaluations have been identified, although the company states that pharmacoeconomic modelling is in progress.

Adverse effects
The company reported that there were no significant adverse events amongst the treated group in the phase II/III trial.

Ongoing or related research
A 36-month open-label extension study to the main phase II/III clinical trial is ongoing. One hundred and ten patients have been enrolled, and will receive fibrillex for an additional 3 years. The primary outcome will be a composite assessment of clinical improvement/worsening of renal function. Improved is defined as an increase in creatinine clearance (>50%) from baseline to end of study, with no clinical milestones of worsening. Worse is defined as at least one of (a) doubling serum creatinine from baseline to the end of study, (b) >50% decrease in the creatinine clearance from baseline to end of study, normalised for body surface area, (c) progression to dialysed/end-stage renal failure by the end of the study, or (d) deaths by the end of the study. Stable is defined as one of these milestones met. Final results are expected to be published late in 2008.

Cost impact and projected diffusion
Without full results of the phase II/III trial and information on cost, it is difficult to predict the potential impact of fibrillex. Evidence from the trial suggests that fibrillex may slow the progression of kidney disease and may therefore offer potential savings in delaying the need for dialysis in some patients. The annual UK cost of peritoneal dialysis and haemodialysis are £20,000-£22,000 per person. Potential savings may also be possible from reductions in immunosuppressant drugs. There may also be potential savings due to reduced hospitalisations from side-effects associated with dialysis (infections and drug toxicity) over the potential 5-month delay that fibrillex may provide, with quality of life gains to patients and carers.

References
1 Patient Plus website, www.patient.co.uk.


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