Ranibizumab (Lucentis) for diabetic macular oedema

April 2009

This technology summary is based on information available at the time of research and a limited literature search. 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.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Ranibizumab (Lucentis) for diabetic macular oedema

Target group
- Diabetic macular oedema (DMO)

Background
Diabetic macular oedema (DMO) is a common complication associated with diabetic retinopathy and can lead to severe visual loss. Clinically significant macular oedema (CSMO) is defined as:
- Retinal thickening at or within 500µm of the fovea, and/or
- Hard exudates at or within 500µm of fovea with associated thickening, and/or
- An area of thickening the equivalent of one optic disc area or more, any part of which is within one disc diameter of the fovea.

DMO occurs mainly as a result of disruption of the blood-retinal barrier, which leads to increased vascular permeability and the accumulation of fluid within the intraretinal layers of the macula. Macular oedema is classified as either diffuse or focal. Diffuse oedema is a generalised thickening caused by extensive capillary dilation or capillary closure whilst focal oedema is associated with a leaking microaneurysm. Hypoxia due to vasoconstriction and capillary loss, up-regulates the expression of vasoproliferative factors such as vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6).

Technology description
Ranibizumab (Lucentis) is a humanised antibody fragment that binds to VEGF-A isoforms of VEGF, thereby preventing binding of VEGF-A to receptors VEGFR-1 and VEGFR-2. Ranibizumab for centre-involving DMO is administered as an intravitreal injection (IVT) with optimum dosing intervals still to be determined from ongoing trials. Ranibizumab is intended to be used either as an addition or substitute to current therapy depending on results of phase III trials.

Ranibizumab is licensed for use by specialists for the treatment of neovascular (wet) age-related macular degeneration.

Innovation and/or advantages
Ranibizumab would be the first licensed pharmacological treatment for diabetic macular oedema. Long-term clinical trials are needed to determine the number of IVT injections required to stabilise disease and whether adjunctive treatment may be required in the long run.

Developer
Novartis Pharmaceuticals UK Ltd.

Availability, launch or marketing dates, and licensing plans:
In phase III trials.

NHS or Government priority area
This topic is relevant to The National Service Framework for Diabetes (2007).

Relevant guidance

Clinical need and burden of disease
It is estimated that up to 10% of patients with diabetes develop macular oedema during their lifetime and, in the UK, it is the most common cause of visual loss in people of working age. DMO occurs more frequently in insulin dependent type 2 diabetes and appears to be more prevalent as the duration of the diabetes and the severity of the retinopathy worsens. Data from one study suggests that the incidence of DMO over a 10 year period was 20.1% in patients diagnosed before the age of 30 (younger onset) and 39.3% in patients diagnosed after 30 years (older onset). The Diabetes Control and Complications trial reported that 27% of patients develop macular oedema within 9 years of diabetes onset. In older age onset diabetes the prevalence of developing macular oedema is 3-8% within 3 years of diagnosis compared to 0.5% within 10 years of diagnosis in younger onset diabetes. In a younger onset diabetic cohort study, macular oedema was associated with a prevalence of visual impairment of 50% and blindness of 20% compared to 16% and 4% respectively in diabetics without macular oedema. If left untreated 24% of eyes with CSMO will have a moderate visual loss within 3 years.

The company estimate that approximately one third of patients with CSMO would be suitable for ranibizumab treatment.

Existing comparators and treatments
Assessment of DMO:
- Fluorescein angiography to determine factors such as pattern of fluid leakage and presence of ischaemia.
- Optical coherence tomography provides high-resolution imaging of the retina and the detection of increased retinal thickness.
- Retinal thickness analyser quantifies and monitors retinal thickness.

Management of DMO:
- Laser photocoagulation (focal or grid) is the first line of treatment as a damage limitation exercise irrespective of visual acuity, and can reduce the risk of visual loss by 50%.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>RESOLVE, NCT00284050: ranibizumab vs sham; phase II.</th>
<th>READ-2, NCT00407381: ranibizumab vs laser photocoagulation; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Novartis.</td>
<td>Johns Hopkins University; Juvenile Diabetes Research Foundation; Genentech.</td>
</tr>
<tr>
<td>Status</td>
<td>Conference abstract</td>
<td>Conference abstract</td>
</tr>
<tr>
<td>Location</td>
<td>Switzerland</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, controlled.</td>
<td>Open-label, randomised, controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=151; centre-involving DMO in at least one eye. Randomised to 3 intravitreal (IVT) injections of ranibizumab 6mg/ml, 10mg/ml or sham injection at monthly intervals.</td>
<td>n=126; centre-involving DMO; serum HbA1c &gt;5.5%; BCVA 20/40 to 20/320; foveal thickness &gt;250µm. Randomised to: Arm1</td>
</tr>
</tbody>
</table>

* An update of trial results is due to be presented at The Association for Research in Vision and Ophthalmology Annual Meeting in May 2009.
<table>
<thead>
<tr>
<th>Follow-up</th>
<th>12 months maximum treatment period.</th>
<th>18 month maximum treatment period.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td>Increased injection volume and re-treatment with allocated drug or sham injection was based on success, futility, and/or safety criteria. Photocoagulation from month 3 if required.</td>
<td>Ranibizumab 0.5ml IVT 4 times in first 6 months, then every 2 months as required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 2 Laser photocoagulation every 3 months as required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm 3 Ranibizumab 0.5ml every 3 months with laser photocoagulation, both as required.</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>Best corrected visual acuity (BCVA); central retinal thickening (CRT).</td>
<td>≥15 letter gain in BCVA or final vision of ≥50 letters (20/25) if baseline visual acuity was 40 letters; retinal thickness.</td>
</tr>
<tr>
<td>Key results</td>
<td>Injection volume doubled in 73%, 65% and 92% for ranibizumab 6mg/ml, 10 mg/ml and sham respectively. Photocoagulation rescue treatment required in 9% with ranibizumab and 33% with sham. Mean change in BCVA at month 12 was +11.8 letters, +8.8 letters and -1.4 letters for ranibizumab 6mg/ml, 10 mg/ml and sham respectively. There was a continual decrease in mean CRT with ranibizumab.</td>
<td>At 6 months: mean gain of 7.62 letters, loss of 1.07 letters and mean gain of 3.8 letters (p=0.001) for ranibizumab 0.5ml; laser photocoagulation; and ranibizumab 0.5ml with laser photocoagulation respectively. Mean reduction in foveal thickness of -56.55%, -10.79% and -41.82% (p=0.044) respectively.</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Most frequent ocular AEs: conjunctival haemorrhage in 23% vs 14% for ranibizumab and sham respectively; eye pain in 18% vs 20% respectively. Serious AEs in 1 sham (retinal detachment) and 4 ranibizumab patients (endophthalmitis, transient retinal artery occlusion, peripheral retinal ischemia). Non-ocular arterial thromboembolic events in 2 sham and 3 ranibizumab (10mg/ml) patients.</td>
<td>No serious adverse events reported.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00444600: laser-ranibizumab-triamcinolone; phase III.</th>
<th>RESTORE, NCT00687804: ranibizumab vs sham; phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>National Eye Institute; Allergan; Genentech.</td>
<td>Novartis.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Recruiting.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>EU (inc UK), Canada, Australia and Turkey.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, controlled.</td>
<td>Double-blind, randomised, controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=691; centre-involving DMO in at least one eye; best corrected Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS) visual acuity letter score ≤78 and ≥24; OCT central subfield ≥240µm. Randomised to: Arm 1 Sham injection + laser photocoagulation 1 week post injection. Injection repeated every 4 weeks with focal photocoagulation every 16 weeks. Arm 2</td>
<td>n=315; centre-involving DMO in at least 1 eye; visual acuity impairment. Randomised to 0.5mg ranibizumab + sham laser, sham injection + laser photocoagulation, or 0.5mg ranibizumab + laser photocoagulation. Ranibizumab given as required, after 3 initial monthly injections. Laser given as required, with at least 3 months between treatments.</td>
</tr>
</tbody>
</table>
Ranibizumab 0.5mg IVT + laser photocoagulation 1 week post-injection. Injection repeated every 4 weeks with focal photocoagulation every 16 weeks.  

**Arm 3:**  
Ranibizumab 0.5mg IVT every 4 weeks. Laser photocoagulation at 24 weeks if no improvement (deferred laser).  

**Arm 4:**  
Triamcinolone acetonide 4mg IVT + photocoagulation laser 1 week-post injection, repeated every 16 weeks with sham injections at 4-week intervals in-between. Re-treatment at 16 weeks (all arms) depends on visual acuity and OCT.  

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>12 months treatment period.</th>
<th>12 month treatment period with 1 year open label extension for all groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Visual acuity.</td>
<td>Mean change in BCVA.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Retinal thickening and retinal volume; number of injections in first year.</td>
<td>Improvement in BCVA; time course of BCVA changes; change in retinal thickness and other anatomical changes; patient-reported outcomes (EQ-5D, VFQ-25).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>RIDE, NCT00473382: ranibizumab vs sham; phase III.</th>
<th>RISE, NCT00473330: ranibizumab vs sham; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Genentech.</td>
<td>Genentech.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>USA.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=366; centre-involving DMO; BCVA 20/40-20/320; central foveal thickness ≥275µm. Randomised to IVT ranibizumab 0.3mg, 0.5mg or sham injection repeated monthly.</td>
<td>n=366; centre involving DMO; BCVA 20/40-20/320; central foveal thickness ≥275µm. Randomised to IVT ranibizumab 0.3mg, 0.5mg or sham injection repeated monthly.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>24 month treatment period.</td>
<td>24 month treatment period.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>≥15 letter gain in BCVA.</td>
<td>≥15 letter gain in BCVA.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Mean change in BCVA; foveal thickness; leakage; mean laser treatments; mean change in National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) distance activities; three-step change in ETDRS; NEI VFQ-25 near activities; Retinopathy Dependent QoL (RetDQoL).</td>
<td>Mean change in BCVA; in foveal thickness; leakage; mean laser treatments; mean change in NEI VFQ-25 distance activities; three-step change in ETDRS; NEI VFQ-25 near activities; RetDQoL.</td>
</tr>
</tbody>
</table>

**Estimated cost and cost impact**  
The cost of ranibizumab for this indication is not yet known.
Potential or intended impact – speculative

Patients

☑ Reduced morbidity
☐ Reduced mortality or increased length of survival
☑ Improved quality of life for patients and/or carers
☐ Other:
☐ None identified

☑ Quicker, earlier or more accurate diagnosis or identification of disease

Services

☐ Increased use
☐ Service reorganisation required
☐ Staff or training required
☐ Decreased use
☑ Other: Uncertain impact compared to the need for laser photocoagulation.
☐ None identified

Costs

☐ Increased unit cost compared to alternative
☑ New costs: Additional treatment option.
☐ Increased costs: more patients coming for treatment
☐ Savings:
☐ Increased costs: capital investment needed
☐ Other:
☐ None identified

Other:

None identified

Quicker, earlier or more accurate diagnosis or identification of disease

Services

Increased use
Service reorganisation required
Staff or training required
Decreased use
Other: Uncertain impact compared to the need for laser photocoagulation.
None identified

Costs

Increased unit cost compared to alternative
New costs: Additional treatment option.
Increased costs: more patients coming for treatment
Savings:
Increased costs: capital investment needed
Other:
None identified

References

The National Institute for Health Research National Horizon Scanning Centre Research Programme is funded by the Department of Health.
The views expressed in this publication are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health

The National Horizon Scanning Centre,