Part 2: An explanation of the background to the treatment of wet AMD patients within the NHS

Wet Age Related Macular Degeneration – wet AMD is the most common cause of blindness in the United Kingdom. Wet AMD develops when abnormal blood vessels grow into the macula. These leak blood or fluid which leads to scarring of the macula and rapid loss of central vision. Wet AMD can develop very suddenly but it can now be treated if caught quickly. Fast referral to a hospital specialist is essential.

The prevalence of late AMD in the UK among people aged 50 years or over is 2.4% (from a meta-analysis applied to UK 2007–09 population data). This increases to 4.8% in people aged 65 years or over, and 12.2% in people aged 80 years or over. The same study found the prevalence of geographic atrophy to be 1.3 to 6.7%, and the prevalence of neovascular AMD to be 1.2 to 6.3%. Estimates indicate that around 39,800 people develop neovascular AMD in the UK each year; given a total UK population of 60 million, this equates to 663 new cases per million per year.

The large number of patients who suffer from wet AMD means that decisions about how wet AMD is to be treated hugely significant the NHS, simply because they affect so many patients each of whom has costly treatments.

Wet AMD is treated by anti-VEGF drugs which are injected directly into the patient's eye at regular intervals. The first anti-VEGF agent to be used in this way was a drug produced by Roche, marketed as Avastin, of which the active ingredient is bevacumizab. Avastin was originally developed for the treatment of colorectal cancer. It was approved for that purpose by the US Food and Drug Administration in 2004, and subsequently for treatments of other cancers, and it is now widely licensed for such purposes internationally. It was licensed by the European Medicines Agency for such use in the EU in January 2005. The use of Avastin for the wholly different purpose of treating Wet AMD was initially experimental but soon became widespread, principally in the US and in developing countries but also to some extent in Europe, including the UK.

The vials of Avastin sold for cancer use are far larger than are required to treat wet AMD patients. The amount required for injection into the eye - known as intravitreal use - is no more than 0.1ml per injection. Avastin is provided in 4ml vials. Accordingly, throughout the world, a process of "compounding", also known as aliquoting, has been developed under which, in sterile circumstances, a single file of Avastin is subdivided into much smaller doses which then become suitable for intravitreal use. We will refer to this process as compounding and the resulting drug is known as compounded bevicuzamab or "CB".

As Lord Justice Underhill observed in the judgment of the Court of Appeal:

> *"At the root of the issues in this case is the fact that Roche has never applied, whether to the FDA or by way of an EU marketing authorisation, to vary the licence for Avastin to cover its use for the treatment of WAMD; indeed its formal "Summary of Product Characteristics" ("SMPC") says in terms that it is "not formulated for intravitreal use".*

Two other anti-VEGF drugs have been developed specifically for ocular use - and thus specifically tailored for treating wet AMD patients. Lucentis was developed by Roche, but another pharmaceutical company, Novartis, is licensed by Roche to market this drug in Europe. Thus, the ultimate intellectual property rights in two of the three drugs involved in this case are held by the same company, namely Roche, albeit that Roche does not market Lucentis in the UK - since that drug is marketed by Novartis. Lucentis was granted a marketing authorisation by the EMA - the European Medicines Agency - in 2007.

The third relevant drug is Eylea which was developed by Bayer and received an EU marketing authorisation in 2012.

Until this case, there was relatively little use of compounded bevicuzamab - CB - by NHS organisations. However, CB is used routinely by hospitals operating in the private sector in the United Kingdom. That has been the position for many years. The same

ophthalmologists often work in the public and private sector. The evidence in this case showed that ophthalmologists used CB to treat wet AMD patients in the private sector but used either Lucentis or Eylea when treating NHS patients.

The primary reason for this difference in practice is the cost. The list prices for Lucentis is around £550 per injection, and the list price cost of Eylea is around £800 per injection, although confidential discounts are provided from these list prices for NHS purchasers. In contrast, CB can be purchased from compounders for approximately £28 per injection. Typically treatment for a wet AMD patient will involve a course of about 10 injections per year. Given the large number of wet AMD patients, and even taking account of the discounts, the difference in cost between the drugs will result in very substantial savings for the NHS if they are allowed to prescribe CB.

There has been a strong professional lobby over a number of years in favour of the use of CB for wet AMD patients because it has been proven to be clinically effective and a more cost-effective medicine. In 2014 the Royal College of Ophthalmologists came out firmly in favour of its members being able to use CB. There were articles in the British Medical Journal in November 2014 urging the government to remove the hurdles to the use of Avastin in the NHS. However, in 2015 the Secretary of State wrote to clinical commissioning groups setting out his view it would be a breach of European law for the NHS to prefer using a drug outside of the terms of its marketing authorisation if an alternative drug was available for use within the terms of a relevant marketing authorisation. That letter, in effect, dissuaded many CCGs from adopting policies in favour of the use of CB for NHS patients.

In January 2018 the National Institute for Health and Care Excellence – known as NICE - published guideline NG 82 on the diagnosis and management of age-related macular degeneration. That guidance reviewed the use of all three drugs that were routinely used for wet AMD patients, namely CB, Lucentis and Eylea. NICE concluded that there were "*no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments that have been seen in trials considered by the guideline committee*". However

the NICE guidance was expressed in measured terms because of the legal uncertainty which existed at that time about the use of drugs outside the terms of their marketing authorisation where there were licence alternatives available. It appears that, at that point, the MHRA were sticking to the line which had been set out by the secretary of state in 2015 but it was unlawful under EU law to do so.

A further complication in this area was the issue of NICE Technology Appraisal Guidelines - known as "TAGs" - in respect of both Lucentis and Eylea. These apply for defined categories of wet AMD patients. The legal effect of NICE producing a TAG is that an NHS patient who falls within the clinical criteria defined in the TAG has an absolute right to require the NHS to fund the recommended treatment for the patient. Thus a wet AMD patient whose clinical condition had progressed sufficiently to come within the terms of the TAG, is entitled to insist on being treated with either Lucentis or Eylea. The choice lies with the patient and that choice cannot be removed by an NHS organisation.

However, the CCGs argued in this case that, in law, there was nothing to prevent an NHS body from offering a wet AMD patient the opportunity to be treated with a different drug which is not the subject of a NICE TAG, provided the patient is not prevented from being able to choose either Lucentis or Eylea. Thus, if it is lawful to do so, it will not breach the terms of the TAG system to offer wet AMD patients the chance of being treated with CB as opposed to choosing to be treated with either Lucentis or Eylea.

Prior to this case, the position was therefore in summary as follows. The NHS was being required to purchase either Lucentis or Eylea for every wet AMD patient - at a cost of several hundred pounds per injection - despite the fact that there was an equally safe and equally clinically effective alternative option available, namely CB, at a cost of about £28 per injection. It was the law, not medicine, which was perceived to prevent the NHS being able to deliver far more cost-effective medicine through offering wet AMD patients the chance to be treated with CB.

Assuming the NICE assessment was correct, wet AMD patients would not suffer any detriment by being treated with CB as opposed to receiving either Lucentis or Eylea. The beneficiaries of a switch of drug would other NHS patients in other specialties because the money saved could fund more nurses, more mental health treatment or more treatment in other areas. It may even allow more wet AMD patients to be treated who are outside the scope of the NICE TAGs were therefore lawfully refused treatment at present.

If it was lawful to do so, the business case was clear that NHS bodies could make substantial savings by switching patients from Lucentis or Eylea to CB. However, any wholesale switch away from Lucentis or Eylea would clearly affect both the income and profits of the pharmaceutical companies that were selling these drugs. Thus the stage was set for an NHS organisation to have the courage to test the legality of encouraging wet AMD patients to choose CB rather than Lucentis or Eylea.

In the next section of this podcast we will explain how the CCG's in the north-east of England rose to that challenge.