NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA274; Ranibizumab for treating diabetic macular oedema

This guidance was issued in April 2013.

The review date for this guidance is February 2015.

1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Original remit(s)

To appraise the clinical and cost effectiveness of ranibizumab within its licensed indication for the treatment of diabetic macular oedema.

3. Current guidance

1.1 Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment **and**
- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.

1.2 People currently receiving ranibizumab for treating visual impairment due to diabetic macular oedema whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop

4. Rationale[1]

The new evidence identified from the literature searches and registered trials does not indicate that a review of the recommendations in technology appraisal 274 is needed, and the marketing authorisation and price has not changed. It is therefore proposed that technology appraisal guidance 274 is transferred to the 'static guidance list'.

[1] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

5. Implications for other guidance producing programmes

There is no proposed or ongoing guidance development that overlaps with this review proposal

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2008 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

The marketing authorisation for ranibizumab at the time of developing technology appraisal 274 was for 'the treatment of visual impairment due to diabetic macular oedema in adults', and has not changed. The company has confirmed that ranibizumab is not likely to receive an extension for treating diabetic macular oedema. In September 2014, the Summary of Product Characteristics (SPC) for ranibizumab was updated to suggest that the frequency of monitoring should be 'as-needed' rather than 'monthly'.

The current list price in the British National Formulary 68 for ranibizumab has not altered since the development of NICE technology appraisal 274. Novartis has indicated it intends to continue the Patient Access Scheme for ranibizumab without any change. The administration cost of the laser (NHS reference cost BZ23Z) has not changed.

Since the development of technology appraisal 274, 2 potential comparators, aflibercept and dexamethasone have gained marketing authorisations for the treatment of diabetic macular oedema. The therapeutic indication for aflibercept is for the same as for ranibizumab. Dexamethasone is licensed for a narrower patient population than ranibizumab, that being for the treatment of 'visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy'. Dexamethasone and aflibercept are both currently undergoing NICE appraisal for treating diabetic macular oedema.

The literature searches for ranibizumab identified 13 relevant references, published since the development of NICE technology appraisal 274.

The Committee for technology appraisal 274 noted there was no evidence of additional benefit in adding laser photocoagulation to ranibizumab, but that this was inconsistent with the expectations of the clinical specialists. In the evidence search, 3 trials were identified that may address this question:

- The READ-2 follow-up trial (Do et al., 2013) compared the treatment of diabetic macular oedema with 0.5mg ranibizumab alone (n=28 patients), laser alone (n=22 patients) or the two treatments in combination (n=24 patients), if foveal thickness was at least 250µm. The results showed that mean improvement from

baseline in best-corrected visual acuity (BCVA) and foveal thickness (FTH) in the ranibizumab alone group was significantly better than the other 2 treatment groups. The changes from baseline in BCVA and FTH were not significantly different in the laser alone or combination group.

- The Jiang, et al., 2014 12 week study compared ranibizumab alone (n=30 eyes in 30 patients) with ranibizumab plus laser (n=30 eyes in 30 patients), for treating diabetic macular oedema. The BCVA and central macular thickness (CMT) were measured by optical coherence tomography and post-operative complications were observed. In the ranibizumab alone group, the BCVA decreased over the 12 week trial and the CMT increased, but this increase was reported as being better than the results before treatment, although no data were available. The study also reported that this group of patients showed a downward trend in BCVA results but that the CMT rose in the follow-up period. For the ranibizumab plus laser treatment group the BCVA decreased over the 12 weeks and the CMT rose but according to the study, these results were significantly better than those of the ranibizumab alone group ($p<0.05$).
- A third study (Mitchell, P et al., 2013) compared the treatment of diabetic macular oedema with ranibizumab plus sham laser (n=116), ranibizumab plus laser (n=118) or sham injections plus laser (n=111). At 12 months the mean composite scores, calculated using National Eye Institute Visual Functioning Questionnaire 25, improved significantly for ranibizumab plus sham laser and for ranibizumab plus laser, each compared with laser alone, but not in the sham injections plus laser group Close up and distant activities also significantly improved for the 2 ranibizumab groups but not the laser group. Overall patients with better baseline visual acuity or lower central retinal thickness had greater improvements with ranibizumab than those with worse baseline visual acuity or higher central retinal thickness. No data was presented comparing ranibizumab plus sham laser with ranibizumab plus laser.

This evidence does not provide enough information to indicate a review should be carried out to determine if ranibizumab plus laser produces significantly better results than ranibizumab alone.

During technology appraisal 274 the Committee also noted that there was a lack of evidence for the treatment of vision with ranibizumab in both eyes and the Committee was uncertain about how the effects demonstrated in the trials would translate into benefits for people in clinical practice. In the trial by Nepomuceno et al., (2013) 48 patients (63 eyes) received either 0.5mg ranibizumab or 1.5mg bevacizumab as a treatment for diabetic macular oedema, if central subfield thickness was greater than 275µm, measured with spectral-domain optical coherence tomography. No data was provided on whether there was a difference in the results when people had 1 or both eyes treated. A case study of a patient who received ranibizumab to treat diabetic and cystoid macular oedema was described by Rotsos, et al., (2014). The patient had diabetic and cystoid macular oedema in both eyes but only the left eye was treated with 2 ranibizumab (0.5mg) injections. Spectral-domain optical coherence tomography indicated that there was an improvement in both eyes although only one eye had been treated. No statistical analyses were provided for the comparison of the 2 eyes. These studies do not provide robust evidence to address the Committee's concern.

Although bevacizumb was considered as a comparator in the scope for technology appraisal 274, the Committee considered that further research directly comparing the clinical and cost effectiveness of ranibizumab and bevacizumab in people with diabetic macular oedema was required to reduce the uncertainties of whether bevacizumab should be a comparator. These uncertainties included the balance between harms and benefit of bevacizumab and the effectiveness of bevacizumab compared with ranibizumab for treating diabetic macular oedema. As described above, Nepomuceno et al., (2013) compared ranibizumab and bevacizumab for the treatment of diabetic macular oedema. A significant improvement in BCVA was observed in both groups ($p<0.05$) with the improvement being significantly greater with ranibizumab than with bevacizumab at weeks 8 ($p=0.032$) and 32 ($p=0.042$). A significant reduction in mean central subfield thickness was observed in both groups ($p<0.05$) with no significant difference between groups. Two other trials were identified, which compared the treatment of diabetic macular oedema with ranibizumab or bevacizumab (Ekinciet al., 2014 and Lang et al., 2014). The first trial concluded that bevacizumab was as effective as ranibizumab when observing visual acuity and foveal thickness but that bevacizumab required fewer injections. The second study (Lang et al., 2014) discussed the observation that bevacizumab but not ranibizumab may accumulate in the retinal and pigment endothelial cells during prolonged treatment and that long term side effects should be observed.

There is not enough consistent evidence to allow a review of this particular question.

The clinical effectiveness evidence identified from the literature searches, registered trials and current list prices of the technologies do not suggest the recommendations of technology appraisal 274 need reviewing. Based on the above information, it is proposed that technology appraisal guidance 274 is transferred to the ‘static guidance list’.

8. Implementation

A submission from Implementation is included in Appendix 3.

Limited data is available on the volume of ranibizumab prescribing in England between October 2010 and June 2014. The ePACT data suggests that less than 15 items were dispensed in this period suggesting ranibizumab is not regularly prescribed in primary care or by hospitals for dispensing in the community.

This is insufficient evidence to make any firm conclusion on the adherence to NICE technology appraisal guidance 274, or whether there is regional variation in clinical practice in England.

9. Equality issues

During the scoping phase of the appraisal, NICE had received evidence that some people in full-time residential care had restricted access to treatment for diabetic macular oedema. However, consultees suggested that the national screening programmes for diabetic retinopathy in England and Wales has reduced this inequality across the NHS. In submissions, the Committee had been made aware that there is a higher prevalence of diabetes in people of South Asian, African and African–Caribbean family origin and that, among people with diabetes, sight-

threatening eye disease is more common in people of African and African–Caribbean family origin than in white Europeans. However, the Committee agreed that this was an issue that could not be addressed in a technology appraisal.

GE paper sign off: Elisabeth George, Associate Director, 29 01 15

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment

- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed

- The treatment is excluded from the Payment by Results tariff

v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

NICE technology appraisals TA301 Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (rapid review of technology appraisal guidance 271). Published: November 2013 Review date: November 2016

NICE technology appraisals TA283 Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion. Published: May 2013 Review date: March 2016

NICE technology appraisals TA271 Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema after an inadequate response to prior therapy Published: January 2013 Review date: November 2015

NICE technology appraisals TA305 Aflibercept for treating visual impairment caused by macular oedema secondary to central retinal vein occlusion Published: February 2014 Review date: February 2017

In progress

Single technology appraisal Aflibercept for treating diabetic macular oedema. Referral date: July 2014. Anticipated publication date: June 2015

Single technology appraisal Dexamethasone intravitreal implant for treating diabetic macular oedema. Referral date: February 2014. Anticipated publication date: April 2015

Suspended/terminated

Pegaptanib sodium for the treatment of diabetic macular oedema. NICE was informed by the manufacturer of Pegaptanib, Pfizer, that they had withdrawn their licensing application for the above indication. Therefore this appraisal topic was suspended. July 2011

Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
The list price of ranibizumab was £742.17 per vial (excluding VAT; 'British national formulary' [BNF] edition 64).	The list price of ranibizumab is £742.17 per vial (excluding VAT; 'British national formulary' [BNF] edition 68). Novartis have indicated they intend to continue the Patient Access Scheme for ranibizumab without any change.

Registered and unpublished trials

Trial name and registration number	Details
A Randomized, Double-masked Study With Intraocular Anti-VEGF (Avastin®/Lucentis®) Compared With Intraocular Triamcinolone (Volon A®) in Patients With Clinical Significant Diabetic Macular Edema (NCT00682539)	Estimated Enrolment: 60 Estimated Study Completion Date: December 2014 This study is currently recruiting participants
Evaluation of an Additional Therapeutic Approach to Diabetic Macular Edema by Combining Standard Therapy (Intravitreal Injection of a VEGF-inhibitor) With Micropulse Diode Laser Treatment in a Randomized, Controlled Proof of Concept Study (NCT02059772)	Estimated Enrolment: 50 Estimated Study Completion Date: January 2017 This study is currently recruiting participants
A Randomized, Open-label Non-inferiority Study to Compare Safety and Efficacy of Labeled Versus Wait and Extend Regimen of Lucentis (Ranibizumab) in Turkish Patients With Visual Impairment Due to Diabetic Macular Edema.(NCT02262260)	Estimated Enrolment: 104 Estimated Study Completion Date: October 2016 This study is not yet open for participant recruitment
A 12-month, Randomized, Double-masked, Multicenter, Laser-controlled Phase III Study Assessing the Efficacy and Safety of 0.5 mg Ranibizumab Dosed PRN in Subjects With Visual Impairment Due to Diabetic Macular Edema in Chinese Patients (NCT02259088)	Estimated Enrolment: 380 Estimated Study Completion Date: March 2017 This study is not yet open for participant recruitment.
Evaluation of ReAding Speed, Contrast Sensitivity, and Work Productivity in Working Individuals With Diabetic Macular Edema Following Treatment With Intravitreal Ranibizumab (NCT02107131)	Estimated Enrollment: 60 Estimated Primary Completion Date: May 2015 This study is not yet open for participant recruitment
A 24 Month Open-label, Multicenter, Phase IIIb Study of the Efficacy and Safety of Lucentis® (Ranibizumab 0,5mg) in Diabetic Patients With Visual Impairment Due to Macular Edema Evaluating a Spaced Out Follow-up After Intensive Loading Phase (NCT02032173)	Estimated Enrolment: 155 Estimated Study Completion Date: February 2017 This study is currently recruiting participants

Trial name and registration number	Details
Treatment for Central-Involved Diabetic Macular Edema in Eyes With Very Good Visual Acuity (NCT01909791)	Estimated Enrollment: 702 Estimated Study Completion Date: March 2017 This study is currently recruiting participants

References

Bressler, N. M., et al., (2014). Vision-Related Function after Ranibizumab Treatment for Diabetic Macular Edema: Results from RIDE and RISE. *Ophthalmology* 121 (12) 2461-2472

Brown, D. M., et al., (2013). Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* 120 (10) 2013-2022

Comyn, O., et al., (2014). A randomized trial to assess functional and structural effects of ranibizumab versus laser in diabetic macular edema (the LUCIDATE study). *American Journal of Ophthalmology* 157 (5) 960-970

Do, D. V., et al (2013). Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. *JAMA Ophthalmology* 131 (2) 139-145Ekinci, M., et al (2014). Treatment of macular edema in diabetic retinopathy: Comparison of the efficacy of intravitreal bevacizumab and ranibizumab injections. *Expert review of ophthalmology* 9 (2) 139-143Jiang, H.-L., et al., (2014). Efficacy of intravitreal ranibizumab injection combined with macular grid photocoagulation for diabetic macular edema. *International Eye Science* 14 (7) 1253-1256Lang, G. E., et al., (2013). Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: Interim analysis of the restore extension study**.** *Ophthalmology*.120 (10) 2004-2012

Lang, G. E., et al., (2014). Treatment of diabetic macular oedema with the VEGF inhibitors ranibizumab and bevacizumab: conclusions from basic in vitro studies**.** *Klinische Monatsblatter fur Augenheilkunde* 231 (5) 527-534

Mitchell, P., et al., (2013). Patient-reported visual function outcomes improve after ranibizumab treatment in patients with vision impairment due to diabetic macular edema randomized clinical trial**.** *JAMA Ophthalmology*.131 (10) 1339-1347

Nepomuceno, A. B., et al., (2013). A prospective randomized trial of intravitreal bevacizumab versus ranibizumab for the management of diabetic macular edema. American Journal of Ophthalmology 156 (3) 502-510

Reznicek, L., et al., (2013). Ranibizumab in diabetic macular edema. Evaluation of functional and morphological aspects. Ophthalmologe.110 (7) 645-653

Rotsos, T., et al., (2014). Significant reduction of diabetic macular edema following intravitreal ranibizumab injection in the fellow eye. International Ophthalmology 34 (6) 1271-1274

Schmidt-Erfurth, U., et al., (2014). Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. Ophthalmology 121 (5) 1045-1053

Appendix 3 – Implementation submission

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Contents

1. Routine healthcare activity data

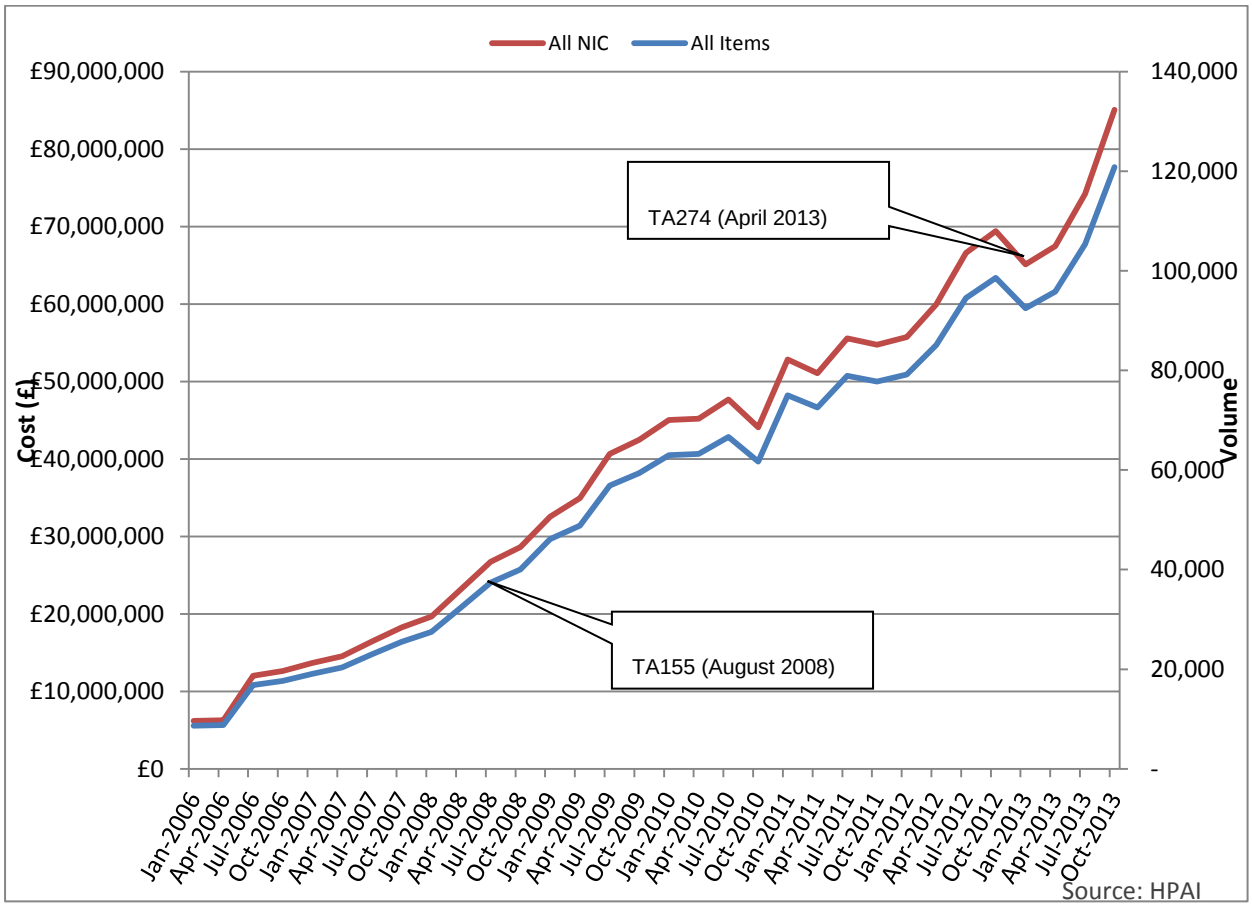
1.1. ePACT data

FP10 and FP10HP cost and volume prescribing data in England for Ranibizumab was extracted for the period October 2010 – June 2014. Less than 15 items were dispensed in the period, suggesting Ranibizumab is not regularly prescribed in primary care or by hospitals for dispensing in the community.

1.2. Hospital Pharmacy Audit Index data

This section presents Hospital Pharmacy Audit Index (HPAI) data on the net ingredient cost (NIC) and volume of Ranibizumab prescribed and dispensed in hospitals by hospital pharmacies between January 2007 and December 2013 in England.

Figure 1 Cost and volume of Ranibizumab prescribed and dispensed in hospitals in England



2. Implementation studies from published literature

Information is taken from the uptake database website.

Richards, M (2010) Extent and causes of international variation in drug usage: A report for the Secretary of State for Health by Professor Sir Mike Richards CBE
Description: This report looks at medicines usage between countries, using IMS Health data. The WHO defined daily dose or the maximum or prescribed daily dose was used to measure usage. Results rank the UK relative to other countries usage and present calculations showing how close or otherwise the UK is to the average use across groups of other countries. It should be noted that countries other than the UK would not be expected to adhere to NICE guidance making comparisons between countries not possible.

3. Qualitative input from the field team

The implementation field team have recorded the following feedback in relation to this guidance:

Feedback	Date
Medical Director of leading eye hospital very pleased with TA274 macular oedema ranibizumab. It is good guidance and confirms what they knew. They are currently discussing it with their commissioners.	18/04/2013
Some calculation had been done in respect of the treatment of macular oedema using aflibercept and other alternatives but from a baseline of no effective treatment having been implemented previously such as ranibizumab and dexamethasone. Southampton hospital trust calculated that the setting up of a service would need to deliver 5300 injections per annum to meet demand in its catchment area alone. The NICE costing tools had proven very helpful in supporting this work. However no exploration of the potential impact of patients avoiding worsening sight and, potentially, blindness had been carried out.	04 06 2014
TA155 Macular degeneration (age-related) - ranibizumab and pegaptanib has given the PCT some cost pressures.	legacy
TA155 Macular degeneration (age-related) - ranibizumab and pegaptanib has not caused difficulties expect in terms of delivery and capacity but this is not unique to this Trust.	legacy
TA155 Ranibizumab (Lucentis) - "has given us a lot of problems" presumably by forcing the PCT to fund the more expensive Lucentis over Avastin.	legacy
TA155 Ranibizumab:- ophthalmology clinical lead expressed disappointment that NICE has not been asked to undertake some kind of comparative appraisal of ranibizumamb and bevacizumab. On clinical/cost effectiveness grounds there seems to be a prima facie case for doing so.	17/06/2013

Appendix A: Healthcare activity data definitions

ePACT

Prescribing analysis and cost tool system

This information comes from the electronic prescribing analysis and cost tool (ePACT) system, which covers prescriptions by GPs and non-medical prescribers in England and dispensed in the community in the UK. The Prescription Services Division of the NHS Business Services Authority maintains the system. PACT data are used widely in the NHS to monitor prescribing at a local and national level. Prescriptions dispensed in hospitals or mental health units, and private prescriptions, are not included in PACT data.

Measures of prescribing

Prescription Items: Prescriptions are written on a prescription form. Each single item written on the form is counted as a prescription item. The number of items is a measure of how many times the drug has been prescribed.

Cost: The net ingredient cost (NIC) is the basic price of a drug listed in the drug tariff, or if not in the drug tariff, the manufacturer's list price.

Data limitations (national prescriptions)

PACT data do not link to demographic data or information on patient diagnosis. Therefore the data cannot be used to provide prescribing information by age and sex or prescribing for specific conditions where the same drug is licensed for more than one indication.

IMS HEALTH Hospital Pharmacy Audit Index

IMS HEALTH collects information from pharmacies in hospital trusts in the UK. The section of this database relating to England is available for monitoring the overall usage in drugs appraised by NICE. The IMS HPAI database is based on issues of medicines recorded on hospital pharmacy systems. Issues refer to all medicines supplied from hospital pharmacies to: wards; departments; clinics; theatres; satellite sites and to patients in outpatient clinics and on discharge.

Measures of prescribing

Volume: The HPAI database measures volume in packs and a drug may be available in different pack sizes and pack sizes can vary between medicines.

Cost: Estimated costs are also calculated by IMS using the drug tariff and other standard price lists. Many hospitals receive discounts from suppliers and this is not reflected in the estimated cost.

Costs based on the drug tariff provide a degree of standardization allowing comparisons of prescribing data from different sources to be made. The costs stated in this report do not represent the true price paid by the NHS on medicines. The

estimated costs are used as a proxy for utilization and are not suitable for financial planning.

Data limitations

IMS HPAI data do not link to demographic or to diagnosis information on patients. Therefore, it cannot be used to provide prescribing information on age and sex or for prescribing of specific conditions where the same drug is licensed for more than one indication.