Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

aflibercept 40mg/mL solution for intravitreal injection (Eylea®)

SMC No. (857/13)

Bayer plc

08 March 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

aflibercept (Eylea®) is accepted for use within NHS Scotland.

Indication under review: in adults for the treatment of neovascular (wet) age-related macular degeneration.

In two pivotal randomised controlled studies the non-inferiority of aflibercept versus monthly injections of another anti-VEGF treatment was demonstrated for the primary endpoint; proportion of patients who maintained vision at week 52.

The economic analysis submitted by the company related to the use of aflibercept in patients with wet AMD who have not previously been treated with anti-VEGF therapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of aflibercept. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In adults for the treatment of neovascular (wet) age-related macular degeneration.

Dosing Information

Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections.

The recommended dose is aflibercept 2mg, equivalent to 50 microlitres as an intravitreal injection. Aflibercept treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with aflibercept, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

Product availability date

5 December 2012

Summary of evidence on comparative efficacy

Neovascular age-related macular degeneration (AMD) is characterised by vision loss resulting from the abnormal growth and leakage of blood vessels in the macula. Around 10% of AMD patients have this neovascular (or wet) form where a localised inflammatory response and release of vascular endothelial growth factor (VEGF) induces choroidal neovascularization (CNV). Aflibercept is an anti-VEGF therapy that binds to VEGF-A, preventing it from interacting with its receptors. It is the third anti-VEGF agent licensed for the treatment of neovascular AMD. [1] In 2008 the National Institute for Health and Clinical Excellence (NICE) multiple technology appraisal recommended ranibizumab as an option for the treatment of wet age-related macular degeneration and did not recommend pegaptanib. [2]

Two pivotal multi-centre, randomised, double-masked phase III studies (VIEW 1 and VIEW 2) have been conducted in patients aged ≥50 years, with a subfoveal CNV lesion secondary to AMD. Subfoveal CNV was defined as presence of subfoveal neovascularisation including juxtafoveal lesions that affect the fovea as evidenced by fluorescein angiography in the study eye. [1] Patients were randomised equally to fixed dose intravitreal injections of either aflibercept 2mg every 4 weeks; aflibercept 0.5mg every 4 weeks; aflibercept 2mg every 8 weeks (after three 4-weekly injections); or ranibizumab 0.5mg every 4 weeks for 52 weeks. The primary endpoint was the proportion of patients who maintained vision at week 52, where a patient was classed as maintaining vision if they lost <15 letters in the Early Treatment Diabetic Retinopathy Study Group (ETDRS) letter score from baseline.

Non-inferiority was tested in a conditional sequence (ranibizumab versus aflibercept 2mg every 4 weeks, then versus aflibercept 0.5mg every 4 weeks then versus aflibercept 2mg every 8 weeks) in the per protocol population using the upper 95% confidence interval (CI) of 10% for

the non-inferiority margin. In both studies non-inferiority was demonstrated for all aflibercept dose regimens versus ranibizumab. Results for the aflibercept 2mg every 8 weeks group (licensed dose) versus ranibizumab are presented in the table below.

Secondary endpoints included change from baseline best corrected visual acuity (BCVA) at week 52 and proportion of patients who gained at least 15 letters of vision from baseline at week 52. Results for these are included in the table below.

Table: primary and key secondary endpoints at week 52 for aflibercept every 8 weeks and ranibizumab arms for VIEW 1 and VIEW 2

Endpoints	**VIEW 1**			**VIEW 2**		
	ranibizumab 0.5mg 4-weekly	aflibercept 2mg 8-weekly	difference* (95.1% CI)	ranibizumab 0.5mg 4-weekly	aflibercept 2mg 8-weekly	difference* 95% CI
Primary endpoint						
Proportion who maintained vision (n/N)	94.4% (254/269)	95.1% (252/265)	-0.7 (-4.5 to 3.1)	94.4% (254/269)	95.6% (258/270)	-1.1 (-4.8 to 2.6)
Secondary endpoints						
Change from baseline BCVA (SD)	8.1 (15.25)	7.9 (15.0)	0.26 (LS mean) (-1.97 to 2.49)	9.4 (13.5)	8.9 (14.4)	-0.9 (LS mean) (-3.06 to 1.26)
Proportion who gained vision	30.9% (94/304)	30.6% (92/301)	-0.4 (-7.7 to 7.0)	34.0% (99/291)	31.4% (96/306)	-2.65 (-10.18 to 4.88)

CI=confidence interval; SD=standard deviation; BCVA=best corrected visual acuity; LS=least squares
*difference; ranibizumab minus aflibercept for primary endpoint and aflibercept minus ranibizumab for secondary endpoints.

Visual quality of life was assessed using the National Eye Institute 25-item visual function questionnaire (with 0 being worst score and 100 being best score). In all groups differences from baseline were within the range 4 to 6 points and were considered to be clinically relevant.

A follow-up study to VIEW 1 and VIEW 2 (up to week 96) was conducted where patients were assessed every 4 weeks and treated (with the same drug previously assigned) at least every 12 weeks and more often if required, based on predetermined re-treatment criteria. These included (but were not limited to) an increase in central retinal thickness ≥100 micrometres compared with the lowest previous value (using optical coherence tomography) or a loss of ≥5 ETDRS letters from the best previous letter score in conjunction with recurrent fluid as indicated by optical coherence tomography. Results at 96 weeks are available from the pooled analysis of VIEW 1 and VIEW 2. [1] Of the 2,457 randomised patients, 2,419 received at least one dose of medication and 2,235 (90%) entered year 2 of the study. At week 96 the proportion of patients maintaining vision was 91.6% (545/595) for ranibizumab and 92.4% (561/607) for aflibercept every 8 weeks; difference -0.8% (95% CI -3.8% to 2.3%).

BCVA gains were 7.9 letters for ranibizumab and 7.6 letters for aflibercept every 8 weeks; difference -0.25 (95% CI -1.98 to 1.49)[3]. The proportion of patients who gained at least 15 letters of vision from baseline at week 96 was 31.6% for ranibizumab and 33.4% for aflibercept every 8 weeks; difference 1.8 (95.1% CI -3.5 to 7.1). The mean number of injections over 96

weeks was 16.5 and 11.2 for ranibizumab and aflibercept every 8 weeks respectively and the mean number of injections from week 52 to week 96 was 4.6 and 4.1. [3]

Summary of evidence on comparative safety

In the pooled safety results of the VIEW 1 and VIEW 2 studies the most common drug-related treatment emergent adverse events were vitreous floaters, reduced visual acuity and increased intraocular pressure. The majority of cases were sporadic with a rate <1%. Macular degeneration was observed in 11 (0.5%) patients in combined aflibercept group compared to no cases in the ranibizumab group. [1]

The most common non-ocular treatment emergent adverse events were nasopharyngitis (7.8% overall), hypertension (6.8% overall) headache (4.2% overall), bronchitis (3.9% overall), and urinary tract infection (3.6% overall]). Treatment-emergent adverse events occurred with similar frequency across all treatment groups. Non-ocular, drug-related treatment-emergent serious adverse events occurred at a higher frequency in aflibercept-treated patients, though the number of events was low; 7 cerebrovascular events (0.8%) in combined aflibercept group (mostly in VIEW 2) versus none in the ranibizumab group. There was a higher frequency of transient ischaemic attacks in the combined aflibercept than ranibizumab group in VIEW 1 but the trend was not observed in VIEW 2, or when arterial thromboembolic events were analysed according to the Anti-Platelet Trialists' Collaboration criteria. [1]

In the pooled 96-week safety results, more patients discontinued the study due to adverse events in the aflibercept every 8 weeks group (4.9%) compared to ranibizumab group (3.5%). These adverse events were mainly mild and moderate, however about 20% of adverse events were severe (21.7% in ranibizumab versus 20.3% in the combined aflibercept groups). [1] There was a total of 68 deaths (2.8%) reported including 20 deaths (3.3%) in the aflibercept every 8 weeks group versus 16 (2.7%) in ranibizumab group. [1]

Summary of clinical effectiveness issues

Two phase III comparative studies have demonstrated non-inferiority of aflibercept (at all doses) versus ranibizumab 0.5mg every four weeks for the primary endpoint, proportion of patients who maintained vision at week 52. Furthermore, data up to week 96 show that the efficacy is maintained over the second year of treatment. The studies have some limitations. There are no long-term efficacy data beyond a treatment duration of 96 weeks. The European Medicines Agency (EMA) considered the primary endpoint (loss of < 15 letters) to be a large vision loss, however were satisfied with the analysis of the mean change in visual acuity at one year, which they considered to be a more stringent endpoint. [1] Also the non-inferiority margin of 10% may be considered to be too wide, however non-inferiority was demonstrated at the 7% margin as well. [1] Finally the pivotal studies used a 4-weekly administration regimen for ranibizumab in year one. However the licensed dose of ranibizumab is 0.5mg given monthly as a single intravitreal injection until maximum visual acuity is achieved and treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD.

In order to compare aflibercept 2mg every 8 weeks with ranibizumab 0.5mg administered as needed, the submitting company included three types of indirect analysis; a Bucher analysis (random effects), a frequentist network analysis (fixed effects) and a Bayesian network analysis

(random effects). Results of the indirect comparisons indicate there are no significant differences between aflibercept 2mg every 8 weeks versus ranibizumab 0.5mg administered when required for maintaining vision, improving vision or improving best corrected visual acuity at 12 months. The Bucher indirect comparison, only, was also conducted at 24 months and showed similar results. The Bucher indirect comparison was used in the economic model and included four studies for the 12 month comparison and three for the comparison at 24 months, for the key efficacy endpoints of maintained and improved vision. Limitations of the indirect comparisons include the small number of studies incorporated, heterogeneity between studies as well as dissimilar baseline characteristics.

The EMA noted some uncertainty in terms of the most appropriate dosage regimen for aflibercept, due to the varying results seen in the pivotal studies. The every 8 week regimen was selected as the licensed dose regimen due to the reduced number of injections. [1] After 12 months the treatment frequency may be extended based on visual and anatomic outcomes and the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections. The company have committed to undertaking a post-authorisation randomised study with a primary objective of comparing the aflibercept 8-weekly injection regimen with a reactive regimen based on visual and anatomic outcomes. [1]

The impact on service delivery of the aflibercept treatment regimen after the first year is unknown. However clinical experts consulted by SMC noted issues with capacity in relation to current practice, and welcomed a treatment that requires less frequent monitoring and administration. In the pooled results of VIEW 1 and VIEW 2 the mean number of injections given over 96 weeks was 16.5 for ranibizumab and 11.2 for the aflibercept every 8 weeks group. In the Comparison of AMD Treatments Trials (CATT) study (comparing ranibizumab with bevacizumab) the mean number of injections over two years in the ranibizumab as required group was 12.6. [4] This level of ranibizumab injection frequency more closely represents actual clinical practice.

The EMA considered the safety of aflibercept to be similar to ranibizumab. However it had some concerns regarding the potential role of aflibercept in arterial thromboembolic events, cerebrovascular events and transient ischaemic attacks. [1] The summary of product characteristics notes that arterial thromboembolic events (as defined by the Antiplatelet Trialists' Collaboration criteria) occurred in 3.3% (60/1824) in the combined aflibercept group compared with 3.2% (19/595) in the ranibizumab group up to week 96. [3] A non-interventional post-marketing study is to be conducted to elucidate the risk of arterial thromboembolic events, cerebrovascular events and transient ischaemic attacks. [1]

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of aflibercept compared to 'as needed' ranibizumab in patients with wet AMD who have not previously been treated with anti-VEGF therapy. The cost-effectiveness in patients who have received prior anti-VEGF therapy has therefore not been demonstrated.

A two-eye state transition Markov model incorporating the BCVA of both eyes was used, with health states in the model defined by BCVA in the treated eye and the fellow eye and whether the patient has bilateral wet AMD. Patients could receive treatment in both eyes if needed and patients who discontinued treatment moved into a best supportive care part of the model and

did not receive further active treatment. The model used 5 different levels of BCVA (no vision impairment/ mild vision impairment/ moderate vision impairment/ severe vision impairment/ blind). The time horizon for the model was 25 years.

Clinical data to drive the flow of patients through the model were taken from an adjusted (Bucher) indirect comparison versus ranibizumab. While the findings in terms of improved or maintained vision were not statistically significant, the numerical differences in favour of aflibercept were used in the base case analysis. It was assumed that the treatment effect at year 2 was maintained out to year 5 of treatment. After 5 years, it was assumed that all patients discontinued treatment and experienced natural history rates of disease progression.

Utility values in the model were estimated from a regression analysis of EQ-5D values collected in the pivotal VIEW 2 study to estimate the utility values for the relevant health state categories in the economic model, with the resultant values assumed to reflect visual acuity for both eyes.

The model assumed that ranibizumab is used in clinical practice on an 'as needed' basis, which would equate to 6.9 injections in year one and 5.7 in year two. For aflibercept, the number of injections was 7.7 and 4 respectively. Thereafter, the same number of injections was assumed with each treatment in years 3 to 5 (3 in year 3, 2 in year 4 and 1 in year 5). Discontinuation rates were assumed to be equivalent between treatments.

Key resource use assumptions in the model related to the monitoring and testing regimes for each treatment. For aflibercept, it was assumed that 7.7 monitoring visits were carried out in year 1, and 6 in years 2 to 5. An optical coherence tomography (OCT) scan was carried out at each visit. For ranibizumab, it was assumed that all patients had a monthly monitoring visit with an ophthalmologist plus an OCT scan for all years of treatment i.e. 12 monitoring visits and 12 OCT scans per year. The costs of blindness were also included in the analysis at a rate of £565 per year, which is lower than the cost seen in other submissions.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the price of the medicine. A PAS is also in place for ranibizumab and the submitting company's analysis has incorporated this discount.

The results with the PAS indicated an incremental quality adjusted life year (QALY) gain with aflibercept of 0.0107 but a lower cost and thus that aflibercept would be the dominant medicine (lower cost, more effective).

Sensitivity analyses indicated that the dominance result was robust but highlighted the results showed greatest sensitivity to assumptions made about the relative number of monitoring visits and OCT scans performed. For example, if fewer ranibizumab visits and scans were assumed (to account for expert opinion which has suggested there are capacity constraints which make it difficult to meet the monitoring level assumed in the base case) the savings with aflibercept fell to around a tenth of the base case value. SMC clinical experts have indicated that the monitoring and scan frequency for ranibizumab assumed in the base case from year 2 onwards may be too high and therefore that the sensitivity analysis result may be more appropriate.

A key issue with the base case results was the uncertainty associated with the outcomes of the indirect comparison. If non-significant differences were removed from the model and the treatments were assumed equivalent in terms of improved and maintained visual acuity, the

base case result with the PAS is still cost-saving in favour of aflibercept (a saving and no difference in QALYs gained). The finding of cost-saving was still maintained in all sensitivity analyses where the non-significant differences were removed, except in one instance. This was where trial discontinuation rates from VIEW 2 were used, resulting in aflibercept being lower cost but less effective than ranibizumab. It should be noted that when monitoring and OCT scans were reduced to account for the likely current practice scenario, the savings with aflibercept under the assumption of no significant differences between treatments fell to less than 10% of the initial level.

The following weaknesses or uncertainties with the analysis were noted:

- The base case used non-significant differences from an indirect comparison. However, removal of these differences from the analysis indicates that aflibercept would still be a cost-saving treatment, even if more conservative assumptions were made regarding monitoring and OCT scans for ranibizumab patients.
- The key uncertainty in the result relates to the assumptions regarding the monitoring and OCT visit schedule for ranibizumab. SMC clinical expert comments suggest that practice is variable and in some cases may not be as high as is assumed in the base case.
- The analysis relies on a range of key assumptions, such as an equivalent discontinuation rate between therapies and no allowance for serious adverse events. However, by contrast, the analysis used relatively conservative unit costs for monitoring visits and the costs associated with being blind compared to those used in other SMC submissions, and thus may be conservative in relation to these aspects.

Despite these limitations, the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group submission was received from Royal National Institute of Blind People (RNIB) Scotland.

Additional information: guidelines and protocols

NICE published technology appraisal guidance 155; Ranibizumab and pegaptanib for the treatment of age-related macular degeneration in August 2008 and it was modified in May 2012 (after a change to the patient access scheme). [2] The following is recommended:

1. Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if:
   - all of the following circumstances apply in the eye to be treated:
     - the best-corrected visual acuity is between 6/12 and 6/96
     - there is no permanent structural damage to the central fovea
     - the lesion size is less than or equal to 12 disc areas in greatest linear dimension
     - there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes)

- and the manufacturer provides ranibizumab with the discount agreed in the patient access scheme (as revised in 2012).

2. It is recommended that treatment with ranibizumab should be continued only in people who maintain adequate response to therapy. Criteria for discontinuation should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy. It is recommended that a national protocol specifying criteria for discontinuation is developed.
3. Pegaptanib is not recommended for the treatment of wet age-related macular degeneration.
4. People who are currently receiving pegaptanib for any lesion type should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Health Improvement Scotland considered the modified version and issued the following recommendation on 23 May 2012: [5]

1. No important differences were identified for this NICE appraisal and Healthcare Improvement Scotland advises that the recommendations are as valid for Scotland as for England and Wales. The Patient Access Scheme Advisory Group (PASAG) for NHSScotland have approved the Patient Access Scheme as valid for NHSScotland.
2. The Scottish Medicines Consortium (SMC) has previously issued guidance to NHSScotland on the use of ranibizumab and pegatanib in this indication (381/07; 290/06). This NICE MTA guidance supersedes the SMC advice.
3. For ranibizumab, there is no material difference between the recommendations of NICE and SMC. SMC advised that ranibizumab was accepted for use in NHSScotland, and it should be stopped if visual acuity falls persistently below 6/60 during treatment (381/07). For pegaptanib, the recommendations of NICE and SMC are not consistent. SMC advised that pegaptanib was accepted for restricted use within NHSScotland (290/06).

The Royal College of Ophthalmologists published; Age-Related Macular Degeneration Guidelines for Management, in February 2009. [6] These guidelines are due to be updated in summer 2012. The guidelines include the following practical points:

- Pegaptanib and ranibizumab can be used to treat all subfoveal CNV. Although there are no direct comparisons, ranibizumab seems to be the more efficacious of the two.

Bevacizumab is unlicensed and its “off-label” status should be clearly stated prior to its use in patients. There are no long-term results on safety and effectiveness of intravitreal bevacizumab.

Additional information: comparators

Ranibizumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Aflibercept	**Aflibercept 2mg as an intravitreal injection every month for three months then every 2 months. After 12 months the treatment interval may be extended based on visual and anatomic outcomes**	**Year 1: 6,528** **Year 2: 3,264***
Ranibizumab	Ranibizumab 0.5mg as an intravitreal injection every month until maximum visual acuity is achieved. Patients are monitored monthly and treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD and monthly injections are restarted as before	Year 1: 5,194** Year 2: 3,710**

Doses are for general comparison and do not imply therapeutic equivalence. Cost of aflibercept from company's submission and cost of ranibizumab from MIMs on 19/12/12. Costs are included for years 1 and 2 only.

*cost is based on four injections in year 2 (from pivotal studies)

** costs are based on seven injections in year 1 and five injections in year 2 (from SMC expert responses)

Additional information: budget impact

The submitting company has estimated the net medicines budget to be £48k in year 1 and £47.6m in year 5 without PAS. However, these estimates do not take account of the PAS discount currently offered on ranibizumab, and as such do not provide a reliable estimate of the true net medicines budget impact. The submitting company has not been able to provide a more appropriate estimate.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. European Medicines Agency. European Public Assessment Report for aflibercept (Eylea). EMEA/H/C/002392/. 20 September 2012. www.ema.europa.eu [Accessed on 10 December 2012]
2. National Institute for Health and Clinical Excellence. Technology appraisal guidance 155; Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. August 2008 (and modified in May 2012). [Accessed on 5 November 2012]. www.nice.org.uk
3. Bayer plc. Summary of product characteristics for alflibercept (Eylea). Last updated 22/11/12. www.medicines.org.uk
4. CATT Research group, Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and Bevacizumab for treatment of neovascular age-related macular degeneration. Two year results. Ophthalmology 2012;119(7):1388-99.
5. Health Improvement Scotland. View on Technology appraisal guidance 155; Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. 23 May 2012. [Accessed on 5 November 2012]. http://www.healthcareimprovementscotland.org/
6. Royal College of Ophthalmologists. Age-Related Macular Degeneration Guidelines for Management. February 2009. [Accessed on 5 November 2012] http://www.rcophth.ac.uk/

This assessment is based on data submitted by the applicant company up to and including 15 February 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.