Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

bortezomib 3.5mg powder for solution for injection (Velcade®) SMC No. (927/13)

Janssen-Cilag Ltd

06 December 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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

bortezomib (Velcade®) is accepted for restricted use within NHS Scotland.

Indication under review: In combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

SMC restriction: use as triple therapy in combination with dexamethasone and thalidomide.

Bortezomib, used in combination with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation improved response rates compared with a dual combination regimen.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Indication

In combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Dosing Information

Combination therapy with dexamethasone

Bortezomib,1.3mg/m^2 body surface area, by intravenous or subcutaneous injection, on days 1, 4, 8, and 11 of a 21-day treatment cycle, with dexamethasone 40mg orally on days 1, 2, 3, 4 and days 8, 9, 10, 11. The treatment course comprises four cycles.

Combination therapy with dexamethasone and thalidomide

Bortezomib, 1.3 mg/m^2 body surface area, by intravenous or subcutaneous injection, on days 1, 4, 8, and 11, of a 28-day treatment cycle, with dexamethasone 40mg orally on days 1, 2, 3, 4 and days 8, 9, 10, 11 and thalidomide 50mg on days 1 to 14 and, if tolerated, increased to 100mg on days 15 to 28, and thereafter may be further increased to 200mg daily. The treatment course comprises four cycles and it is recommended that patients with at least partial response receive two additional cycles.

Treatment must be initiated and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Product availability date

31 July 2013

Summary of evidence on comparative efficacy

Bortezomib is a reversible proteasome inhibitor which disrupts homeostasis in cancer cells causing their destruction. It is currently accepted for use in NHS Scotland for a number of specific groups of multiple myeloma patients. The licence has been extended to include use as part of an induction treatment for patients with multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. The submitting company has requested that SMC considers the use of bortezomib only when positioned as triple therapy in combination with both thalidomide and dexamethasone.

The evidence for this new indication is from one phase III randomised, open-label, controlled study; PETHEMA/GEM, which had three treatment phases: induction (including stem cell mobilisation and collection), autologous stem cell transplantation (ASCT) (including conditioning with high dose melphalan and stem cell infusion) and maintenance.[1] Eligible patients were aged ≤65 years with newly diagnosed, untreated symptomatic multiple myeloma who were eligible for ASCT, had life expectancy >3 months, had measurable serum and/or urine M protein, and were of performance status ≤2.

Three hundred and eighty-six patients were randomised in a 1:1:1 ratio to receive one of three induction regimens but as one was not considered a relevant comparator, results were presented for the following two induction treatment groups only:

- Bortezomib, thalidomide and dexamethasone (VTD) = bortezomib 1.3mg/m^2 by intravenous injection on days 1, 4, 8, 11 plus thalidomide 200mg orally daily (dose titrated in first cycle: 50mg on days 1 to 14, 100mg on days 15 to 28); plus dexamethasone 40mg orally on days 1 to 4 and 9 to12 of a 28-day cycle for a total of six cycles.
- Thalidomide and dexamethasone (TD) = thalidomide 200mg orally daily (dose titrated in first cycle: 50mg on days 1 to 14, 100mg on days 15 to 28); plus dexamethasone 40mg orally on days 1 to 4 and 9 to 12 of a 28-day cycle for a total of six cycles.

All patients were to receive high dose melphalan (200mg/m^2) followed by ASCT and patients failing to achieve sufficient stem cell collection were removed from the study. In the VTD group, 81% (105/130) patients received ASCT compared with 61% (78/127) in the TD group. Three months after transplantation, patients who received ASCT were re-randomised (irrespective of induction regimen) to receive one of three maintenance therapies: interferon alpha-2b, thalidomide or bortezomib plus thalidomide, which were continued for up to three years or until disease progression.

The primary outcome was response rate but the definition varied in different reference sources:

- complete response (CR) post-induction and post-ASCT[1]
- composites of CR, near CR (nCR) and partial response (PR) post-induction and of CR and nCR post-ASCT.[2,3]
- CR and nCR post-induction and post-ASCT[4]

The primary outcome was analysed in the intention to treat population which included all randomised patients and was achieved in significantly more patients with VTD than with TD in all definitions.

Table 1: Primary outcome response rates[2]

ITT population	**VTD n=130**	**TD n=127**	
Post-induction response rate			**Odds ratio (95% CI)**
CR	35%	13%	3.54 (1.90 to 6.62)*
CR+nCR	49%	17%	4.63 (2.61 to 8.22)*
CR+nCR+PR	85%	61%	3.46 (1.90 to 6.27)*
Post-transplant response rate			
CR	47%	24%	2.86 (1.67 to 4.88)*
CR+nCR	55%	35%	2.34 (1.42 to 3.87)*
CR+nCR+PR	78%	57%	2.66 (1.55 to 4.57)*

ITT=intention to treat; VTD=bortezomib, thalidomide, dexamethasone; TD=thalidomide, dexamethasone, CI=confidence interval; CR=complete response; nCR=near complete response; PR=partial response *p<0.001

After a median follow-up of 35.9 months, there was no significant difference between treatment groups in the secondary outcome of median overall survival (defined as date of randomisation to date of death or last visit): 55.5 months in the VTD group and not estimable in the TD group; hazard ratio (HR) 0.80 (95%CI: 0.48 to 1.34), p=0.393. After a median follow-up of 35.2 months, median progression free survival (defined as date of randomisation to the date of relapse, progression, or death from any cause) was significantly improved in the VTD compared with the TD group: 55.5 months versus 27.9 months; HR 0.65 (95% CI: 0.45 to 0.92), p=0.015. Median time to progression (defined as the interval between the date of randomisation and the date of disease progression or death due to disease progression, whichever occurred first) was significantly improved in the VTD compared with the TD

group: not estimable versus 29.0 months; HR 0.64 (95% CI: 0.44 to 0.93), p=0.017.[2] In patients with high-risk cytogenetics, the CR rate was significantly higher with VTD compared with TD (35% [8/23] versus 0% [0/22]), p= 0.002.[1] Health-related quality of life was not evaluated in the study.

Summary of evidence on comparative safety

The following safety data relate to the induction treatment phase only. The median duration of induction treatment was 24 weeks and there was a median of six cycles in both treatment groups.[4] There were no unexpected adverse events associated with bortezomib.

In the VTD versus TD groups, adverse events were reported in 85% (110/130) versus 81% (102/126) patients and serious adverse events in 26% (34/130) versus 33% (42/126) patients.[1] Adverse events leading to discontinuation of induction treatment were reported in 6% of patients in the TD and VTD groups. There were adverse events leading to dose modification in 35% of VTD and 7% of TD patients. The dose of bortezomib was reduced in 31% of VTD patients.[2]

In the VTD versus TD groups, treatment-related adverse events were reported in 75% (97/130) versus 52% (66/126) patients, most commonly constipation 28% (36/130) versus 25% (32/126); peripheral neuropathy 32% (42/130) versus 4.0% (5/126); and asthenia 15% (19/130) versus 10% (13/126.[3] Treatment-related serious adverse events were reported in 10% (13/130) versus 10% (12/126) of patients in the respective groups.[2] Treatment-related grade 3 or 4 adverse events were reported in 24% (31/130) of patients in the VTD group versus 13% (17/126) in the TD group: neutropenia 10% (13/130) versus 14% (18/127); thrombocytopenia 7.7% (10/130) versus 4.7% (6/127); deep vein thrombosis/pulmonary embolism 12% (15/130) versus 4.7% (5/127); infection 21% (27/130) versus 16% (21/127).[1]

The proportion of patients with peripheral neuropathy in the VTD group versus the TD group was 45% versus 12%, and this was at least grade 2 in 31% versus 2%, at least grade 3 in 5% versus 0, and led to discontinuation of treatment in 5% versus 1%, respectively.[2]

A pooled analysis across three studies compared patients receiving bortezomib and non-bortezomib regimens and found that the adverse events with the largest between-regimen differences were thrombocytopenia, peripheral neuropathy, peripheral sensory neuropathy, and herpes zoster.[2]

There is some evidence of an improved safety profile if bortezomib is administered subcutaneously rather than intravenously.[4]

Summary of clinical effectiveness issues

Bortezomib is currently used at various stages in the multiple myeloma treatment pathway and is the first drug to be approved in Europe for induction therapy. The principal aim of induction therapy is to reduce tumour size rapidly without damaging the haematopoietic progenitor cells, so as to achieve the best possible response before transplantation.[2] Current national guidelines recommend triple drug induction regimens followed by ASCT in patients who are young and sufficiently fit.[5] Clinical experts consulted by SMC have advised that the standard of care in Scotland is the unlicensed induction regimen cyclophosphamide, thalidomide and dexamethasone (CTD). They identified an unmet need in patients with aggressive disease who may particularly benefit from the combination of bortezomib, dexamethasone and thalidomide. The submitting company has requested that SMC considers bortezomib only when positioned for use in combination with both thalidomide and dexamethasone.

The pivotal study demonstrated a significant improvement in the primary outcome of response rate in patients who received bortezomib in addition to thalidomide plus dexamethasone (VTD) compared with TD alone.[1,2]

The main limitation of the submitted evidence is that the pivotal study did not compare VTD against the predominant standard of care in Scotland. The submitting company has assumed that the efficacy of TD is comparable to CTD and justified the use of TD as a proxy comparator because the systematic review that it conducted did not find any studies that would allow a mixed treatment comparison. Recent reviews published in The Oncologist and the British Medical Journal confirm that triple drug combinations are standard induction regimens.[6,7] Clinical experts consulted by SMC advised that, in the absence of comparative evidence with the current standard of care, the comparison with TD is acceptable.

Another limitation of the study is that the primary outcome of response rate is a surrogate outcome, although a good induction response is reported to be correlated with improved progression free survival and overall survival.[2,7] It is difficult to interpret the results of the direct health outcome of overall survival in the pivotal study (no significant difference between treatment groups) as the data are immature and are confounded by subsequent treatments which include bortezomib as second or third-line treatment options.

The pivotal study excluded patients over 65 years which differs from clinical practice in Scotland as experts have advised that some older patients receive ASCT. The submitting company also acknowledged that the use of maintenance therapies in the pivotal study is a limitation as it does not reflect current standards of care in Scotland and confounds long-term outcomes. This hampers interpretation and understanding of post-transplant outcomes: overall survival, progression free survival and time to progression.

As the VTD and CTD regimens have not been compared, it is not possible clearly to determine relative advantages and disadvantages. However, one advantage is that bortezomib is the only licensed induction treatment option for patients with newly diagnosed multiple myeloma eligible for ASCT. Disadvantages include the parenteral administration required for bortezomib compared with orally administered CTD. More frequent monitoring of full blood counts is required with bortezomib treatment than with cyclophosphamide.[4,8] Aciclovir prophylaxis is recommended with bortezomib treatment due to increased incidence of varicella zoster infection.[5] No new safety concerns for bortezomib have been reported in the indication under review. There are substantial differences between the safety profiles of bortezomib and cyclophosphamide and there is no evidence comparing the safety of the VTD and CTD regimens.[4,8]

Summary of comparative health economic evidence

The company submitted a cost-utility analysis of bortezomib in combination with thalidomide and dexamethasone (VTD) compared with TD alone for the induction treatment of multiple myeloma. Current practice in Scotland consists of the use of cyclophosphamide in combination with TD (CTD), but the company used TD as a proxy comparator on the grounds that the efficacy of TD and CTD can be considered comparable. The use of TD as a proxy for CTD was generally supported by SMC clinical experts. Hence, data from the head to head study of VTD versus TD (the PETHEMA/GEM study) was used in the economic model. A Markov model structure was used in which treatment-naïve patients receive induction therapy for up to 6 cycles and was designed to isolate the effect of response to treatment on survival outcomes. Health states consisted of complete response (CR), partial response (PR) or no response (NR), and from each of these health states patients had a probability of receiving stem cell transplant (SCT) which was close to 100% in patients achieving CR,

and between 80-90% with PR. Post induction/SCT patients could experience up to 3 relapses over a 30 year time horizon. VTD was modeled so that a proportion of patients who were estimated to have a less than a partial response at 4 cycles would discontinue induction treatment with VTD, in line with the bortezomib Summary of Product Characteristics.

The PETHEMA/GEM trial data was used to estimate induction therapy response, use of SCT and post induction progression-free survival (PFS) to first relapse. Overall survival (OS) post-induction dependent on response was estimated using 5 year median OS data from the SCT arm of a published MRC study of SCT versus standard chemotherapy[9], with an exponential function fitted to extrapolate survival outcomes over the 30 year time horizon. Based on these data, a constant monthly mortality probability over time was applied for CR (0.8%), PR (1.7%) and NR (2.7%). The time to second relapse and to third relapse was based on fitting the exponential function to data from an alternative study of bortezomib in relapsed multiple myeloma (the APEX study). No differences in relapse probability were assumed for these phases between the VTD and TD treatment arms. The mortality probabilities for second and third relapse by response were assumed to be the same as those applied for the time to first relapse. Survival from third relapse to death was the remaining time estimated using the extrapolated MRC survival data.

Utility estimates for each health state were based on data from published and unpublished studies in multiple myeloma or other lymphomas (with most estimates based on EQ- 5D data), and a disutility assumed for adverse events. Costs for each health state consisted of induction drug and administration costs, drug prophylaxis, monitoring and administration costs, adverse event management costs, the costs of SCT, and costs associated with first and second relapse treatment and management. The only costs estimated for 3rd relapse to death were those for monthly patient monitoring.

The base case results were an estimated incremental cost per quality adjusted life year (QALY) gained for VTD compared to TD of £23,077 (with the company assuming the same incremental cost effectiveness ratio [ICER] would be estimated versus CTD), with an incremental cost of £24k, incremental life years gained of 1.47 and incremental QALYs of 1.04. The life years and QALY gains were driven by a higher CR probability for the VTD group. The main incremental cost driver for VTD was the higher drug acquisition costs from adding bortezomib and the resource costs associated with parenteral administration. There were also additional costs for VTD associated with greater time spent progression-free prior to first relapse, and from third relapse to death.

The base case ICER was moderately sensitive to varying the per cycle mortality probability to first relapse by ±20%, varying between £19.2k/QALY and £31.8k/QALY. Scenario analyses based on using the 95%CI's for VTD and TD post induction response produced an ICER range of £16.7k/QALY to £37.4k/QALY. The ICER improved to below £20k/QALY when alternative published randomised controlled trial data for 5 year post-SCT survival were used. Shortening the time horizon to 15 and 10 years resulted in ICERs of £27.9k/QALY and £35k/QALY respectively. Threshold analysis performed indicated that the efficacy of TD at achieving CR would need to increase from 17.3% to at least 26% (compared to the CR efficacy of VTD of 49.2%) for the ICER to exceed £30k/QALY.

There were several issues and limitations with the economic evaluation:

- Despite general SMC clinical expert acceptance for using TD as a proxy for CTD outcomes, there is still uncertainty over the possible benefits (and hence impact on the ICER) associated with adding cyclophosphomide to the TD regimen. Hence, the base case ICER is likely to be an underestimation as it assumes zero efficacy impact of adding cyclophosphomide to TD (even allowing for any cost and AE impact of cyclophosphomide).
- Key weaknesses with the analysis related to the predicted levels of survival gains with treatment. The difference in overall survival was non-significant in the PETHEMA/GEM study. There were limitations in the extrapolation using the alternative MRC OS data in that it was

only possible to fit an exponential function due to data limitations. In addition, an alternative published UK registry data source for assessing long run survival post-SCT in multiple myeloma was not used[10], and median survival outcomes from this study are lower for a complete response and higher for a partial response than in the MRC study. A scenario applying these data resulted in an increase in the ICER to £52,937/QALY gained.

- The time horizon of 30 years relies on long extrapolation from post induction response and the committee had particular concerns around this aspect, as above. The use of shorter time horizons with shorter extrapolation requirements resulted in ICERs of £29k/ QALY and £35k/QALY at 15 and 10 years respectively.
- In the model, it appears that patients attain survival outcomes associated with SCT based on the MRC study data regardless of whether they received SCT or not (i.e. receiving SCT has no direct differential impact on survival outcomes between treatment arms), but only those patients receiving SCT incur the costs of this intervention. As a higher proportion of VTD patients received SCT this may favour the comparator to some extent. The company provided sensitivity analysis which showed the ICER decreased to £21k/ QALY when the model was adjusted to account for improved outcomes for patients receiving SCT.
- The estimate of a cost of £83 per month for monitoring only post-third relapse to death is likely to represent an underestimate of the costs of this state as it does not include any drug costs. Any increase to the average monthly cost in this health state would increase the ICER. A scenario in which the costs are assumed to be the same as for the second relapse state (£42,583) marginally reduced the ICER, which appears counter-intuitive given the longer time estimated to be spent in this phase by VTD patients.

SMC considered the likely range of cost-effectiveness ratios for bortezomib in this setting and the remaining uncertainties in the economic case. The committee considered the benefits of bortezomib in the context of the SMC decision modifiers and agreed that the criterion for a bridge to a definitive therapy was satisfied. Although there were some limitations in the economic analysis, the committee agreed that the relatively high cost per QALY was acceptable given the expected benefits of the treatment and in the context of the decision modifiers.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Myeloma UK.

Additional information: guidelines and protocols

The Haemato-oncology Task Force of the British Committee for Standards in Haematology and the UK Myeloma Forum published "Guidelines for the diagnosis and management of multiple myeloma" in 2010 and these were updated in 2013. They state that for patients where high dose therapy is planned, or is a possible future option, the aim of induction treatment is to induce high remission rates rapidly and with minimal toxicity and to preserve haemopoietic stem cell function to ensure successful mobilisation of peripheral blood stem cells**.** Combinations, such as bortezomib, thalidomide, dexamethasone (VTD), have given response rates of 82 to 92% with complete response rates of 18 to 29% without an increase in serious adverse events in three-drug combinations.[5]

The European Society for Medical Oncology (ESMO) published Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in 2010. These state that in randomised studies, combinations of novel agents (thalidomide or bortezomib) plus dexamethasone are superior to the classical VAD regimen (vincristine, adriamycin and high-dose dexamethasone). Triple combinations might be even more effective.[11]

Additional information: comparators

The triple regimen of cyclophosphamide, thalidomide and dexamethasone (CTD) which is an unlicensed induction regimen.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Bortezomib, thalidomide, dexamethasone	By intravenous or subcutaneous injection bortezomib 1.3mg/m^2 on days 1, 4, 8, 11 plus oral thalidomide 200mg daily (dose titrated in first cycle: 50mg on days 1 to 14, 100mg on days 15 to 28); plus oral dexamethasone 40mg on days 1 to 4 and 9 to12 of a 28 day cycle	**3,667**	**14,520 to 21,854***
Cyclophosphamide, thalidomide, dexamethasone	Oral cyclophosphamide 500mg once a week, oral thalidomide 100mg daily increasing to 200mg daily if tolerated, and oral dexamethasone 40mg on days 1 to 4 and 12 to 15 of a 21-day cycle	475 to 922**	3,137 to 5,534**

Doses are for general comparison and do not imply therapeutic equivalence. Costs of cyclophosphamide and dexamethasone from eVadis on 04.10.13. Costs of bortezomib and thalidomide from MIMS online on 04.10.13. *Cost includes thalidomide dose titration in first cycle and is based on 4 to 6 cycles as per Summary of Product Characteristics for bortezomib. ** Range of costs reflects thalidomide dose range and costs are based on 6 cycles as per expert advice.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 76 per year with an estimated uptake rate of 5% in year 1 (4 patients) and 27% in year 5 (20 patients). The gross impact on the medicines budget for the introduction of VTD was estimated to be £86k in year 1 and £465k in year 5. Taking into account the estimated displacement of TD, the net medicines budget impact is expected to be £85k in year 1 and £459k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Rosinol L, Oriol A, Teruel AI et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood 2012;120:1589-96.

2. The European Medicines Agency (EMA) European Public Assessment Report. Bortezomib powder for solution for injection (Velcade®). EMEA/H/C/000539/II/0059 June 2013.

3. Janssen-Cilag Ltd. CSR: 26866138-MMY-3010 (GEM05MENOS65): A phase III national, open label, multicenter, randomized, comparative study of VBMCP-VBAD/Velcade versus thalidomide/dexamethasone versus Velcade/thalidomide/dexamethasone as induction therapy, followed by high-dose chemotherapy with autologous hematopoietic transplantation and subsequent maintenance treatment with interferon alpha-2b versus thalidomide versus thalidomide/Velcade in patients with multiple myeloma. 2012.

4. Janssen-Cilag Ltd. Bortezomib powder for solution for injection (Velcade®) Summary of product characteristics. Electronic Medicines Compendium. Last updated 20 August 2013.

5. Bird JM, Owen RG, D'Sa S et al on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum Guidelines for the diagnosis and management of multiple myeloma 2013

6. Ludwig H, Avet-Loiseau H, Blade J et al. European perspective on multiple myeloma treatment strategies: update following recent congresses. Oncologist 2012;17:592-606.

7. Smith D, Yong K. Multiple myeloma. BMJ 2013; 346:f3863

8. Pharmacia Limited. Cyclophosphamide 50mg tablets (Cyclophoshamide 50) Summary of product characteristics. Electronic Medicines Compendium. Last updated 26 March 2012

9. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003 May 8;348(19):1875-83

10. Cook G, Jackson GH, Morgan GJ, Russell N, Kirkland K, Lee J, et al. The outcome of high-dose chemotherapy and auto-SCT in patients with multiple myeloma: a UK/Ireland and European benchmarking comparative analysis. Bone Marrow Transplant 2011 Sep;46(9):1210-8

11. Harousseau JL, Dreyling M on behalf of the ESMO Guidelines Working Group. Multiple Myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology 2010;21 (Supplement 5): v155–v157.

This assessment is based on data submitted by the applicant company up to and including 18 November 2013.

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.

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.