Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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liraglutide 6mg/mL prefilled pen for injection (3mL) (Victoza®) SMC No. (1044/15)

Novo Nordisk

10 April 2015

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

liraglutide (Victoza®) is accepted for use within NHS Scotland.

Indication under review: For the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with basal insulin when this, together with diet and exercise, does not provide adequate glycaemic control.

The addition of liraglutide to basal insulin in combination with another anti-diabetic agent was associated with a significant reduction in HbA1c compared with placebo and an alternative insulin regimen.

Liraglutide has previously been accepted for restricted use as a third line antidiabetic agent for use in combination with oral antidiabetic agents. This now extends the advice to include its use in combination with insulin.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 May 2015

Indication

For the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

Dosing Information

To improve gastro-intestinal tolerability, the starting dose is liraglutide 0.6mg daily. The dose should be increased after at least one week to 1.2mg. Some patients are expected to benefit from an increase in dose from 1.2mg to 1.8mg and based on clinical response, after at least one week, the dose can be increased to 1.8mg to further improve glycaemic control. Daily doses higher than 1.8mg are not recommended. Liraglutide is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. However it is preferred that liraglutide is injected around the same time of the day, when the most convenient time of the day has been chosen. Liraglutide must not be administered intravenously or intramuscularly.

Liraglutide can be added to existing metformin or to a combination of metformin and a thiazolidinedione. The current dose of metformin and thiazolidinedione can be continued unchanged.

Liraglutide can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy or a basal insulin. When liraglutide is added to sulphonylurea therapy or basal insulin, a reduction in the dose of sulphonylurea or basal insulin should be considered to reduce the risk of hypoglycaemia.

Product availability date

28 April 2014

Summary of evidence on comparative efficacy

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist which acts in a glucose dependant manner to stimulate insulin secretion and lower inappropriately high glucagon secretion.[1] This submission is for an extension to the marketing authorisation to include use in combination with basal insulin. Liraglutide was previously licensed for dual therapy in combination with metformin or a sulphonylurea, and for triple therapy in combination with metformin and a sulphonylurea or metformin and a thiazolidinedione. Liraglutide was accepted for restricted use by SMC as a third line antidiabetic agent for these combinations.

The key evidence to support this licence extension for use in combination with basal insulin comes from two studies: LIRA-ADD2BASAL and BEGIN: VICTOZA ADD-ON.[2,3,4] The LIRA-ADD2BASAL study compared the efficacy and safety of adding liraglutide versus placebo to stable basal insulin (glargine or detemir at a minimum dose of 20 units/day for ≥8 weeks) with or without metformin (at a stable dose of metformin ≥1500mg/day) in patients with type 2 diabetes (451 patients randomised and 450 patients in the full analysis set).[2,3,5,6] Eligible patients were aged 18 to 80 years, with type 2 diabetes for at least 180 days, had inadequate glycaemic control with a glycosylated haemoglobin (HbA1c) of 7.0 to 10.0% and a body mass index (BMI) of 20 to 45kg/m.[2] Patients were randomised equally to receive liraglutide (0.6mg daily increased to 1.2mg daily after one week and then to 1.8mg daily after two weeks until the end of the study) or placebo daily by subcutaneous injections. Any pre-

screening medication (metformin or basal insulin [insulin glargine and insulin detemir]) was continued at the same stable dose unless HbA1c was ≤8.0%, and in these patients the insulin dose was reduced by 20% to reduce the potential risk of hypoglycaemia.[6]

The BEGIN:VICTOZA ADD-ON study compared the efficacy and safety of adding liraglutide versus insulin aspart to insulin degludec plus metformin in 177 patients with type 2 diabetes who had completed two previous studies which compared insulin degludec and insulin glargine and were receiving treatment with insulin degludec plus metformin.[4,7,8] Eligible patients were aged ≥18 years with type 2 diabetes for ≥6 months before starting the previous study and had inadequate glycaemic control with an HbA1c ≥7.0% at the end of the previous study. Patients were randomised to receive liraglutide (0.6mg daily, increased to 1.2mg daily after one week until after week 5, when it could be increased to 1.8mg daily if required) or insulin aspart (4 units once daily before the largest daily meal and titrated once weekly). Liraglutide or insulin aspart was given with insulin degludec plus metformin. Insulin degludec was administered once daily with the main evening meal at the dose used in the previous study with weekly titrations. In the liraglutide group, the insulin degludec dose was reduced by 20% at randomisation until week 6 to reduce the risk of potential hypoglycaemia.

In both studies, the primary outcome was the change from baseline in HbA1c after 26 weeks. Secondary outcomes included the proportion of responders (HbA1c<7.0%), responders without confirmed hypoglycaemia and without weight gain, change from baseline in fasting plasma glucose (FPG), change from baseline in body weight and change from baseline in self-monitoring of blood glucose (SMBG) profile. In both studies, liraglutide was associated with a significantly greater reduction in HbA1c at 26 weeks than the comparator. Details of primary and secondary outcomes are presented in the table below.

Table: Primary and secondary outcomes in studies assessing liraglutide in combination with basal insulin

	LIRA-ADD2BASAL [2,3,5]		BEGIN:VICTOZA ADD-ON [4,7,8]	
	Liraglutide (n=225)	Placebo (n=225)	Liraglutide (n=88)	Insulin Aspart (n=89)
Primary outcome: change from baseline in HbA1c after 26 weeks				
Baseline HbA1c	8.22%	8.28%	7.7%	7.7%
Change from baseline in HbA1c after 26 weeks	-1.30%	-0.11%	-0.74%	-0.39%
Difference (95% CI), p-value	-1.19% (-1.39 to -0.99), p<0.0001.		-0.32% (-0.53 to -0.12), p=0.0024	
Secondary outcomes				
Responders (HbA1c<7.0%)	59%	14%	58% (51/88)	45% (40/89)
Odds ratio (95% CI)	8.91 (5.45 to 14.59), p<0.0001		NR p=NS	
Responders without confirmed hypoglycaemia or weight gain	41%	8.6%	49%	7.2%
Odds ratio (95% CI)	7.50 (4.36 to 12.92), p<0.0001		13.79 (5.24 to 36.28), p<0.0001.	
Change from baseline in FPG	-1.44	-0.16	-0.12	-0.18

Difference (95% CI)	-1.28mmo/L (-1.70 to -0.86), p<0.0001.		-0.06mmo/L (-0.65 to 0.77)	
Change from baseline in body weight	-3.54kg	-0.42kg	-2.8kg	0.9kg
Difference (95% CI)	-3.11kg (-3.85 to -2.37), p<0.0001.		-3.75kg (-4.70 to -2.79), p<0.0001.	

CI = confidence interval; NR = not reported; NS = not significant; FPG = fasting plasma glucose

In study LIRA-ADD2BASAL, the change from baseline in mean SMBG profile was significantly greater in the liraglutide than placebo group (using a 7-point profile)[5] but there were no significant differences between liraglutide and insulin aspart (using a 9-point profile) in the BEGIN:VICTOZA ADD-ON study[4].

Summary of evidence on comparative safety

The comparative safety data are limited to liraglutide versus placebo and insulin aspart only.

The most frequently reported adverse events in the liraglutide versus placebo comparison were: nausea (22% versus 3.1%), diarrhoea (11% versus 4.9%), decreased appetite (9.8% versus 2.2%), vomiting (8.9% versus 0.9%), increased lipase (7.1% versus 2.2%), dyspepsia (7.1% versus 0.9%), nasopharyngitis (5.8% versus 6.2%), back pain (5.3% versus 5.3%), influenza (3.6% versus 7.1%) and headache (3.6% versus 7.1%). The incidence of confirmed hypoglycaemia (defined as SMBG corresponding to a plasma glucose level of <3.1mmol/l) was 18% in the liraglutide group and 12% in the placebo group. The rate of confirmed hypoglycaemic episodes was 126 per 100 patient-years and 83 per 100 patient-years respectively. There were no severe hypoglycaemic events reported in either group. These were defined as those requiring assistance from another person.[5]

The most frequently reported adverse events in the liraglutide versus insulin aspart comparison were: nausea (21% versus 0%), nasopharyngitis (10% versus 13%); diarrhoea (10% versus 0%), increased lipase (6.9% versus 0%), vomiting (5.7% versus 0%), pain in extremity (5.7% versus 1.2%). The incidence of confirmed hypoglycaemia was 28% in the liraglutide group and 67% in the insulin aspart group. The rate of confirmed hypoglycaemic episodes was 100 per 100 patient-years and 815 per 100 patient-years respectively. There were no severe hypoglycaemic events reported in either group.[4,7]

Summary of clinical effectiveness issues

This submission is for an extension to the marketing authorisation for liraglutide to include use in combination with basal insulin. Liraglutide is one of four GLP-1 receptor agonists (the others being exenatide, lixisenatide and albiglutide) which are licensed for use in combination with insulin. Exenatide has been accepted for use by SMC for use with basal insulin and lixisenatide has been accepted for restricted use by SMC for use with basal insulin when a GLP-1 agonist is appropriate, as an alternative to existing GLP-1 agonists. Albiglutide is awaiting launch and is under review by SMC.

In the pivotal studies, the primary outcome of change from baseline in HbA1c level is a surrogate outcome measure of blood glucose control over the preceeding two to three months; however, this is a widely accepted measure of long-term glycaemic control and reductions in the risk of microvascular complications of diabetes have been linked with reductions in HbA1c. Treatment guidelines recommend HbA1c targets in the treatment of diabetes.[9,10] In the UK, HbA1c results are expressed as mmol/mol rather than as a percentage. The equivalent of the HbA1c targets of 6.5% and 7.0% are 48mmol/mol and 53mmol/mol in the new units.

The addition of liraglutide to basal insulin with or without metformin was associated with a statistically significant reduction in HbA1c of -1.19% compared with placebo and of -0.39% compared with insulin aspart.[2,3,4] While HbA1c has been linked with reductions in the long-term complications of diabetes, there are no direct health outcome data demonstrating liraglutide in combination with insulin reduces micro- and/or macro-vascular complications and data are limited to 26 weeks duration.

There are a number of limitations in the generalisability of the study data to Scottish practice. In the comparison with insulin aspart, the dose of insulin aspart used, once daily as opposed to multiple daily injections, was potentially too low for patients with inadequate glycaemic control and needing further therapy, making the comparison less valid. In addition, this study was open-label and may have introduced the potential for bias.[4,5]

While this licence extension allows liraglutide to be used in combination with glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control, in the two studies described, liraglutide was used in combination with basal insulin (glargine, detemir or degludec) with or without metformin only. In the LIRA-ADD2BASAL study, 92-93% of patients were taking concomitant metformin and in the BEGIN VICTOZA ADD-ON study, all patients were taking metformin. There are no data on use with other oral antidiabetic agents.[2,3,4,6]

There are no directly comparative data with other GLP-1 agonists when used in combination with basal insulin. The company therefore presented results of an indirect comparison with exenatide and lixisenatide using a Bayesian network meta-analysis which included three studies. The target population was patients with type 2 diabetes who remained uncontrolled after at least three months of insulin treatment. The comparators were exenatide plus insulin glargine and lixisenatide plus insulin glargine. There were a number of outcomes assessed including change from baseline HbA1c, in weight, in BMI, in FPG, in proportion of patients achieving HbA1c <7.0% and in the incidence of overall, severe and mild/non-severe hypoglycaemic events. There was heterogeneity among the studies with differences in terms of duration, outcomes, concomitant medicines and results in the control arms.

Liraglutide is administered as a once daily subcutaneous injection at around the same time each day and independent of meals[1]. This may offer advantages over exenatide, which is administered twice daily and within a 60-minute period before the morning and evening meals. Lixisenatide is administered once daily at around the same time each day but within an hour before a meal. Clinical experts consulted by SMC considered that the place in therapy of liraglutide is in patients who were obese or where gaining weight from use of insulin was an issue.

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

Summary of comparative health economic evidence

The submitting company presented a lifetime cost-utility analysis that compared liraglutide with exenatide and lixisenatide as add-on to basal insulin plus metformin for patients with type 2 diabetes who are not adequately controlled (HbA1c>7.5% [59mmol/mol]) on basal insulin. The company used the IMS CORE Diabetes Model (CDM) to assess the cost-effectiveness of liraglutide against the comparators. The CDM is a computer simulation model developed to predict the long-term health outcomes and economic consequences of type 1 and type 2 diabetes.

In terms of model structure, patients at the model start were assumed to be treated with liraglutide, exenatide or lixisenatide and remained on treatment until their level of HbA1c reached the control threshold of 7.5% (59mmol/mol). When patients met this threshold they were then switched to basal bolus insulin regimen for the remainder of the time horizon. Disease progression was captured in the model through modifiable risk factors and risk equations. Disease-related complications were taken into account through a series of interdependent Markov-sub models.

The sources of the clinical data used in the model were the LIRA-ADD2BASAL study, the published literature and an indirect comparison. The LIRA-ADD2BASAL study and the published literature mainly informed the baseline patient characteristics and disease progression values which were inputted into the model. The indirect comparison informed the comparative efficacy of the treatments in terms of HbA1c (%), BMI and non-severe hypoglycaemia.

The company selected utility values from the published literature and, where possible, health state utilities were measured using the EQ-5D from a UK population with type 2 diabetes.

Medicine acquisition costs were included in the model, as were the costs associated with needles, test strips and lancets. The model also accounted for management costs associated with type 2 diabetes and its complications and the event costs relating to adverse events.

The base case results indicated that the incremental cost-effectiveness ratio (ICER) for liraglutide versus lixisenatide was £244 per quality-adjusted life year (QALY) gained on the basis of an incremental cost of £52 and an incremental gain of 0.214 QALYs versus lixisenatide. The ICER for liraglutide versus exenatide was £5,308 per QALY gained on the basis of an incremental cost of £533 and an incremental gain of 0.100 QALYs versus exenatide.

The sensitivity analysis indicated that, for the comparisons versus lixisenatide and exenatide, the model was most sensitive to HbA1c treatment effect from the indirect comparison using upper credible interval, UKPDS 82 risk equations, using a 5-year time horizon and a 10-year time horizon. When these values were applied to the analysis versus lixisenatide the ICERs increased to £5,463, £5,263, £10,424 and £6,945 per QALY gained respectively. For the comparison versus exenatide the ICERs increased to £22,719, £12,595, £21,125 and £16,499 respectively. The company also provided a probabilistic sensitivity analysis and a cost-effectiveness acceptability curve for both comparators. The result indicated that liraglutide has a 100% probability of being cost-effective when compared to lixisenatide and assuming a willingness to pay (WTP) threshold of £30,000. The results also indicated that liraglutide has an 86% probability of being cost-effective when compared to exenatide and assuming a WTP threshold of £30,000.

The main weaknesses with the economic analysis were as follows:

- The main driver of the economic analysis was differences in the initial reduction of Hb1Ac for each of the comparators which was derived through the NMA. In addition, the economic model was sensitive to changes in this parameter as when the upper credible interval from the NMA was used in the analysis the ICER increased to £5,463 for the comparison versus lixisenatide and £22,719 versus exenatide. As noted above, the NMA was associated with some limitations. However, the analysis was considered sufficiently robust to support the clinical data that were used in the economics.
- The base case analysis included results derived from the NMA which were not statistically significant. The company did provide revised analyses with non-significant results removed and the ICER for the comparison versus lixisenatide increased to £277 per QALY gained. For the comparison versus exenatide, the ICER reduced to £4,714 per QALY gained. In addition, the base case ICERs were sensitive to the upper limit of the credible interval of HbA1c treatment effect, and UKPDS 82 risk equations. Therefore, the company was also asked to

provide two sensitivity analyses which used the upper limit of HbA1c treatment and UKPDS 82 risk equations respectively, with non-significant effects removed. The results of these analyses had minimal impact on the ICERs provided in the base case.

- The company used utility values from a published source that has been referenced in other similar health technology assessments. However, the utility values in this submission do not appear to be taken from the main results of the paper. The company provided an analysis with revised utility values that reflected the main results reported in the paper, which had minimal impact on the ICERs.

Despite these issues, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published updated guidance on the "Management of diabetes" in March 2010.[9] The guideline recommends that treatment targets should be individualised to balance the harms of hypoglycaemia and weight gain with the benefits in reducing the risk of microvascular and macrovascular disease. Target glycosylated haemoglobin (HbA1c) of 7.0% (53mmol/mol) is reasonable in people with type 2 diabetes mellitus, and in newly diagnosed patients, this target may be intensified to 6.5% (48mmol/mol). The treatment algorithm notes several options for second and third-line treatment of type 2 diabetes mellitus to be added in combination with metformin and/or sulfonylurea; additional oral anti-diabetic drugs, pioglitazone or DPP-4 inhibitors; or injections of GLP-1 analogues or commencement of insulin. Treatment should be continued if an individualised target is reached or the HbA1c falls at least 0.5% in 3 to 6 months. With respect to using insulin in patients with type 2 diabetes, oral sulphonylurea and metformin therapy should be continued when insulin is initiated to maintain or improve glycaemic control. Once daily, neutral protamine Hagedorn insulin is the first choice of insulin to be used, but basal insulin analogues can be considered if there are concerns regarding the risk of hypoglycaemia. The bedtime basal insulin should be titrated against the morning or fasting glucose and if HbA1c targets are not reached then the addition of prandial insulin should be considered. SIGN currently recommended that Liraglutide may be used as a third line agent to further improve glycaemic control in obese adults *(BMI ≥30kg/m2)* with type 2 diabetes who are already prescribed metformin and a thiazolidinedione and who do not reach target glycaemia.

The National Institute for Health and Care Excellence published NICE Clinical Guideline 87 – Type 2 diabetes - newer agents, in May 2009.[10] The guideline considered sulfonylurea, DPP-4 inhibitors or pioglitazone as suitable second-line options to be used in combination with metformin and advised on cost effective use of exenatide as a third-line agent. The guideline recommended that patients using basal insulin regimens (e.g. neutral protamine Hagedorn or long-acting analogues) be monitored for the need to increase the dose and/or intensify the regimen using short-acting insulin before meals, or pre-mixed insulin. Patients using pre-mixed insulin should be monitored to determine if they need further injections of short-acting insulin before meals or conversion to a basal-bolus regimen. Combination of pioglitazone and insulin was considered appropriate for patients; who have inadequate glycaemic control despite high-dose insulin therapy; or who have had a significant response to thiazolidinedione therapy in the past.

The guidelines predate the extension to the marketing authorization of liraglutide, and as such do not consider the role of GLP-1analogues in combination with insulin.

Additional information: comparators

The most relevant comparators are the other GLP-1 receptor agonists, exenatide and lixisenatide, which are also licensed for use in combination with insulin. There are, however, a number of other medicines licensed for use with insulin including pioglitazone, dapagliflozin and linagliptin, which have been accepted by SMC, and canagliflozin, alogliptin, saxagliptin and vildagliptin which have not been recommended by SMC.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Liraglutide	**1.2 to 1.8mg once daily**	**952 to 1,428**
Exenatide	5 to 10 micrograms twice daily	828
Lixisenatide	20 micrograms once daily	704

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 7 January 2015.

Additional information: budget impact

The submitting company estimated there to be 2,060 patients eligible for treatment with liraglutide in year 1, and 2,060 patients in year 5. Treatment uptake was estimated at 0.5% in year 1, rising to 2.5% in year 5. The discontinuation rate was estimated to be 0%. This resulted in 10 patients assumed to be treated in year 1, rising to 51 patients in year 5.

The submitting company estimated the gross medicines budget impact to be £20k in year 1 and £102k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £6k in year 1 and £32k in year 5. The submitting company also estimated resource use savings associated with a reduction in needles required per day compared to exenatide. The company estimated these savings to be £441 in year 1, rising to £2k in year 5 and, therefore, the net total budget impact was estimated to be £6k year 1, rising to £29k 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. Novo Nordisk A/S. Victoza® Summary of Product Characteristics, 19 December 2014, Version 12.

2. Conway JR et al. Efficacy and Safety of Liraglutide vs. Placebo When Added to Basal Insulin Analogues in Subjects with Type 2 Diabetes (LIRA-ADD2BASAL): A Randomized, Placebo-Controlled Trial. Canadian Journal of Diabetes 2014;38 (5) suppl: S7

3. Lahtela J, Ahmann A, Rodbard HW et al. Efficacy and safety of liraglutide vs. placebo when added to basal insulin analogues in subjects with type 2 diabetes (LIRA-ADD2BASAL): a randomised, placebo-controlled trial. Diabetologia 2014;57 (suppl 1):abstract 37.

4. Mathieu C, Rodbard HW, Cariou B et al. A comparison of adding liraglutide versus a single daily dose of insulin aspart to insulin degludec in subjects with type 2 diabetes (BEGIN: VICTOZA ADD-ON). Diabetes, Obesity and Metabolism 2014;16:636-44.

5. NCT01617434. The Effect of Liraglutide Versus Placebo When Added to Basal Insulin Analogues With or Without Metformin in Subjects With Type 2 Diabetes www.clinicaltrials.gov [accessed 9 January 2015]

6. Clinical Trial Report - Trial ID: NN2211-3917, 25-April-2014, Version 1.0 accessible from: http://novonordisk-trials.com/WebSite/search/TrialDetail.aspx?Command=GetTrialDetail&TrialId=NN2211-3917&Index=0

7. European Medicines Agency. Public Assessment Report: liraglutide (Victoza®), procedure number EMEA/H/C/001026/II/0023. www.ema.europa.eu [accessed 9 January 2015].

8. NCT01388361. Comparison of the Efficacy and Safety of Two Intensification Strategies in Subjects With Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin (BEGIN™) www.clinicaltrials.gov [accessed 9 January 2015]

9. Scottish Intercollegiate Guidelines Network. SIGN 116 Management of diabetes: A national clinical guideline. March 2010. [online] Available from www.sign.ac.uk [Accessed January 2015].

10. National Institute for Health and Clinical Excellence. NICE Clinical Guideline 87 - Type 2 diabetes: the management of type 2 diabetes. May 2009 [online] Available from www.nice.org.uk [Accessed January 2015]

This assessment is based on data submitted by the applicant company up to and including 12 March 2015**.**

**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. 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.