Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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aclidinium/formoterol fumarate dihydrate 340/12 micrograms inhalation powder (Duaklir Genuair®) SMC No. (1034/15)

Almirall / AstraZeneca

6 March 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

aclidinium/formoterol fumarate dihydrate (Duaklir Genuair®) is accepted for use within NHS Scotland.

Indication under review: Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease.

In two 24-week comparator- and placebo-controlled phase III studies, treatment with aclidinium/formoterol 340/12 microgram resulted in statistically significant improvements in FEV_1 % predicted pre-dose (versus a LABA) and post-dose (versus a LAMA).

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease.

Dosing Information

The recommended dose is one inhalation of aclidinium/formoterol 340 micrograms/ 12 micrograms twice daily.

Product availability date

December 2014.

Summary of evidence on comparative efficacy

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterised by airflow limitation, which is not fully reversible. Symptoms include dyspnoea, cough and sputum production.[1] Aclidinium/formoterol 340/12 microgram is a combination product which delivers treatment via the Genuair® inhaler.[2] It contains two bronchodilators: a long-acting muscarinic antagonist (LAMA), aclidinium, plus a long-acting beta agonist (LABA), formoterol. This document refers to the delivered dose (dose leaving the mouthpiece) i.e. 396 micrograms of aclidinium bromide (equivalent to 340 micrograms of aclidinium) and 12 micrograms of formoterol fumarate dihydrate. This corresponds to a metered dose of 400 micrograms of aclidinium bromide and 12 micrograms of formoterol fumarate dihydrate.[1]

Two 24-week placebo- and active-controlled, double-blind phase III studies (ACLIFORM and AUGMENT) have been conducted in patients aged ≥40 years with a clinical diagnosis of stable COPD according to the Global Initiative for Chronic Lung Disease (GOLD) guidelines. Patients were required to be current or ex-cigarette smokers, with a smoking history of at least 10 pack-years, have an FEV_1/forced vital capacity (FVC) at the screening visit of <70% and an FEV_1 % of the predicted normal value of ≥30% and <80% (when measured 10 to 15 minutes post inhalation of 400 micrograms of salbutamol). This equates to stable moderate to severe COPD according to GOLD criteria. Patients hospitalised for COPD exacerbation within three months prior to screening visit were excluded.[1,2]

After a two to three week run-in period, patients with stable COPD were randomised in a ratio of 2:2:2:2:1 (ACLIFORM) or 1:1:1:1:1 (AUGMENT) to aclidinium/formoterol 340/12 microgram, aclidinium/formoterol 340/6 microgram, aclidinium 322 microgram, formoterol 12 microgram or placebo, all given twice daily for 24 weeks. Patients were permitted to continue with inhaled corticosteroids, low doses of oral corticosteroids, oxygen therapy (if less than 15 hours/day) or methylxanthines (all at stable doses), and to use salbutamol as rescue medication.[1,2]

The co-primary endpoints, assessed at 24 weeks, were change from baseline in morning pre-dose (trough) FEV_1 (compared to formoterol) and change from baseline in 1-hour post-morning dose FEV_1 (compared to aclidinium). These were assessed in the intent-to-treat (ITT) population, defined as all randomised patients who took at least one dose of study medication and had a baseline and at least one post baseline FEV_1 assessment. Results for the licensed

dose of aclidinium/formoterol (340/12 microgram) are reported in this document. Results for the primary endpoints for the ACLIFORM, AUGMENT studies are included in table 1 and for the pooled analysis in table 2. [1.2]

Table 1: co-primary endpoints for ACLIFORM and AUGMENT studies[1]

	aclidinium/formoterol 340/12 microgram	**aclidinium 322 microgram**	**formoterol 12 microgram**	**placebo**
ACLIFORM				
Number randomised	385	385	384	194
Pre-dose FEV_1 from baseline to week 24				
LS mean change (standard error)	83mL (0.012)	56mL (0.012)	-2mL (0.012)	-61mL (0.018)
Difference versus formoterol:	85mL (95% CI 51 to 119), p<0.0001	-	-	-
Difference versus placebo	143mL (95% CI 101 to 185), p<0.0001	-	-	-
1-hour post dose FEV_1 from baseline to week 24				
LS mean change (standard error)	269mL (0.013)	144mL (0.013)	129mL (0.013)	-30mL (0.018)
Difference versus aclidinium	125mL (95% CI 90 to 160), p<0.0001	-	-	-
Difference versus placebo:	299mL (95% CI 255 to 343), p<0.0001	-	-	-
AUGMENT				
Number randomised	338	340	339	337
Pre-dose FEV_1 from baseline to week 24				
LS mean change (standard error)	95mL (0.012)	66mL (0.012)	50mL (0.012)	-35mL (0.013)
Difference versus formoterol:	45mL (95% CI 11 to 79), p=0.01	-	-	-
Difference versus placebo:	130mL (95% CI 95 to 165), p<0.0001	-	-	-
1-hour post dose FEV_1 from baseline to week 24				
LS mean change (standard error)	247mL (0.013)	139mL (0.013)	165mL (0.013)	-37mL (0.014)
Difference versus aclidinium:	108mL (95% CI 73 to 144), p<0.0001	-	-	-
Difference versus placebo:	284mL (95% CI 247 to 320), p<0.0001	-	-	-

LS=least squares; CI=confidence interval; FEV_1=forced expiratory volume in one second.

Table 2: co-primary endpoints for pooled analysis of ACLIFORM and AUGMENT studies

	aclidinium/formoterol 340/12 microgram	**aclidinium 322 microgram**	**formoterol 12 microgram**	**placebo**
Number randomised	723	725	723	531
Pre-dose FEV_1 from baseline to week 24				
LS mean change (standard error)	90mL (0.009)	61mL (0.009)	21mL (0.009)	-49mL (0.011)
Difference versus formoterol:	68mL (95% CI 44 to 92), p<0.0001	-	-	-
Difference versus placebo:	138mL (95% CI 111 to 165), p<0.0001.	-	-	-
1-hour post dose FEV_1 from baseline to week 24				
LS mean change (standard error)	259mL (0.009)	141mL (0.009)	145mL (0.009)	-33mL (0.011)
Difference versus aclidinium:	118mL (95% CI 93 to 143), p<0.0001	-	-	-
Difference versus placebo:	293mL (95% CI 265 to 321), p<0.0001	-	-	-

LS=least squares; CI=confidence interval; FEV_1=forced expiratory volume in one second.

Secondary endpoints included transition dyspnoea index (TDI), which measures change from baseline in the patient's dyspnoea by scoring three categories (functional impairment, magnitude of task, and magnitude of effort), and exacerbation rates; these are reported for the pooled population in this document. The LS mean change from baseline in TDI focal score at 24 weeks was 2.29 (standard error 0.13) for aclidinium/formoterol 340/12, 1.85 (0.13) for aclidinium, 1.81 (0.13) for formoterol and 0.85 (0.16) for placebo. Treatment with aclidinium/formoterol 340/12 resulted in improvements relative to aclidinium of 0.44 units (95% CI, 0.08 to 0.79, p=0.016) and to formoterol of 0.47 units (95% CI 0.12 to 0.83, p=0.009). The proportions of patients with clinically meaningful improvements from baseline in TDI focal score (≥1 point) were similar for aclidinium/formoterol 340/12 (62%), aclidinium (56%) and formoterol (57%). [1]

For aclidinium/formoterol 340/12 versus placebo, exacerbation rates (using the healthcare resource utilisation [HRU] definition) classified as moderate/severe resulted in a rate ratio of 0.71 (95% 0.51 to 0.98, CI p=0.036), and for any severity 0.76 (95% 0.56 to 1.03, CI p=0.079). The times to first moderate/severe exacerbation and exacerbation of any severity were significantly delayed by aclidinium/formoterol 340/12 compared to placebo. Using Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) criteria COPD exacerbation rate (any severity) resulted in a rate ratio for aclidinium/formoterol 340/12 versus placebo of 0.78; 95% 0.65 to 0.94, CI p=0.01. [1]

Quality of life was measured using the St George's Respiratory Questionnaire (SGRQ) with decreases indicating an improvement. The LS mean change from baseline in SGRQ total score at week 24 was -6.80 (standard error 0.51) for aclidinium/formoterol 340/12, -6.01 (0.51) for aclidinium, -5.09 (0.51) for formoterol and -4.09 (0.63) for placebo. Only the difference versus formoterol was statistically significant (-1.71 units [95% CI -3.16 to -0.30, p=0.018]). A pooled comparison of aclidinium/formoterol 340/12 versus placebo was not undertaken due to a large and unexpected placebo effect in the ACLIFORM study, resulting in heterogeneity between the studies for this endpoint. The proportions of patients with clinically meaningful improvements in

SGRQ total score (≥4 points) were similar for aclidinium/formoterol 340/12 (57%), aclidinium (54%) and formoterol (52%).[1]

In an extension study (LAC-36), patients who had completed the treatment phase of the AUGMENT study continued to receive the treatment they were originally assigned for an additional 28 weeks. The number of patients who entered LAC-36 was 184, 194, 192 and 146 in the aclidinium/formoterol 340/12, aclidinium, formoterol and placebo groups respectively. The adjusted mean treatment difference for change from baseline in morning pre-dose (trough) FEV_1 between aclidinium/formoterol 340/12 and placebo ranged from 118mL to 152mL over the 52-week treatment period, ($p<0.0001$). The difference between aclidinium/formoterol 340/12 and aclidinium or formoterol were numerically higher at all time points up to week 52. The adjusted mean treatment difference for change from baseline in 1-hour post-morning dose FEV_1 between aclidinium/formoterol 340/12 and placebo ranged from 284mL to 299mL over the 52-week treatment period, ($p<0.0001$). The difference between aclidinium/formoterol 340/12 and aclidinium or formoterol were statistically significant at all time points up to week 52. Rates of HRU and EXACT defined COPD exacerbations were lower for aclidinium/formoterol 340/12 than placebo but not statistically significant.[1]

Summary of evidence on comparative safety

The adverse effect profiles of the constituents (aclidinium and formoterol) are well characterised and no new issues became evident in the phase III studies.

Safety data were from a pooled analysis of the phase III studies (presented in the efficacy section) and an additional active-controlled study (LAC-32). The proportion of patients with at least one treatment-emergent adverse event in the aclidinium/formoterol 340/12, aclidinium, formoterol and placebo groups was 68%, 63%, 68% and 62% respectively. The proportion of patients with a treatment-emergent adverse event that led to study discontinuation was 8.3%, 6.8%, 6.2% and 8.4% in the respective groups. Most treatment-emergent adverse events were mild (42% to 48%) or moderate (38% to 46%) in intensity.[1]

In the placebo-controlled phase III studies, the most commonly reported treatment-emergent adverse events (incidence >5%) in patients treated with aclidinium/formoterol were COPD exacerbation, nasopharyngitis and headache. COPD exacerbations were reported in 17% of patients in the aclidinium/formoterol 340/12 group versus 21% in the placebo group, and severe COPD exacerbations (requiring hospitalisation) in 4.0% versus 4.6% of patients, respectively. COPD exacerbations led to permanent treatment discontinuation in ≤2.5% of patients in any treatment group.[1]

In the placebo-controlled phase III studies, any major adverse cardiac event occurred in 0.8% (6/720) of patients treated with aclidinium/formoterol 340/12 and non-fatal myocardial infarction occurred in 0.6% (4/720) of patients. Event rates were generally similar for the other treatment groups and the majority of patients who experienced cardiac events had pre-existing cardiovascular risk factors. The proportion of patients with cerebrovascular events was <1% in all treatment groups, there were no notable differences between treatments and the majority of events occurred in the 52-week studies.[1]

Summary of clinical effectiveness issues

Clinical presentation, disease severity and rate of disease progression vary greatly in patients with COPD and the degree of airflow limitation (measured by FEV_1) is known to be poorly correlated to the severity of their symptoms.[1] The GOLD strategy recommends COPD assessment based on the impact of COPD on the individual patient, taking into consideration symptomatic assessment, spirometric classification and/or risk of exacerbations.[3]

Aclidinium/formoterol is the third LABA/LAMA inhaler (combining both drugs in one inhalation device) to be licensed for COPD in the UK. Two other LABA/LAMA combination inhalers have been assessed by SMC: umeclidinium/vilanterol (Anoro®) and indacaterol/glycopyrronium (Ultibro Breezhaler®). Single component inhalers licensed for maintenance treatment in COPD include LABAs (formoterol, indacaterol, salmeterol, olodaterol) and LAMAs (aclidinium, umeclidinium, glycopyrronium, tiotropium).

In the two 24-week phase III studies, treatment with aclidinium/formoterol 340/12 microgram resulted in statistically significant improvements in FEV_1 pre-dose (versus formoterol and placebo) and post-dose (versus aclidinium and placebo). However, the improvement in pre-dose FEV_1 for aclidinium/formoterol versus formoterol and improvements in TDI versus aclidinium and versus formoterol were not considered to be clinically significant. The European Medicines Agency (EMA) commented that post hoc responder analysis for clinically meaningful effect on FEV_1 (as well as symptomatic endpoints) provides reassurance that aclidinium contributes to the overall effect of the aclidinium/formoterol combination.

There were statistically significant differences in exacerbation rates for aclidinium/formoterol 340/12 versus placebo in the 24-week studies but not in the extension study. However, the reduction in exacerbations (by EXACT criteria) relative to placebo of 0.33/patient/year for aclidinium/formoterol 340/12 in the 24-week studies are unlikely to be clinically significant.[1]

There are no direct comparative data versus combinations of LABA plus LAMA either delivered in one inhaler or as separate inhalers. Consequently, the submitting company performed a network meta-analysis (NMA) to evaluate the relative efficacy and safety of the combination inhalers, aclidinium/formoterol 340/12 microgram, umeclidinium/vilanterol 55/22 microgram, indacaterol/glycopyrronium 85/43 microgram and tiotropium 18 microgram + formoterol 10 microgram (delivered as separate inhalers). The NMA was conducted in adult patients with moderate to severe COPD. Six studies were included in the analysis, with four efficacy endpoints (peak FEV_1, trough FEV_1, TDI focal score and SGRQ total score) and two safety endpoints (any adverse event and serious adverse event) being assessed. Aclidinium/formoterol had a >99% probability of being better than placebo for all efficacy endpoints. The submitting company concluded that aclidinium/formoterol was shown to be broadly comparable to other LAMA/LABA combinations in terms of bronchodilation, breathlessness, health status and safety. There was no comparison with salmeterol + tiotropium (or indacaterol + tiotropium), delivered as separate inhalers, as no studies met the inclusion criteria. However, the comparable efficacy of aclidinium/formoterol with LABA plus LAMA comparators was accepted.

Clinical experts consulted by SMC confirmed that aclidinium/formoterol would be used in patients whose COPD is inadequately controlled with a LAMA or LABA separately, and its use

would avoid the requirement for two separate inhalers. They noted that another LAMA/LABA combination inhaler has been accepted for use by SMC which requires once daily administration. Differences in delivery devices were also noted.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis which compared aclidinium/formoterol against the following LAMA/LABA combinations: tiotropium+formoterol, umeclidinium/vilanterol, indacaterol/glycopyrronium, salmeterol+tiotropium and indacaterol+tiotropium.

A one year time horizon was used and the analysis was performed from a Scottish NHS perspective.

Data used to support the comparable efficacy of these combinations were derived from a NMA. The company stated that aclidinium/formoterol is expected to be more efficacious than umeclidinium/vilanterol in terms of peak FEV_1, and aclidinium/formoterol is expected to be less efficacious than indacaterol/glycopyrronium in terms of trough FEV_1. However, all differences observed were lower than the minimal clinically important difference (MCID), suggesting comparable efficacy between treatments. In all other efficacy and safety end points, aclidinium/formoterol is expected to produce similar improvements compared to umeclidinium/vilanterol, indacaterol/glycopyrronium and tiotropium+formoterol. Salmeterol+tiotropium and indacaterol+tiotropium were not included in the NMA due to a lack of evidence, and the published literature was referenced in order to support the comparable efficacy of these treatments compared to aclidinium/formoterol.

The cost-minimisation analysis focussed on medicine costs only and no other costs were considered in the analysis.

The results of the cost-minimisation analysis indicated that the cost per year of aclidinium/formoterol was £395.69, which was the same as the estimated yearly cost of umeclidinium/vilanterol. In addition, the cost per year of aclidinium/formoterol was reported as less than the associated costs of indacaterol/glycopyrronium, tiotropium+formoterol, indacaterol+tiotropium and salmeterol+tiotropium which were estimated as £448.70, £553.73, £765.49 and £765.49 respectively. On this basis, aclidinium/ formoterol would be considered a cost-effective treatment option.

The company also provided a supporting cost-utility analysis which compared aclidinium/formoterol with aclidinium monotherapy. The company submitted a Markov model, which estimated that the incremental cost-effectiveness ratio (ICER) for aclidinium/formoterol versus aclidinium was £2,976 per quality adjusted life year (QALY) gained. This result was based on an incremental cost of aclidinium/formoterol versus aclidinium of £41 and an incremental QALY gain of 0.014 QALYs. However, the company stated this to be a supportive analysis only as it asserted that the key comparators for aclidinium/formoterol were included in the cost-minimisation analysis and, as such, that the cost-minimisation analysis represented the relevant base case for consideration by the New Drugs Committee (NDC).

The main weakness related to the evidence base underpinning the economic analysis. Two of the comparators, salmeterol+tiotropium and indacaterol+tiotropium, were not formally evaluated

in the NMA. The company justified not including other LAMA and LABA combinations in the NMA as no studies met the inclusion criteria. However, the New Drugs Committee concluded that comparable efficacy of aclidinium/formoterol with an appropriate range of LAMA plus LABA comparators had been adequately demonstrated

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published an update to clinical guideline 101; Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care, in June 2010.[5] The guideline recommends the following:
In people with stable COPD who remain breathless or have exacerbations despite use of short-acting bronchodilators as required, offer the following as maintenance therapy:

- FEV_1 ≥50% predicted: either LABA or LAMA
- FEV_1 <50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler, or LAMA alone. Consider LABA plus LAMA instead of LABA plus inhaled corticosteroid if the corticosteroid is declined or not tolerated

In people with FEV_1 ≥50% predicted who have persistent exacerbations or breathlessness despite treatment with a LABA, offer a LABA plus inhaled corticosteroid in a combination inhaler. Consider LABA plus LAMA if the corticosteroid is declined or not tolerated.

Offer LAMA in addition to LABA plus inhaled corticosteroid to people with COPD who remain breathless or have exacerbations despite taking LABA plus inhaled corticosteroid, irrespective of their FEV_1.

The following points are also included:

- Choose a drug based on the person's symptomatic response and preference, the drug's side effects, potential to reduce exacerbations and cost.
- Do not use oral corticosteroid reversibility tests to identify patients who will benefit from inhaled corticosteroids.
- Be aware of the potential risk of developing side effects (including non-fatal pneumonia) in people with COPD treated with inhaled corticosteroids and be prepared to discuss this with patients.

The Global initiative for chronic Obstructive Lung Disease (GOLD) updated their global strategy for diagnosis management and prevention of chronic obstructive pulmonary disease in January 2014.[3] In terms of pharmacological treatment, four patient groups are identified and treatments for these include;

- Group A: In patients with few symptoms and a low risk of exacerbations the use of a short acting bronchodilator when required is recommended as first choice. Alternative choices are a combination of short acting bronchodilators or use of a long acting bronchodilator.
- Group B: In patients with more significant symptoms but at a low risk of exacerbations the use of long acting bronchodilators is recommended with no class recommended over

another for initial treatment. In patients with severe breathlessness the use of a combination of long acting bronchodilators is an option.

- Group C: In patients with few symptoms but a high risk of exacerbations a fixed combination of ICS plus LABA or a LAMA is recommended as first choice. Alternative choices are use of two long acting bronchodilators or ICS plus LAMA.
- Group D: In patients with many symptoms and a high risk of exacerbations the first choice is ICS plus LABA or LAMA. A second choice is ICS plus LABA plus LAMA.

Additional information: comparators

Relevant comparators to umeclidinium/vilanterol are combination treatments with an inhaled LABA and an inhaled LAMA: formoterol, indacaterol, salmeterol, olodaterol (LABAs) and aclidinium, umeclidinium, glycopyrronium, tiotropium (LAMAs). The combination products, indacaterol/glycopyrronium (Ultibro Breezhaler®) and umeclidinium/vilanterol (Anoro®) are also licensed.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Aclidinium/formoterol	**340/12 micrograms twice daily**	**394**
Umeclidinium/vilanterol	55/22 micrograms once daily	394
Indacaterol/glycopyrronium	85/43 micrograms once daily	447
Long-acting beta agonists		
Indacaterol	150 to 300 micrograms once daily	355
Salmeterol	50 micrograms twice daily	355
Olodaterol	5 micrograms once daily	320
Formoterol	12 micrograms twice daily*	144
Long-acting muscarinic antagonists		
Tiotropium (Spiriva Handihaler®)	18 micrograms once daily	406
Tiotropium (Spiriva Respimat®)	5 micrograms once daily	406
Aclidinium	322 micrograms twice daily	347
Glycopyrronium	44 micrograms once daily	334
Umeclidinium	55 micrograms once daily	334

Doses are for general comparison and do not imply therapeutic equivalence. *There is some dose variation among different formulations of formoterol. For cost of LABA plus LAMA comparators, the costs of individual treatments should be added. Costs are from eVadis and MIMS on 19 December 2014 and 27 January 2015 (for aclidinium/formoterol).

Additional information: budget impact

The submitting company estimated there to be 105,000 patients eligible for treatment with aclidinium/formoterol in year 1 and 111,180 patients in year 5. Treatment uptake was estimated at 2% in year 1, rising to 14% in year 5. The discontinuation rate was estimated to be 0%. This resulted in 2,100 patients assumed to be treated in year 1 rising to 15,009 patients in year 5.

The submitting company estimated the gross medicines budget impact to be £831k in year 1 and £6m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of £655k in year 1 rising to a saving of £4.8m in year 5.

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. Assessment report for aclidinium/formoterol (Duaklir Genuair). EMA/CHMP/713778/2014 25 September 2014.
2. Summary of product characteristics for aclidinium/formoterol (Duaklir Genuair®).
3. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis Management and Prevention of Chronic Obstructive Pulmonary Disease. January 2014.
4. National Institute for Health and Care Excellence. CG101; Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). June 2010.

This assessment is based on data submitted by the applicant company up to and including 13 February 2015.

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.