Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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tedizolid phosphate 200mg film-coated tablets and 200mg powder for concentrate for solution for infusion (Sivextro®) SMC No. (1080/15)

Cubist (UK) Limited/Merck Sharp & Dohme Limited

10 July 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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tedizolid phosphate (Sivextro®) is accepted for restricted use within NHS Scotland.

Indication under review: The treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

SMC restriction:

- Use in patients with ABSSSI caused by Gram-positive *Staphylococcus aureus* (specifically methicillin-resistant *Staphylococcus aureus* [MRSA] isolates)
- Use of tedizolid phosphate is restricted to use as an alternative oxazolidinone antibacterial on the specific advice of local microbiologists or specialists in infectious disease.

In two randomised, double-blind clinical studies, tedizolid phosphate was non-inferior to another oxazolidinone antibacterial in adult patients with ABSSSI.

The presenting company did not submit any evidence for SMC to consider around the use of tedizolid phosphate in "mixed infections", where the infection involves both Gram-positive and Gram-negative organisms.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Published 10 August 2015

Indication

The treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Dosing Information

Tedizolid phosphate film-coated tablets or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to the oral one when clinically indicated.

The recommended dosage is 200mg once daily for six days.

The safety and efficacy of tedizolid phosphate when administered for periods longer than six days have not been established.

Product availability date

7 May 2015

Summary of evidence on comparative efficacy

Tedizolid phosphate is an oxazolidinone prodrug which is converted to the active drug, tedizolid, by intestinal alkaline phosphatase enzymes. It acts as an antibacterial by binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis. Tedizolid is bacteriostatic against enterococci, staphylococci, and streptococci *in vitro* and is primarily active against Gram-positive bacteria.[1] It is the second oxazolidinone antibacterial to be licensed for use in patients with ABSSSI; linezolid was the first and its use predates SMC.[2]

The submitting company has requested that SMC considers tedizolid phosphate when positioned for use in patients with ABSSSI caused by Gram-positive *Staphylococcus aureus* (specifically methicillin-resistant *Staphylococcus aureus* [MRSA] isolates) only. The company did not wish SMC to consider the use of tedizolid phosphate in "mixed infections"; that is, where the infection involves both Gram-positive and Gram-negative organisms.

Evidence to support the marketing authorisation comes from two phase III, double-blind, double-dummy, multi-centre, randomised, controlled studies designed to investigate the non-inferiority of tedizolid phosphate versus linezolid in patients with ABSSSI; ESTABLISH-1 and ESTABLISH-2.[3-5]

ESTABLISH-1 enrolled adults (≥18 years) with cellulitis/erysipelas, major cutaneous abscess or wound infection surrounded by erythema with a minimum total lesion surface area of 75cm^2, which was accompanied by at least one local and one regional (lymphadenopathy) or one systemic (oral temperature ≥38^{o}C, white blood cell count ≥10,000/µL or <4,000/µL, or >10% of immature neutrophils) sign of infection and a Gram-positive pathogen was suspected or documented. Patients were randomised equally and stratified by presence or absence of fever at baseline, geographic region (North America, Latin America, Europe), and type of ABSSSI (cellulitis/erysipelas, major cutaneous abscesses [maximum of 30% of the total study

population], or wound infection) to receive tedizolid phosphate 200mg orally once daily for six days or linezolid 600mg orally twice daily for 10 days.[3]

The primary outcome was early clinical response at the 48 to 72 hour assessment in the intention to treat (ITT) analysis set. Patients were categorised as treatment responders if they were afebrile (temperature ≤37.6°C at the 48 to 72 hour assessment and confirmed within the next three to 24 hours), had cessation of primary ABSSSI lesion spread (defined as no increase in lesion surface area) compared with baseline, did not receive prohibited concomitant antibiotics, and did not die of any cause.[3] The European Medicines Agency (EMA) requested additional co-primary endpoints: investigator's assessment of clinical success at the post-therapy evaluation (PTE) visit in the ITT and clinically evaluable (CE)-PTE populations.[5]

The early clinical response rates were 80% (264/332) in the tedizolid phosphate group and 79% (266/335) in the linezolid group, treatment difference 0.1% (95% confidence interval [CI]: -6.1 to 6.2). As the lower limit of the 95% CI was greater than -10% then non-inferiority was demonstrated.[3]

Secondary outcomes are presented in Table 1; all comparisons demonstrated non-inferiority of tedizolid phosphate to linezolid.[3] Sustained clinical response used the same criteria as early response but the patient was additionally considered a treatment failure at the end of treatment (EOT) if they reported pain or if the investigator determined that the patient's tenderness was worse than mild. Clinical success was assessed by the investigator and was considered to be the resolution of most disease-specific signs and symptoms, including systemic signs of infection present at baseline, and no new signs, symptoms, or complications attributable to the acute bacterial skin and skin structure infection such that further antibiotic therapy is required to treat the primary lesion.

Table 1. ESTABLISH-1 secondary outcomes[3]

Outcome	**Tedizolid phosphate**	**Linezolid**
Objective sustained clinical response at EOT in the ITT analysis set	69% (230/332)	72% (241/335)
Objective sustained clinical response at EOT in the CE-EOT analysis set	80% (219/273)	81% (232/286)
Investigator's assessment of clinical success at PTE in the ITT analysis set (EMA co-primary endpoint)	86% (284/332)	86% (288/335)
Investigator's assessment of clinical success at PTE in the CE-PTE analysis set (EMA co-primary endpoint)	95% (264/279)	95% 267/280)

EOT: end of treatment, day 11. PTE: post-therapy evaluation, seven to 14 days after the EOT.
CE-EOT: clinically evaluable EOT population. CE-PTE: clinically evaluable PTE population

Investigator assessment of clinical success (similar to above ITT definition) at PTE in patients with MRSA isolates at baseline was 85% (75/88) and 86% (77/90) in the tedizolid phosphate group and the linezolid group respectively.[3]

ESTABLISH-2 enrolled patients who were ≥12 years of age with ABSSSI, accompanied by at least one regional or systemic (lymphadenopathy, raised body temperature, white blood cell count ≥10,000/μL or <4,000/μL, or >10% of immature neutrophils) sign of infection and a Gram-positive pathogen was suspected or documented.[4]

Patients were randomised and stratified in the same manner as ESTABLISH-1 to receive tedizolid phosphate 200mg by intravenous (IV) infusion once daily for six days or linezolid 600mg by IV infusion twice daily for 10 days, with optional oral step-down.

Patients who had received at least two IV doses of study treatment could be switched to oral treatment at the investigators discretion if at least two of the following criteria were satisfied:

- no increase from baseline in primary lesion area, length or width
- temperature less than 37.7^{o}C
- no worsening of local signs and symptoms at the primary infection site
- improvement of one or more local signs or symptoms since the previous visit.

The primary outcome was early clinical response at the 48 to 72 hour assessment in the ITT analysis set.[4] Patients were categorised as treatment responders if they had a ≥20% reduction from baseline in the primary lesion, did not receive any systemic concomitant antibiotics with Gram-positive activity, and did not die from any cause within 72 hours of the first dose.[4] The EMA again requested additional co-primary endpoints of investigator's assessment of clinical success at the PTE visit in the ITT and CE-PTE populations.[5]

The early clinical response rates were 85% (283/332) in the tedizolid phosphate group and 83% (276/334) in the linezolid group, treatment difference 2.6% (95% CI: -3.0 to 8.2). As the lower limit of the 95% CI was greater than -10%, non-inferiority was demonstrated.[4] Exploratory analyses of the subgroups generally supported the primary outcome. In the patients with MRSA at baseline, 83% (44/53) in the tedizolid phosphate group achieved early clinical response at the 48 to 72 hour assessment compared with 79% (44/56) in the linezolid group, treatment difference 4.4% (95% CI: -10.8 to 19.5).[4]

Selected secondary outcomes are presented in Table 2. Clinical success at 48 to 72 hours and day seven was defined as improvement in overall clinical status of ABSSSI compatible with continuation of study drug. Clinical success at PTE was defined as resolution or near resolution of disease-specific signs and symptoms, absence or near resolution of baseline systemic signs of infection, and no further antibiotic treatment required for treatment of primary ABSSSI lesion. Clinical success at late-follow up defined as no new signs or symptoms of primary ABSSSI after post-therapy assessment and was only assessed in patients who were clinically evaluable and deemed clinical successes at post-therapy assessment. All comparisons demonstrated non-inferiority of tedizolid phosphate to linezolid.[4]

Table 2. ESTABLISH-2 secondary outcomes .[4,5]

Outcome	Tedizolid phosphate	Linezolid
Clinical success at 48 to 72 hours in the ITT analysis set	92% (304/332)	90% (302/334)
Clinical success at day seven in the ITT analysis set	93% (309/332)	92% (308/334)
Clinical success at PTE in the ITT analysis set (EMA co-primary endpoint)	88% (292/332)	88% (293/334)
Clinical success at late follow-up in the ITT analysis set	98% (262/268)	99% (266/269)
Clinical success at PTE in the CE-PTE analysis set (EMA co-primary endpoint)	92% (268/290)	96% (269/280)

PTE: post-therapy evaluation, seven to 14 days after the end of treatment. Late follow-up: 18 to 25 days after end of treatment. CE-PTE: clinically evaluable PTE population

A favourable microbiological response was defined as eradication (absence of baseline pathogen) or presumed eradication (no source specimen to culture and patient assessed as clinical success by the investigator). At the post-therapy assessment visit in the microbiological ITT population (patients with a gram-positive pathogen isolated at baseline) a favourable microbiological response was demonstrated in 88% (168/192) of patients in the tedizolid phosphate group and 89% (177/199) of patients in the linezolid group, difference -1.4% (95% CI: -8.0 to 5.1). In patients with MRSA, 81% (43/53) of patients in the tedizolid phosphate group and 77% (43/56) of patients in the linezolid group had a favourable microbiological response, difference 4.3% (95% CI: -11.4 to 19.8).[4]

The mean time to oral switch (standard deviation) was 1.7 days (1.18) in the tedizolid phosphate group and 1.8 days (1.35) in the linezolid group, p=0.99.[4]

Summary of evidence on comparative safety

Treatment was generally well tolerated in both studies and most adverse events were mild to moderate. Nausea, headache and diarrhoea were commonly reported treatment-emergent adverse events.[3-5]

In ESTABLISH-1, treatment-emergent adverse events were reported in 41% (135/331) of patients in the tedizolid phosphate group and 43% (145/335) of patients in the linezolid group. Serious treatment-emergent adverse events were reported in 1.5% and 1.2% of patients in the respective groups. An adverse event leading to study drug discontinuation occurred in two patients in each treatment group.[3,5]

In ESTABLISH-2, treatment-emergent adverse events were reported in 45% (148/331) of patients in the tedizolid phosphate group and 43% (141/327) of patients in the linezolid group. Serious treatment-emergent adverse events were reported in 2.1% and 2.7% of patients in the

respective groups. An adverse event leading to study drug discontinuation was reported by one patient in the tedizolid phosphate group and four patients in the linezolid group.[4,5]

In ESTABLISH-2, platelet counts less than the lower limit of normal (<150x10^9/L) were reported in 8.6% and 13% of patients in the tedizolid phosphate group and linezolid group respectively (p=0.071). Absolute neutrophil counts less than the lower limit of normal (<1.6x10^9/L) were reported in 2.8% and 7.0% of patients in the tedizolid phosphate and linezolid groups respectively (p=0.024). Post-baseline haemoglobin values below the lower limit of normal were similar between the treatment groups.[4,5]

Summary of clinical effectiveness issues

ABSSSI are common in both the hospital and community setting and are a significant source of morbidity and mortality.[5] A glycopeptide (e.g. vancomycin or teicoplanin) can be used for severe skin and soft-tissue infections associated with MRSA. , If a glycopeptide is unsuitable, linezolid can be used on expert advice.[2] Ceftaroline, tigecycline and daptomycin are also licensed for the treatment of complicated skin and soft-tissue infections[2] and SMC has accepted all three drugs for restricted use on the advice of microbiologists or specialists in infectious diseases. The use of ceftaroline and daptomcyin is further restricted to patients with known or suspected MRSA. The submitting company has indicated that the proposed eligible population for tedizolid phosphate is patients with ABSSSI caused by MRSA, where there is no Gram negative involvement, and in whom vancomycin is considered ineffective or not appropriate by local microbiologists or specialists in infectious disease. The patient population in the clinical studies does not match this proposed positioning.

The primary outcome of the studies was a surrogate marker, early clinical response at 48 to 72 hours. The definition was more stringent in ESTABLISH-2 than ESTABLISH-1; treatment responders in ESTABLISH-1 had cessation of primary ABSSSI lesion spread compared with baseline, in ESTABLISH-2 a ≥20% reduction in the primary lesion from baseline was required. The co-primary outcomes requested by the EMA were clinical success at the post-therapy evaluation (seven to 14 days after the end of treatment) measured in the ITT population and the CE-PTE population. Clinical success was defined as resolution or near resolution of disease-specific signs and symptoms, absence or near resolution of baseline systemic signs of infection, and no further antibiotic treatment required for treatment of primary ABSSSI lesion. This could be considered a direct health outcome and non-inferiority of tedizolid phosphate to linezolid was demonstrated in both studies.[5]

A low number of patients with concomitant bacteraemia were enrolled in the clinical studies therefore evidence for these patients is limited.[5] Patients with burns, infected diabetic foot ulcers and local complications including osteo-articular or necrotising infections were excluded from the studies, however this was considered acceptable by the EMA.[5] Patients with neutropenia (neutrophil counts <1000 cells/mm^3) or who were severely immunocompromised were also excluded.[1] Exploratory analyses demonstrated a numerically lower response rate in the tedizolid phosphate group compared with the linezolid group in patients with a higher body mass index, in patients with diabetes and in patients with major cutaneous abscess.[5]

In ESTABLISH-1 tedizolid phosphate was administered orally and in ESTABLISH-2 most patients in the tedizolid phosphate group only received one IV dose before switching to oral treatment, therefore most of the evidence relates to the use of oral tedizolid phosphate.[5] Patients were prohibited from taking medications with potential adrenergic or serotonergic

activity, e.g. selective serotonin re-uptake inhibitors, or triptans, as this is a contraindication to taking linezolid. Therefore, there are limited data on the safety of tedizolid phosphate in combination with these medications.[1,5,6] Tedizolid phosphate should only be used for six days; the safety and efficacy of longer treatment courses has not been established.[1]

Tedizolid phosphate and linezolid are available as both oral and IV preparations. Vancomycin, teicoplanin, ceftaroline, daptomycin and tigecycline are only available as IV preparations for the indication under review.[2] Tedizolid phosphate is administered once daily compared to twice daily linezolid and it requires a shorter treatment course than linezolid, six days versus 10 to 14 days. Patients receiving linezolid who are at risk of myelosuppression should have their blood counts monitored closely and all patients should have a full blood count checked weekly, this is not required with tedizolid phosphate.[1,6] Clinical experts consulted by SMC considered that tedizolid phosphate provides an alternative to treatment with linezolid.

Summary of comparative health economic evidence

The submitting company presented a cost minimisation analysis (CMA) comparing tedizolid phosphate with linezolid for the treatment of ABSSSI in adults. The company positioned tedizolid phosphate for the use of patients with ABSSSI caused by Gram-positive staphylococcus aureus (specifically methicillin-resistant isolates) only. From the SMC clinical expert responses received, the comparator seems appropriate. The time horizon in the analysis was based upon the duration of antibiotic treatment; this was assumed to be 6 days for tedizolid phosphate and 10 days for linezolid. The company highlighted this may include the period of hospitalisation and the period after discharge related to the treatment period of the antibiotic.

The clinical data used to support the analysis were from the ESTABLISH-1 and ESTABLISH-2 studies described above. The results suggested that non-inferiority had been demonstrated between tedizolid phosphate and linezolid in terms of efficacy. This was used to support the assumption of comparable efficacy which underpinned the CMA.

Medicines costs were included in the analysis; in addition, costs associated with administering and monitoring treatment have been included.

The company estimated in the base case that the cost of a course of treatment with tedizolid phosphate was £928 and the cost of a course of treatment of linezolid was £1,020, resulting in savings of £92 per course of treatment with tedizolid phosphate. The cost savings were driven by lower monitoring costs associated with tedizolid phosphate.

The company performed a variety of one way and scenario sensitivity analyses. The results were most sensitive to reducing the proportion of patients being monitored on linezolid. When this was reduced to 80% and 60% the savings fell to £82 and £72 respectively.

In terms of limitations, as noted above in the submission tedizolid phosphate is expected to displace the use of linezolid in a post-vancomycin treatment setting (or where vancomycin is not appropriate) on the specific advice of local microbiologists or specialists in infectious disease. The patient population in the clinical studies does not match this proposed positioning, which may introduce some uncertainty. However, on reflection this was judged as not likely to change the overall conclusion.

Tedizolid phosphate has demonstrated comparable efficacy to linezolid and based on this assumption, is cost-saving. Given this, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from MRSA Action UK, a registered charity.
- MRSA Action UK has received pharmaceutical company funding in the past two years but not from the submitting company.
- Wound and skin infections present problems, ranging from wounds not healing, to infection spread and anxiety for patients and their families. When infection has not responded well to treatment, bloodstream infections arise and sometimes death.
- Difficulties for patients at home who have persistent infection include keeping items separate and doing frequent laundering of bedding, towels and associated items particularly if they are unwell and may not have the support at home to help them. For patients in hospital, it can lead to a more lengthy stay in hospital when infected wounds do not heal.
- The antimicrobial resistance problem is a national / global one that has been well reported. Therefore any additional medicines that can help alleviate the symptoms of infections and aid in the healing process would be welcomed by patients and their families.
- Tedizolid has the potential to significantly help patients who experience skin and wound infections, having a significant impact on the quality of life for patients and those caring for them.

Additional information: guidelines and protocols

The Scottish Antimicrobial Prescribing Group (SAPG), in conjunction with the Scottish Microbiology and Virology Network, published a best practice algorithm for the management of patients with *Staphylococcus aureus bacteriaemia* (SAB) in 2015. The algorithm indicates that empirical antibiotic therapy should be initiated promptly in all patients presenting with confirmed or suspected SAB. If MRSA is suspected this should consist of treatment with vancomycin in accordance with local protocols. In patients who are intolerant, allergic or not responding well to vancomycin, alternative treatment options should be discussed with an infectious disease specialist or microbiologist.[7] Evidence for the use of tedizolid phosphate in patients with SAB is limited.

The 2008 British Society for Antimicrobial Chemotherapy (BSAC) evidence based guideline for the management of MRSA infections in the UK includes a number of recommendations for management of skin and soft tissue infections (table 3). The guideline states that no recommendations could be made regarding new licensed agents due to a lack of real world data.[8]

Table 3. BSAC 2008 guideline recommendations for MRSA skin and soft tissue infections

Indication	**Suggested treatment (dependent on susceptibility testing)**
Impetigo and boils	• Topical mupirocin or fusidic acid
Cellulitis/surgical site infections; non-hospitalised	• Doxycycline or clindamycin unless the infection is severe or there is a high risk of bacteraemia or endocarditis • If MRSA strain is resistant then glycopeptides or linezolid should be used. Co-trimoxazole may also be considered. • Glycopeptides or daptomycin parental therapy may be considered cost effective for outpatient treatment where IV treatment is necessary
Cellulitis/surgical site infections; hospitalised	• Glycopeptides, linezolid or daptomycin for severe infection or where there is a high risk of bacteraemia • Tigecycline monotherapy may be considered in polymicrobial infections • *There is insufficient evidence to make a recommendation on treatment options after failure of glycopeptide monotherapy.*
Intravenous infusion sites	• Glycopeptide or linezolid • Mild infection may respond to oral agents

The BSAC guidance on the treatment of MRSA infections presenting in the community was also published in 2008.[9] A number of empirical antibiotic regimens are suggested for MRSA skin and soft tissue infections:

- Rifampicin (300mg orally twice daily) PLUS sodium fusidate (500mg three times a day) OR doxycycline (100mg orally twice daily) for five to seven days.
- Rifampicin (300mg orally twice daily) PLUS trimethoprim (200mg orally twice daily) for five to seven days.
- Linezolid (600mg orally twice daily) following discussion with Consultant Microbiologist or Infectious Disease physician.

Additional information: comparators

Vancomycin, teicoplanin, linezolid, ceftaroline, tigecycline and daptomycin are licensed for the treatment of complicated skin and soft-tissue infections.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
tedizolid phosphate	**200mg orally or by IV infusion once daily for six days**	**862**
linezolid	600mg orally or by IV infusion every 12 hours for 10 to 14 days	890 to 1246
daptomycin	4mg/kg to 6mg/kg by IV infusion once daily	434 to 1240
ceftaroline	600mg by IV infusion every 12 hours	525 to 1050
tigecycline	Initial dose of 100mg by IV infusion followed by 50mg by IV infusion every 12 hours	485 to 937
vancomycin	500mg by IV infusion every six hours or 1g by IV infusion every 12 hours	203 to 406
teicoplanin	400mg by IV injection/infusion or by intramuscular injection every 12 hours for three doses followed by 6mg/kg by IV injection/infusion or intramuscular injection once daily	59 to 110

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and Monthly Index of Medical Specialties on 23 April 2015. Costs are based on 7 to 14 days treatment duration unless otherwise specified. Dose per weight calculations are based on a body weight of 70kg.

Additional information: budget impact

The submitting company estimated there to be 40 patients eligible for treatment with tedizolid phosphate each year with an estimated uptake rate of 5% in year 1 and 45% in year 5. It is not possible to deduce from the SMC clinical expert responses received if these estimates are reasonable.

The submitting company estimated the gross medicines budget impact to be £2k in year 1 and £16k in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated as a saving of £56 in year 1 and £500 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. Tedizolid phosphate 200mg film-coated tablets and 200mg powder for concentrate for solution for infusion (Sivextro®) Summary of product characteristics. Cubist (UK) Ltd. European Medicines Agency www.ema.europa.eu Last accessed 14/04/2015
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7. Scottish Antimicrobial Prescribing Group (SAPG) and Scottish Microbiology and virology network. *Staphylococcus aureus* bacteraemia management algorithm. 2015.
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9. Nathwani D, Morgan M, Masterton R.G. et al. Guidelines for UK practice for the diagnosis and management of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presenting in the community. J. Antimicrob. Chemother. *(*2008) 61 (5): 976-994.

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