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

Resubmission

fingolimod (as hydrochloride), 0.5mg hard capsules (Gilenya®)

SMC No. (763/12)

Novartis Pharmaceuticals UK Ltd

10 August 2012

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 resubmission

fingolimod (Gilenya®) is accepted for restricted use within NHS Scotland.

Indication under review:
As single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon.
  These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion.
  A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

- Patients with rapidly evolving severe RRMS defined by two or more disabling relapses in one year, and with one or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

SMC restriction: restricted to use as single disease modifying therapy in highly active RRMS in adult patients with high disease activity despite treatment with a beta-interferon with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

Fingolimod reduced the annualised relapse rate significantly more than a beta-interferon in patients with clinically active RRMS. An indirect comparison also demonstrated similar efficacy to another disease modifying therapy in established use in RRMS.

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

Published 10 September 2012

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Indication

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- Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion.
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or

- Patients with rapidly evolving severe RRMS defined by two or more disabling relapses in one year, and with one or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Dosing Information

One 0.5mg capsule taken orally once daily with or without food.
The treatment should be initiated and supervised by a physician experienced in multiple sclerosis.

Product availability date

11 April 2011

Summary of evidence on comparative efficacy

Fingolimod (as hydrochloride) is the first sphingosine 1-phosphate (S1P) receptor modulator to be licensed. After metabolism by sphingosine kinase, the active metabolite, fingolimod phosphate, acts as a functional antagonist of S1P receptors on lymphocytes, preventing lymphocytes from crossing the blood-brain barrier and causing damage to nerve cells in the brain and spinal cord. It is thought that the disease modifying effect in multiple sclerosis is due to this redistribution, reducing the infiltration of pathogenic lymphocyte cells into the central nervous system where they would be involved in nerve inflammation and nervous tissue damage.

Fingolimod is the first disease modifying preparation that may be administered orally in the treatment of multiple sclerosis (MS). It has a marketing authorisation for use as a single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis (RRMS) in patients with high disease activity despite treatment with a beta-interferon and in patients with rapidly evolving severe relapsing-remitting multiple sclerosis. The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of this product when positioned for use in the population of patients with high disease activity despite treatment with a beta-interferon and with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

The evidence to support the marketing authorisation is from two double-blind studies, TRANSFORMS[1] and FREEDOMS[2], that recruited patients between 18 and 55 years of age with RRMS (revised McDonald criteria) and at least one documented relapse during the previous year or at least two documented relapses during the previous two years. Patients were required to have a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS) (range 0 to 10, with higher scores indicating a greater degree of disability). Previous recent therapy with a beta-interferon or glatiramer acetate was permitted in TRANSFORMS but was required to have been stopped at least three months before randomisation in FREEDOMS.

TRANSFORMS was a 12-month study in 1,292 patients and FREEDOMS was a 24-month study in 1,272 patients. Both studies randomised patients in a 1:1:1 ratio, with stratification for site, to treatment with oral fingolimod 0.5mg or 1.25mg once daily or, in the TRANSFORMS study, intramuscular interferon beta 1a 30 micrograms (Avonex®) once weekly, and in the FREEDOMS study, oral placebo once daily. Baseline characteristics in both studies were consistent with a patient population with clinically active RRMS. The mean number of relapses in the previous year was 1.5 in both studies, and in the previous two years was 2.3 and 2.1 in TRANSFORMS and FREEDOMS, respectively. Mean EDSS scores were 2.2 and 2.4 and the proportions of patients that had received prior disease modifying treatment were 57% and 41% in TRANSFORMS and FREEDOMS, respectively.

The primary efficacy end point in both studies was the annualised relapse rate (ARR), defined as the number of confirmed relapses per year, analysed in the intention-to-treat (ITT) populations. Results for fingolimod are presented for the licensed dose only (0.5mg once daily).

In the TRANSFORMS study, fingolimod reduced ARR at 12 months significantly more than Avonex®: 0.16 (95% confidence interval [CI]: 0.12 to 0.21) versus 0.33 (95% CI: 0.26 to 0.42), respectively, $p<0.001$. Only one of the two key secondary endpoints was achieved. Patients receiving fingolimod had significantly fewer mean new or enlarged hyperintense lesions on T2-weighted images at 12 months than those receiving Avonex®: 1.7 versus 2.6, respectively. There was no significant difference between treatment groups in progression of disability as 94% (95% CI: 92 to 96%) of fingolimod patients and 92% (95% CI: 89 to 95%) of Avonex® patients had no confirmed disability progression defined as a 1.0-point increase in EDSS score (0.5-point increase for baseline EDSS score ≥5.5), confirmed 3 months later in the absence of relapse.

In the FREEDOMS study, ARR results were: fingolimod 0.18 (95% CI: 0.15 to 0.22) and placebo 0.40 (95% CI: 0.34 to 0.47), a significant relative reduction of 54%. Relapse rate was significantly reduced with fingolimod regardless of the use of prior disease modifying treatment. Fingolimod reduced the risk of disability progression (key secondary endpoint) over 24 months compared with placebo (hazard ratio, 0.70 [95%CI: 0.52 to 0.96]. The cumulative probability of disability progression (confirmed after 3 months) was 18% for fingolimod and 24% for placebo.

The submitting company presented a post hoc analysis in a subgroup (n=374/1,292) of the TRANSFORMS study, defined as patients receiving any prior disease modifying therapy in the year before the study, with an unchanged or increased relapse rate or ongoing severe relapses, as compared with the previous year. ARR for fingolimod 0.5mg compared with Avonex® was 0.252 versus 0.506 ($p< 0.001$). A similar post hoc analysis in a subgroup (n=169/1,272) of the FREEDOMS study resulted in an ARR for fingolimod 0.5mg compared with placebo of 0.214 versus 0.542 ($p<0.001$).

Summary of evidence on comparative safety

In the TRANSFORMS study the safety profile of fingolimod was comparable to that of Avonex®. Most adverse events were mild or moderate in severity. Discontinuation due to adverse events occurred in 5.6% of the fingolimod 0.5mg group and 3.7% of the Avonex® group. The infection rate was similar across study groups (51 to 53%), and serious infections occurred in <2% of patients.

Initiation of fingolimod treatment causes a transient bradycardia which is usually asymptomatic. In patients receiving fingolimod 0.5mg, atrioventricular block was reported on the first day of treatment in one patient (0.2%), and macular oedema was confirmed on central review in two patients (0.5%). Three basal cell carcinomas occurred in the fingolimod 0.5mg group and one in the Avonex® group; three melanomas (all limited to the epidermis) occurred in the fingolimod 0.5mg group; and one squamous cell carcinoma occurred in the Avonex® group. Raised alanine aminotransferase (ALT) levels (>3 times upper limit of normal) were more frequent with fingolimod (36 patients [8%] in the 0.5mg group) than Avonex® (10 patients [2%]). Hypertension was reported in 16 patients (3.7%) in the fingolimod 0.5mg group and in 8 patients (1.9%) in the Avonex® group.

During fingolimod treatment, recommended monitoring includes observation of all patients for six hours at treatment initiation for signs and symptoms of bradycardia and an ophthalmological evaluation (for macular oedema) after three to four months. Elimination of fingolimod, and resolution of lymphocytopenia, following discontinuation of therapy may take up to two months and vigilance for infection should therefore be continued throughout this period.

The European Medicines Agency (EMA) considered that there were safety concerns including bradycardia, atrioventricular block, leucopenia, risk of increased frequency and seriousness of infections, occurrence of lymphoma and neurological manifestations. The EMA conducted a safety review of fingolimod following cases of death and serious cardiovascular events. New advice has been issued to healthcare professionals to reduce the risk of adverse effects on the heart associated with the use of fingolimod. This recommends that treatment with fingolimod is not recommended for patients at known risk of cardiovascular adverse events and recommends extended early monitoring for those with significant bradycardia or heart block after the first dose.

Summary of clinical effectiveness issues

Fingolimod is a disease modifying therapy licensed for the treatment of patients with highly active RRMS in patients with high disease activity despite treatment with a beta-interferon and in patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one year. The submitting company has, however, requested that SMC considers the use of fingolimod when positioned for use in the sub-optimal responder population i.e. in patients with high disease activity despite treatment with a beta-interferon and with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year despite prior treatment.

In the pivotal TRANSFORMS study, fingolimod reduced ARR significantly more than interferon beta 1a (Avonex®) but there was no significant difference between the drugs in the risk of

disability progression, an endpoint of clinical relevance to patients with MS. However, the study was not designed to demonstrate this. Comparative data are only available for 12 months which is very short for this life-long condition. The TRANSFORMS and FREEDOMS studies included broader patient populations than the licensed indication or the positioning proposed by the company. There was no requirement for study patients to have had an inadequate response to prior beta-interferon (or to any other disease modifying treatment).

Information concerning the proportion of study patients with a prior sub-optimal response to the comparator, Avonex®, is not known. It may have been more appropriate to allow any such patients to be randomised to another beta-interferon rather than continue with one which resulted in a sub-optimal response.

It is not known if the efficacy of the beta-interferon used in the FREEDOMS and TRANSFORMS studies (Avonex®) can be reliably extrapolated to other beta-interferons in the relevant patient population.

The submitting company presented unpublished post hoc analyses of a subgroup of patients that received the recommended dose (0.5mg) of fingolimod (n=191) or Avonex® (n=183) from TRANSFORMS, and fingolimod 0.5mg (n=90) and placebo (n=79) from FREEDOMS as a proxy for the target population in the proposed positioning. The study subgroups are defined as ”patients receiving any prior disease modifying therapy in the year before the study, with an unchanged or increased relapse rate or ongoing severe relapses, as compared with the previous year”. The submitting company stated that patients included in these subgroups did not require to be receiving disease modifying treatment at the time of relapse The impact on the economic model of using data from a population that does not directly correspond to the target population in the proposed positioning is not clear. The Summary of Product Characteristics (SPC) does, however, note that analysis of pooled results from TRANSFORMS and FREEDOMS “showed a consistent and statistically significant reduction in ARR compared to comparator in subgroups defined by gender, age, prior MS therapy, disease activity or disability levels at baseline. Further analyses of clinical trial data demonstrate consistent treatment effects in highly active subgroups of RRMS patients”.

Despite the availability of direct head to head data to compare fingolimod with Avonex®, the submitting company used an indirect comparison of Avonex® versus placebo in the economic case and stated that this was necessary to allow use of an existing economic model. Statistical expert advice sought by SMC concluded that it would have been more appropriate to use the available head to head data in a direct comparison of fingolimod with Avonex®.

SMC clinical experts noted a need for treatment alternatives in patients who do not have an adequate response to beta-interferon and highlighted the potential to consider fingolimod as an alternative to natalizumab in some patients, particularly those at significant risk of developing progressive multifocal leukoencephalopathy (PML).

In the resubmission, therefore, the submitting company presented an additional indirect comparison of fingolimod versus natalizumab. This indirect comparison used the subgroup of the FREEDOMS study[2] (previously defined) and the ITT population from a study comparing natalizumab with placebo (AFFIRM).[4] There was some uncertainty as to whether the clinical characteristics of the subgroup from FREEDOMS and the AFFIRM study population reflect the target patient population for fingolimod proposed by the submitting company. There were also differences in the ARR in the placebo arms of these studies which suggests that the populations were not similar. Despite these limitations, the results of the indirect comparison suggest that

fingolimod and natalizumab have similar efficacy and support the assumption of equivalent efficacy in the economic analysis. It was also noted that the European Medicines Agency European Public Assessment Report (EPAR) states that "the efficacy of fingolimod in the treatment of multiple sclerosis could be regarded as broadly similar to that of natalizumab. However, the efficacy and safety of fingolimod in relation to drugs other than Avonex® used for treatment of MS could only be assessed by head-to-head comparisons".[3]

Fingolimod has a complex safety profile and long-term safety data are lacking. Special precautions are warranted to reduce the risk of adverse cardiac effects.

SMC clinical experts identified an unmet need for a disease modifying therapy that can be administered orally as all treatments currently in use are given by injection. Fingolimod is the only disease modifying therapy for multiple sclerosis that can be administered orally and this is an important patient and service benefit.

Summary of comparative health economic evidence

The submitting company presented two cost-utility analyses comparing fingolimod with Avonex® and fingolimod with natalizumab in MS patients with high disease activity despite treatment with a beta-interferon and with an unchanged or increased relapse rate or ongoing severe relapses as compared to the previous year. A Markov model over a 50 year time horizon was used which modelled patients as they moved through the various health states of the model. The model used transition probabilities to progress patients through 21 disability states defined by EDSS score which captured the disability of patients with RRMS and secondary progressive MS (SPMS), and death. In each cycle, patients could progress to poorer EDSS health states or remain in the same health state. It was assumed patients would not be able to move to a better EDSS health state based on the assumption used in the NICE appraisal of natalizumab.

The clinical data used for the comparison with Avonex® were taken from the two key fingolimod studies. In order to use an existing model structure, the company did not use the direct trial data from the TRANSFORMS study as the basis of the model. Instead, for the fingolimod arm the relative risks of progression and relapse versus placebo from the FREEDOMS study were used, and for the Avonex® arm the relative risks were derived from a Bucher method indirect comparison using data from both TRANSFORMS and FREEDOMS where fingolimod was the common treatment.

The clinical data used in the model for the comparison with natalizumab were based on an indirect comparison of fingolimod and natalizumab using the Bucher method. The FREEDOMS study was included for the fingolimod arm and the natalizumab data were taken from the AFFIRM placebo-controlled study. The base case analysis used data from the subgroup of population 1b from the FREEDOMS study and the ITT population of the AFFIRM trial, and a sensitivity analysis was also provided comparing both ITT populations. The results of the indirect comparison indicated that there was no statistically significant difference between fingolimod and natalizumab. The natural history of MS progression was also included in the model based on a 25-year cohort study undertaken in Canada. Data from this study formed the baseline risk of disease progression in the model to which the relative risks were applied.

Utility values were selected from a published study and were applied in the model according to EDSS score. The two fingolimod studies were rejected as sources of utility estimates as data were not available for all the health states in the model. However, a sensitivity analysis using the study data was provided. Disease management costs by EDSS state were included based on the estimates used in the NICE natalizumab review. Additional costs associated with fingolimod and natalizumab treatment were included, such as the initial consultation visit to start treatment and ongoing monitoring costs.

For the comparison with Avonex® the base case cost per quality-adjusted life year (QALY) was estimated to be £59,901 based on an incremental cost of £50,152 and a QALY gain of 0.837. A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was offered on the list price of the medicine. The cost per QALY with the PAS was £11,736 based on an incremental cost of £9,826 and a QALY gain of 0.837.

A number of weaknesses were noted with this analysis:

- As noted above, this analysis used an indirect comparison rather than the direct clinical data which were available.
- The cost effectiveness ratios showed upward sensitivity to changes in assumptions regarding the relative risk of progression and long term treatment effects.
- Responses from SMC clinical experts suggest that in patients who have had a sub-optimal response to a beta-interferon it is not usual practice to prescribe that the use of an alternative beta- interferon product.

For the comparison with natalizumab the company estimated a base case cost per quality-adjusted life-year (QALY) of £39,511 based on an incremental cost of £14,564 and a QALY gain of 0.369. With the PAS fingolimod was estimated to dominate natalizumab based on cost savings of £31,299 and a QALY gain of 0.369.

The following weaknesses were noted:

- The company's analysis estimated a QALY gain with fingolimod by using the point estimates from the indirect comparison. This may not be appropriate as the indirect comparison indicated fingolimod and natalizumab may have comparable efficacy. A cost-minimisation analysis was considered to be more appropriate and one subsequently provided by the company indicated that fingolimod treatment would result in cost savings of £10,846 (£45,426 with the PAS) compared with natalizumab over a lifetime horizon. A cost-minimisation analysis over a one-year time horizon was also provided and showed that fingolimod remained cost-saving.
- There are a number of weaknesses with the indirect comparison. In particular, there are differences in the rates of ARR with placebo which suggest that the populations in the studies may not be similar and it was unclear why ARR was not used as the outcome measure for the indirect comparison. However, additional analysis provided by the company showed that using ARR as the outcome measure did not change the conclusion that there is no significant difference between fingolimod and natalizumab.

Despite these weaknesses, the committee considered it was reasonable to conclude that fingolimod has broadly similar efficacy to natalizumab and that the economic case had been demonstrated.

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

Summary of patient and public involvement

A Patient Interest Group Submission was received from MS Society Scotland.

Additional information: guidelines and protocols

The Association of British Neurologists published consensus guideline in 2009: Revised (2009) Guidelines for Prescribing in Multiple Sclerosis but they do not include recommendations for second-line treatment.

The Health Technology Board for Scotland (HTBS) published the following statement in January 2002: The Health Technology Board for Scotland welcomes the Risk Sharing Scheme for beta interferons and glatiramer acetate, announced by the Scottish Executive. We are pleased that this is based on the National Institute for Clinical Excellence (NICE) recommendation to work with manufacturers to secure these medicines for patients in a cost effective manner. In light of the exceptional circumstances created by the Risk Sharing Scheme, HTBS and the Scottish Executive have agreed that HTBS will not provide a Comment on the NICE Technology Appraisal Guidance No 32: Beta interferons and glatiramer acetate for the treatment of multiple sclerosis. This decision was taken after careful consideration of the needs of patients and health professionals in Scotland. As the Health Department Letter detailing the Risk Sharing Scheme addresses the implications for Scotland, we believe further authoritative advice in the form of an HTBS Comment is not only unnecessary, but may cause unhelpful confusion at this time. HTBS will work to ensure that the Scottish data from the Risk Sharing Scheme is taken into account in future advice to NHS Scotland on these treatments.

Additional information: comparators

Beta-interferons, glatiramer acetate, and natalizumab. Mitoxantrone has also been used but is unlicensed for this indication and is associated with serious adverse events.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Fingolimod	**0.5mg orally once daily**	**19,110**
Natalizumab†	300mg infused intravenously every four weeks	14,690Δ
Interferon beta 1a (Rebif®)*	After initial titration, 44 micrograms subcutaneously three times a week	10,572
Interferon beta 1a (Avonex®)*	30 micrograms intramuscularly once a week	8,502
Interferon beta 1b (Betaferon®)*	After initial titration, 250 micrograms subcutaneously every other day	7,239
Interferon beta 1b (Extavia®)	After initial titration, 250 micrograms subcutaneously every other day	7,239
Glatiramer acetate*	20mg subcutaneously once daily	6,681Δ

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 29 May 2012 except Δ from MIMS February 2012. † restricted by SMC for use in patients with rapidly evolving severe RRMS defined by two or more disabling relapses in one year and with one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI. *Included in the Multiple Sclerosis Risk Sharing Scheme

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 579 in year 1, rising to 644 in year 5. Based on an estimated uptake of 3% in year 1 (17 patients) rising to 46% in year 5 (287 patients), the impact on the medicines budget was estimated at £322k in year one rising to £5.5m in year 5 without the PAS. The net medicines budget impact was estimated as £157k in year 1 and £2.7m in year 5 without the PAS.

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

References

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

1. Cohen JA, Barkhof F, Comi G, Hartung H-P et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis [TRANSFORMS]. N Engl J Med 2010; 362:402-15.
2. Kappos L, Radue E-W, O'Connor P, Polman C et al for the FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. New Eng J Med 2010; 362:387-401
3. European Medicines Agency European Public Assessment Report (EPAR).for Gilenya® EMEA/H/C/2202 www.ema.europa.eu
4. Poleman CH, O'Connor PW, Havrdova E et al. A randomised, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910.

This assessment is based on data submitted by the applicant company up to and including 13 July 2012**.**

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

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

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

Advice context:

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

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