

# ocrelizumab 300mg concentrate for solution for infusion (Ocrevus®)

Roche Products Ltd

6 December 2019

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 NHSScotland. The advice is summarised as follows:

**ADVICE:** following a full submission assessed under the orphan medicine process

**ocrelizumab (Ocrevus®)** is accepted for use within NHSScotland.

**Indication under review:** for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

In a randomised, double-blind, phase III study, the risk of disability progression was significantly reduced in patients who received ocrelizumab compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

**Chairman**  
**Scottish Medicines Consortium**

## Indication

For the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

## Dosing Information

The initial 600mg dose is administered as two separate intravenous infusions; first as a 300mg infusion, followed two weeks later by a second 300mg infusion. Subsequent doses of ocrelizumab thereafter are administered as a single 600mg intravenous infusion every six months. The first subsequent dose of 600mg should be administered six months after the first infusion of the initial dose. A minimum interval of five months should be maintained between each dose of ocrelizumab.

Ocrelizumab should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions.

See Summary of Product Characteristics (SPC) for further information, including recommended pre-medication and infusion adjustments in case of infusion-related reactions.<sup>1</sup>

## Product availability date

January 2018. Ocrelizumab meets SMC orphan equivalent criteria for this indication.

## Summary of evidence on comparative efficacy

Primary progressive multiple sclerosis (PPMS) is a less common type of multiple sclerosis than the relapsing forms. It is characterised by a progressive course from disease onset, superimposed with infrequent discrete clinical attacks or relapses. Ocrelizumab is a recombinant humanised immunoglobulin G1 monoclonal antibody that selectively targets CD20-expressing B cells. It is thought that ocrelizumab has an immunomodulatory effect by reducing the number and function of CD20-expressing B cells however its precise mechanism of action in MS is not fully understood. Ocrelizumab is licensed for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.<sup>1,2</sup> Ocrelizumab has previously been accepted for restricted use for the treatment of relapsing remitting multiple sclerosis (RRMS) in adults with active disease defined by clinical or imaging features who are contra-indicated or otherwise unsuitable for alemtuzumab.

The clinical evidence comes from one, randomised, double-blind, phase III study (ORATORIO) which assessed the efficacy and safety of ocrelizumab in patients with PPMS. Eligible patients were aged 18 to 55 years with a diagnosis of PPMS according to the revised McDonald criteria (2005). They had an

Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 (range 0 to 10.0 with higher scores indicating higher degree of disability), a Functional Systems scale pyramidal functions component score of  $\geq 2.0$  (range 0 to 6) that was due to lower extremity findings, a duration of MS symptoms of  $<15$  years in those with an EDSS score of  $>5$ , and a duration of MS symptoms of  $<10$  years in those with an EDSS score of  $\leq 5$ . Eligible patients also had a documented history or presence of elevated immunoglobulin G (IgG) index or at least one IgG oligoclonal band detected in the cerebrospinal fluid. Patients were randomised, (in a ratio of 2:1) to receive ocrelizumab 600mg by intravenous infusion (as two 300mg infusions given two weeks apart for the first cycle) and then every 24 weeks (as a single infusion) or matching placebo, for at least 120 weeks. Randomisation was stratified by geographical region (US or rest of the world) and by age ( $\leq 45$  years or  $>45$  years). All patients received methylprednisolone 100mg intravenously approximately 30 minutes before each infusion of study medication to reduce the risk of infusion related reactions. Analgesic or antipyretic and antihistamine prophylaxis could also be given before infusions.<sup>2,3</sup>

The primary outcome was the proportion of patients with disability progression confirmed at 12 weeks in a time to event analysis. Disability progression was defined as an increase in the EDSS of  $\geq 1.0$  point from baseline and sustained on subsequent visits for  $\geq 12$  weeks if the baseline score was  $\leq 5.5$  or an increase of  $\geq 0.5$  points that was sustained on subsequent visits for  $\geq 12$  weeks if the baseline score was  $>5.5$ .<sup>2,3</sup> The primary analysis was performed in the intention-to-treat (ITT) population which comprised all randomised patients and was based on a total of 256 events. A 12-week confirmed disability progression occurred in 33% (160/487) of ocrelizumab and 39% (96/244) of placebo patients: hazard ratio (HR) 0.76 (95% confidence interval [CI]: 0.59 to 0.98). The key secondary outcome was 24-week confirmed disability progression and this was also significantly reduced with ocrelizumab compared with placebo.<sup>2,3</sup> The results of the primary outcome, key secondary outcome and other secondary outcomes are detailed in Table 1. The median study duration was 2.9 years in the ocrelizumab group and 2.8 years in the placebo group.

**Table 1: Results of the primary and secondary outcomes in the ORATORIO study<sup>1-3</sup>**

	ITT population	
	Ocrelizumab (n=488)	Placebo (n=244)
<b>12-week confirmed disability progression (primary outcome)</b>	<b>33% (160/487)*</b>	<b>39% (96/244)</b>
<b>Hazard ratio (95% CI)</b>	<b>0.76 (0.59 to 0.98), p=0.03</b>	
24-week confirmed disability progression	30% (144/487)*	36% (87/244)
Hazard ratio (95% CI)	0.75 (0.58 to 0.98), p=0.04	
Mean change in timed 25-foot walk from baseline to week 120	39%	55%
Percentage reduction versus placebo	29% (-1.6 to 52), p=0.04	

\*One patient in the ocrelizumab group was excluded from the analysis due to missing data on the EDSS score at baseline.

Pre-specified, non-powered. subgroup analyses of the primary endpoint were conducted in patients with T1 gadolinium-enhancing lesions at baseline and showed 12-week confirmed disability progression

in 43/133 (32%) patients in the ocrelizumab groups versus 27/60 (45%) patients in the placebo group.<sup>3</sup> The company presented results from post-hoc analyses in a wider magnetic resonance imaging (MRI) active subgroup considered to represent the licensed population, defined as patients with T1 gadolinium-enhancing lesions at screening or baseline, or patients with new T2 lesions between screening and baseline. However, these data are academic in confidence so cannot be reported here.

The proportion of patients with a 20% increase in the 9-hole peg test time was assessed as an exploratory outcome. This is a validated test which measures upper limb function and a 20% increase sustained over 12 or 24 weeks is considered to indicate a clinically meaningful decline in upper limb function. In the ITT population, there was a 20% increase in the 9-hole peg test time in 17% (83/488) of ocrelizumab patients and 27% (66/244) of placebo patients confirmed at 12 weeks (HR 0.56 [95% CI: 0.41 to 0.78]) and in 14% (69/488) and 23% (57/244) of placebo patients confirmed at 24 weeks (HR 0.55 [95% CI: 0.38 to 0.77]).<sup>3</sup>

Quality of life was measured as a secondary outcome using the Short-Form Health Survey (SF-36) physical component summary score. In the ITT population there was no significant difference between ocrelizumab and placebo in the adjusted mean change in this outcome from baseline to week 120.<sup>3</sup> Results were not presented for the MRI active subgroup.

Other data were also assessed but remain confidential.\*

## Summary of evidence on comparative safety

In the ORATORIO study, an adverse event was reported in 95% (462/486) of ocrelizumab and 90% (215/239) of placebo patients and these were considered serious in 20% and 22% of patients respectively. Adverse events led to discontinuation for study medication in 4.1% of ocrelizumab and 3.3% of placebo patients. The most frequently reported adverse events in the ocrelizumab and placebo groups respectively were: infusion-related reactions (40% and 26%), nasopharyngitis (23% and 27%), urinary tract infection (20% and 23%), headache (13% and 14%), back pain (12% and 15%), influenza (12% and 8.8%), upper respiratory tract infection (11% and 5.9%), depression (7.6% and 13%), pain in extremity (6.8% and 10%) and fatigue (5.6% and 10%).<sup>3</sup>

During the study, five patients died: four patients in the ocrelizumab group (due to pulmonary embolism, pneumonia, pancreatic carcinoma and aspiration pneumonia) and one patient in the placebo group (due to a road traffic accident).<sup>2,3</sup>

The SPC states that ocrelizumab is associated with infusion-related reactions and it should not be given to patients with an active infection.

The SPC also notes that an increased number of malignancies (including breast cancers) has been observed in studies in patients treated with ocrelizumab, compared to control groups. In patients with

known risk factors for malignancies and in patients who are being actively monitored for recurrence of malignancy the risk versus benefit of treatment with ocrelizumab should be considered.<sup>1</sup>

## Summary of clinical effectiveness issues

Multiple sclerosis is a chronic, inflammatory, demyelinating disease of the central nervous system resulting in neurological impairment and severe disability. The majority of patients (approximately 85%), have a relapsing form of MS. However, 10% to 15% have PPMS which is characterised by a progressive course from disease onset, superimposed with infrequent discrete clinical attacks or relapses. A diagnosis of PPMS requires evidence of disease progression for at least one year from first symptoms, plus a combination of lesions in brain or spinal cord and/or presence of oligoclonal bands or elevated immunoglobulin G index in cerebrospinal fluid. The mean age of PPMS onset is approximately 40 years and men are almost as frequently affected as women.<sup>2</sup> To date, no other treatment has been found to significantly slow the progression of disability in patients with PPMS and no other medicines are licensed for use in this type of MS. Clinical experts consulted by SMC indicated that current treatment is with supportive therapies and rehabilitation. Experts considered that there is an unmet need for an effective disease-modifying therapy for PPMS. Ocrelizumab meets SMC orphan equivalent criteria.

In the key ORATORIO study ocrelizumab significantly reduced the risk of disability progression (measured by the primary outcome of 12-week confirmed disability progression) compared with placebo. This was supported by results of secondary outcomes, including 24-week confirmed disability progression, timed 25-foot walk test and changes in total T2-lesion volume and brain volume.<sup>2, 3</sup> There was a 24% relative reduction in risk of 12-week confirmed disability progression with ocrelizumab compared with placebo, however the absolute risk reduction may be considered modest.<sup>2</sup> Although this primary outcome was considered appropriate by the European Medicines Agency (EMA), it also recognises that EDSS does not adequately assess upper limb function and cognitive impairment and so the use of additional neurological rating scales may be useful as secondary outcomes.<sup>4</sup> Results of the exploratory composite outcome, no evidence of progression, was used to capture different aspects of disability measured by an overall absence of progression from baseline to week 120 to include: no 12-week clinical progression of EDSS plus no 12-week confirmed  $\geq 20\%$  progression on timed 25-foot walk plus no 12-week confirmed  $\geq 20\%$  progression on timed 9-hole peg test. More ocrelizumab than placebo patients had no evidence of progression.<sup>5</sup>

There was no difference in quality of life between the treatment groups and quality of life results were not reported for the MRI active subgroup that represents the licensed population. The study duration was relatively short considering this is a lifelong condition.

Ocrelizumab is licensed for patients with early PPMS, in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity and the SPC notes that “with regard to disease activity, features characteristic of inflammatory activity, even in progressive MS, can be imaging-related, (that is, T1 gadolinium-enhancing lesions and/or active [new or enlarging] T2 lesions). MRI evidence should be used to confirm inflammatory activity in all patients”.<sup>1</sup> Study patients were not

required to have evidence of inflammatory activity. Greater reduction in 12-week confirmed disability progression was shown in the pre-specified subgroup of patients with gadolinium-enhancing T1 lesions at baseline: 32% in the ocrelizumab groups versus 45% in the placebo group, an absolute difference of 13%.<sup>3</sup>

The company performed unconfirmed post-hoc analyses in an MRI active subgroup considered to represent the licenced population. This MRI active subgroup included patients with T1 gadolinium-enhancing lesions at screening or baseline, or patients with new T2 lesions between screening and baseline but not patients with enlarging T2 lesions as they were not assessed between screening and baseline in the study. The SPC also noted that post-hoc analyses suggested that younger patients with T1 gadolinium-enhancing lesions at baseline may benefit from a greater treatment effect.<sup>1</sup> Post-hoc subgroup analyses are descriptive only and should be interpreted with caution.

There is no evidence in patients >55 years or in those with severe disability (patients that are restricted to a wheelchair, chair or bed, that is an EDSS score >6.5). It is therefore unclear how the ORATORIO study results would generalise to older patients with more severe disease in clinical practice.

Clinical experts consulted by SMC noted that there may be difficulty in determining eligibility for treatment with ocrelizumab in practice in terms of confirming the duration and onset of disease and in MRI criteria, which may overlap with RRMS. The SPC notes that MRI evidence should be used to confirm inflammatory activity.<sup>1</sup> There may be uncertainty in when the treatment should be stopped.

The introduction of ocrelizumab for the treatment of PPMS would offer a licensed medicine for this group of patients who currently have no licensed treatment options. There may be an impact on the service in terms of higher demand for MRI imaging to identify eligible patients and in staff and clinic time to administer the treatment.

## Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ocrelizumab, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- PPMS is a progressive, incurable and life-long disease with gradual worsening of symptoms from the onset and accumulation of disability over time. It affects young adults of working age and symptoms include fatigue, weakness, walking difficulty, bladder problems, muscle spasms, visual problems and memory difficulties. Patients gradually lose their independence and mobility and become reliant on carers. The disease can lead to significant emotional, psychological and financial effects on patients and their families.

- There is currently no treatment available for PPMS. Patients receive supportive therapies and rehabilitation to manage symptoms, but there is no treatment to slow progression of the disease.
- Ocrelizumab may address the unmet need by delaying progression of disability. This would benefit patients and their families, since patients could stay active, remain in work and continue with family and caring responsibilities. Patients would maintain their independence and mobility for longer and maintain their quality of life.
- PACE participants considered that ocrelizumab would be suitable for patients with early PPMS (within 10 to 15 years of diagnosis) who are still able to walk and who have active disease, assessed by brain imaging.
- Ocrelizumab is administered every six months, requiring a clinic visit for infusion. Patients would require blood monitoring for potential risk of infection. Side-effects are considered to be manageable.

### **Additional Patient and Carer Involvement**

We received patient group submissions from The MS Society and the MS Trust, both organisations are registered charities. The MS Society has received 0.5% pharmaceutical company funding in the past two years, including from the submitting company. The MS Trust has received 11.4% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

### **Summary of comparative health economic evidence**

The company submitted a cost- utility analysis comparing ocrelizumab to best supportive care. The population reflected treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity. Ocrelizumab is the only disease modifying treatment available for this population so there will be no displacement of current treatments.

Base case results were presented for the early inflammatory PPMS population, but only for the MRI active subgroup. This was a post hoc subgroup of the population in the main clinical study who were considered to align best with the indication and clinical practice.

A Markov model with a 50 year time horizon was used. The model consisted of two treatment arms i.e. PPMS on ocrelizumab and PPMS on best supportive care. Each treatment arm comprised nine disability health states reflecting disease progression on EDSS. Patients entered the model in the PPMS on treatment arm and could either transition between EDSS states in PPMS, withdraw from active treatment

(and receive best supportive care) or die. Patients received active treatment until modelled treatment withdrawal, progressing to EDSS 8 or long term treatment waning.

Ocrelizumab treatment effect was based on confirmed disability progression after 24 weeks, which was a secondary endpoint in the ORATORIO study. This was considered more clinically meaningful than the primary endpoint of disability progression confirmed at 12 weeks, because confirming disability after a longer period is more reliable in PPMS. Parameters for baseline EDSS scores, treatment discontinuation, relapse rates, adverse event risks and patient utilities were also derived from the main study. Baseline transition probabilities used to move patients through EDSS states in the model were taken from natural history data of PPMS patients in the MSBase registry, which is an international observational database representing real-world MS clinical practice.<sup>6</sup> Treatment effects in the form of hazard ratios were derived from the main ORATORIO study and then applied to the natural history data probabilities of EDSS progression.

Utility values were based on EQ-5D-3L data from the ORATORIO study (collected at baseline and each follow-up) and the values were then linked to EDSS states through regression analysis. The base case economic model also included average disutility associated with adverse events (weighted for serious and non-serious events), disutilities associated with loss of upper limb functionality (not captured by the EDSS score), carer burden and relapse.

Medicine acquisition, administration and monitoring costs were calculated for year 1 and years 2 onwards. The cost of relapse and background resource use by EDSS health state were included and taken from published literature. Adverse event costs for all treatments were also included in the economic analysis.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

The base case analysis presented by the submitting company produced an incremental cost-effectiveness ratio (ICER) of £143,604 at list price.

SMC prefers to provide the with-PAS cost-effectiveness estimates that informed the decision. As the company has advised that these are commercial in confidence due to the PAS, however, only the without-PAS figures are included.

Results from key sensitivity analyses are reported in table 2.

**Table 2: Selected scenario analyses results**

	<b>Scenario</b>	<b>ICER at list prices</b>
1	50% waning assumed after 7 years	£157,220
2	Using (lower) patient utilities from Orme et al	£160,924
3	Exclude upper limb impairment disutility	£163,012
4	Exclude caregiver disutilities	£156,606
5	Stopping rule set to EDSS 7	£142,073
6	Combined scenario – 50% waning after 7 years + stopping rule EDSS 7	£154,036

There were a number of limitations with the analysis which include the following;

- The evidence on clinical effectiveness is based on unconfirmed post hoc analyses. The inclusion criteria for the primary study meant that the trial population may not represent older, more severe PPMS patients seen more generally in clinical practice. It is therefore plausible that the treatment effects included in the economic model may be an overestimation.
- There was some inconsistency in sources of input data for the MRI active population. Whilst treatment effect for this group was applied, other parameters such as the transition probabilities, treatment withdrawal rates and relapse rates could either not be estimated for patients with MRI active disease or was derived from the ITT population of the main study.
- The treatment effect of ocrelizumab on upper limb impairment was based on an exploratory outcome. There is some concern regarding the selective use of exploratory outcomes and it is also not clear whether the 9-hole peg test reflects changes in upper limb function that correlate with actual day-to-day functional benefits for patients, such as the ability to wash, dress and feed themselves. Sensitivity analysis shows that excluding disutilities associated with upper limb impairment leads to an increase in ICER (table 2, scenario 3). The combined application of upper limb disutility, and decreasing utility for progressive EDSS states in the base case analysis may overestimate the effect of ocrelizumab.
- There is considerable uncertainty around a suitable stopping rule for discontinuing ocrelizumab. Whilst the implementation of a more conservative stopping rule (EDSS 7) in isolation actually leads to a lower ICER compared to the base case (table 2 scenario 5), combining this with a more conservative estimate for treatment waning effect (50% discontinuation after 7 years) increases the ICER (table 2 scenario 6).
- The trial based utility values for different EDSS states were higher than those reported in other sources (i.e. Orme et al)<sup>7</sup>, which was likely due to the younger age of patients enrolled in ORATORIO. Using lower utility values from Orme et al decreases cost-effectiveness (table 2 scenario 2), and given that PPMS patients seen more generally in clinical practice may be older and more severely affected, there is the potential for ocrelizumab in real world settings to have a higher ICER than that of the base case analysis.
- The base case economic analysis includes caregiver disutilities. Sensitivity analysis showed that excluding these factors increased the ICER of ocrelizumab (table 2, scenario 4).

The Committee also considered the benefits of ocrelizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as ocrelizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted ocrelizumab for use in NHSScotland.

Other data were also assessed but remain confidential.\*

### Additional information: guidelines and protocols

No published clinical guidelines were identified which made specific recommendations regarding the treatment of PPMS.

### Additional information: comparators

None

### Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
<b>Ocrelizumab</b>	<b>Initial dose: 600mg administered as two separate 300mg intravenous (IV) infusions two weeks apart.</b> <b>Subsequent doses: 600mg IV infusion every 6 months.</b>	<b>19,160</b>

Costs from MIMS online on 02 September 2019. Costs do not take any patient access schemes into consideration.

### Additional information: budget impact

The company estimated there would be 42 patients eligible for treatment with ocrelizumab in year 1 rising to 180 in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

Other data were also assessed but remain confidential.\*

## References

1. Ocrelizumab (Ocrevus) Summary of product characteristics. Roche Products Limited. Electronic Medicines Compendium [www.medicines.org.uk/emc/](http://www.medicines.org.uk/emc/) Last updated 3 April 2018.
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6. Butzkueven H, Chapman J, Cristiano E et al. MSBase: an international online registry and platform for collaborative outcomes research in multiple sclerosis. Multiple Sclerosis. 2016;12(6):769-74.
7. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value in Health. 2007;10(1):54-60.

This assessment is based on data submitted by the applicant company up to and including 11 October 2019.

*\*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](http://www.scottishmedicines.org.uk/About_SMC/Policy)

Medicine 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine 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 NHSScotland 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 NHSScotland 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.*