Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-Submission

roflumilast, 500 microgram, film-coated tablet (Daxas®) SMC No 635/10

AstraZeneca UK Ltd

4 August 2017

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

roflumilast (Daxas®) is not recommended for use within NHS Scotland.

Indication under review: for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume in one second [FEV_1]) post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

The addition of roflumilast, compared with placebo, to combination inhaled corticosteroid (ICS) / long-acting beta agonist (LABA) treatment did not reduce the annual rate of moderate or severe COPD exacerbations in two double-blind, randomised studies of COPD patients with severe airflow limitation and history of at least two moderate or severe exacerbations in the previous year.

The submitting company did not present a sufficiently robust clinical or economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Roflumilast is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume in one second [FEV_1]) post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.[1]

Dosing Information

The recommended dose is 500 micrograms (one tablet) roflumilast orally once daily.[1]

Roflumilast may need to be taken for several weeks to achieve its effect and has been studied in clinical studies for up to one year. The tablet should be swallowed with water and taken at the same time every day. It can be taken with or without food.[1]

Product availability date

July 2010

Summary of evidence on comparative efficacy

Roflumilast is an oral selective phosphodiesterase 4 (PDE4) inhibitor which has anti-inflammatory activity designed to target both the systemic and pulmonary inflammation associated with COPD.[1] It is a maintenance treatment and has no direct bronchodilator activity.[2]

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers roflumilast when positioned for use in patients with severe to very severe COPD (FEV1% predicted < 50%) and at least 2 moderate or severe COPD exacerbations within the previous year including at least one hospitalisation despite triple therapy (inhaled corticosteroid [ICS] plus long-acting beta agonist [LABA] plus long-acting muscarinic antagonist [LAMA]). Roflumilast would be added to triple therapy.

The evidence is from two phase III / IV, international, multicentre, randomised, double-blind, placebo-controlled studies, REACT (n=1,945) and RE^2SPOND (n=2,354).[3-5] The studies recruited patients ≥40 years, who were current or former smokers (cessation ≥1 year before enrolment) with a smoking history ≥20 pack-years. Patients had a history of COPD for at least 12 months prior to baseline, associated with symptoms of chronic bronchitis (chronic productive cough for three months in each of the two years prior to baseline); FEV_1 / forced vital capacity (FVC) ratio (post-bronchodilator) <70%; FEV_1 (post-bronchodilator) ≤50% of predicted. Patients were also required to have a history of ≥2 moderate (required oral or parenteral corticosteroids) or severe (required hospitalisation) exacerbations in the previous year; pre-treatment with inhaled combination of ICS / LABA for at least 12 months before baseline (REACT only); and at a constant dose as a fixed combination in the three months prior to recruitment; and total cough and sputum score of ≥14 (sum of daily scores on four-point scales for cough and sputum) during the week preceding the randomisation visit (REACT only).[3, 6]

Patients in both studies entered a single-blind baseline period (four-week in REACT; two-week in RE^2SPOND) during which all patients received placebo in addition to their current COPD treatment (fixed dose of ICS / LABA with or without the addition of a LAMA). Patients with suitable compliance in the placebo run-in were then randomised equally (stratified in RE^2SPOND according to LAMA use) to double-blind treatment with roflumilast 500 micrograms or placebo once daily for 52 weeks. In both studies inhaled salbutamol was permitted as rescue medication. In REACT other COPD treatments (short-acting muscarinic antagonists, monotherapy with ICS or LABA, systemic corticosteroids [except

for COPD exacerbation], oral beta-2 agonists, or any inhaled short-acting beta-2 agonist apart from salbutamol) were not permitted. In RE²SPOND, a short-acting muscarinic antagonist (eg, oxitropium or ipratropium) was allowed for patients not using a LAMA and H1-antihistamines (e.g., loratadine) or corticosteroids (oral, parenteral, intranasal) were allowed if required.[3, 4]

The primary outcome in both studies was the rate of moderate to severe COPD exacerbations (required systemic corticosteroid therapy, hospitalisation or led to death) per patient per year assessed in the intention to treat (ITT) population. The ITT population consisted of all randomised patients who received at least one dose of study treatment.[3, 4] The primary outcome was not achieved in either study. See Table 1 below.

Table 1: Results of primary outcome in REACT and RE²SPOND[3, 4]

	Rate of moderate to severe COPD exacerbations per patient per year (95% CI)	**Rate ratio (95% CI)**
REACT (Poisson regression analysis=primary analysis)		
Roflumilast, n=973	0.805 (0.724 to 0.895)	0.868 (0.753 to 1.002)
Placebo, n=972	0.927 (0.843 to 1.020)	p=0.0529
REACT (Negative binomial analysis=pre-specified sensitivity analysis)		
Roflumilast, n=973	0.823 (0.738 to 0.917)	0.858 (0.740 to 0.995)
Placebo, n=972	0.959 (0.867 to 1.061)	p=0.0424
RE²SPOND (Negative binomial analysis=primary analysis)		
Roflumilast, n=1,178	1.17 (1.06 to1.28)	0.92 (0.81 to 1.04)
Placebo, n=1,176	1.27 (1.17 to 1.39)	p=0.163

CI=confidence interval; n=number

As there was no significant difference between treatments in the primary outcome in either study, secondary outcomes were treated as exploratory only. Mean change from baseline to 52 weeks in post-bronchodilator (pre-bronchodilator in RE²SPOND) FEV_1 and rate of severe COPD exacerbations per year were key secondary outcomes of both studies.[3 4] After 52 weeks of treatment, there were small improvements over placebo in FEV_1: 56mL in REACT and 53mL in RE²SPOND.[3 4] In REACT there was a relative reduction of 24% in severe exacerbations for roflumilast over placebo: 0.239 versus 0.315 (rate ratio 0.757 [95% CI: 0.601 to 0.952]).[3] In RE²SPOND there was no difference between treatments in the rate of severe exacerbations.[4] There was no significant difference in mortality rate between roflumilast and placebo groups: 1.8% versus 1.9% in the REACT study and 2.5% versus 2.1% in the RE²SPOND study. [3, 4]

No significant health related quality of life benefits were reported in either study as assessed by change in COPD Assessment Test (CAT) in both studies and with the Exacerbation of Chronic Pulmonary Disease Tool – Patient Reported Outcome in RE²SPOND.[3, 4]

A *post hoc* pooled analysis was conducted in the subgroup of patients from the REACT and RE²SPOND studies who had been hospitalised for COPD in the year before study entry (but had not necessarily been receiving triple therapy). The results were presented at the American Thoracic Society conference in May 2017.[9] This subgroup included 703 patients in the roflumilast group and 683 patients in the placebo group. Treatment with roflumilast versus placebo reduced the relative rate of moderate or severe COPD exacerbations by 26% (1.06 versus 1.43) and the relative rate of severe exacerbations by 30% (0.42 versus 0.60).[9]

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

Summary of evidence on comparative safety

Treatment emergent adverse events (TEAEs) were reported by 67% of roflumilast patients (648/968) versus 59% (572/967) of placebo patients in REACT and by 68% (804/1,178) of roflumilast patients versus 65% (758/1,174) of placebo patients in RE^{2}SPOND.[3 4] Serious adverse events were reported by 26% of roflumilast patients versus 29% of placebo patients in REACT and by 15% of roflumilast patients versus 14% of placebo patients in RE^{2}SPOND.[3 4] The proportions of patients that discontinued study treatment due to an adverse event were 11% of roflumilast patients versus 5.4% of placebo patients in REACT and 12% of roflumilast patients versus 5.5% of placebo patients in RE^{2}SPOND.[3 4]

In REACT, the most frequently reported adverse events (incidence ≥5% in either treatment group) in the roflumilast versus placebo groups were COPD exacerbation (15% versus 19%); diarrhoea (10% versus 3.6%); weight decrease (9.1% versus 2.8%); nausea (5.7% versus 1.6%); and nasopharyngitis (5.5% versus 5.4%).[3] Self-reported weight loss was reported by 9.1% (88/968) and 2.8% (27/967) of patients in the roflumilast and placebo groups respectively. The mean weight loss in the roflumilast group was 2.65kg compared with 0.15kg in the placebo group.[3] During the treatment phase of the REACT study, 17 (1.8%) deaths occurred in the roflumilast group and 18 (1.9%) in the placebo group. The primary cause of death was reported as being COPD exacerbation for seven patients in both groups (0.7% in both groups). The primary cause of death for the remaining patients who died in both groups is reported as being an adverse event; 1.0% (10/969) roflumilast and 1.1% (11/966) placebo.[3]

In RE^{2}SPOND the most frequently reported adverse events (incidence ≥5% in either treatment group) in the roflumilast versus placebo groups were diarrhoea (10% versus 3.2%); weight decrease (7.7% versus 2.4%); headache (6.8% versus 4.1%); pneumonia (5.6% versus 5.6%); nausea (5.4% versus 2.6%); and upper respiratory tract infection (5.1% versus 5.6%). The RE^{2}SPOND study utilised the Columbia-Suicide Severity Rating Scale as part of the safety analysis. In the roflumilast versus placebo groups, suicidal ideation was reported by 8.4% versus 7.7% of patients; suicidal behaviour by 2.5% versus 1.7% of patients and suicide attempts by 1.1% versus 1.0% of patients in the respective groups. During the treatment phase of the RE^{2}SPOND study, 30 (2.5%) deaths occurred in the roflumilast group and 25 (2.1%) occurred in the placebo group. One death in the roflumilast was considered to be treatment related where the patient committed suicide.[4]

The summary of product characteristics (SPC) notes that roflumilast is subject to additional monitoring and that a higher incidence of weight decrease, decreased appetite, headache and depression was observed in the COPD studies in patients receiving ICS / LABA / LAMA and randomised to roflumilast in comparison with placebo. It notes an increased risk of psychiatric disorders and that (rarely) instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression, usually within the first weeks of treatment. All patients should be informed about the risks of roflumilast and the precautions for safe use and should be given a patient card.[1]

Summary of clinical effectiveness issues

COPD is a major cause of morbidity and mortality, and severe COPD is associated with exacerbations of respiratory symptoms requiring intensive treatment and often resulting in hospitalisation.[3]

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely that some patients continue to be symptomatic despite optimal current treatment. They advised that roflumilast would be added to existing therapy and would not displace any medicine in the proposed positioning, (i.e. in patients with severe COPD and at least 2 moderate or severe COPD exacerbations within the previous year including at least one hospitalisation despite triple therapy [ICS / LABA / LAMA]).

Updated guidance from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) includes the addition of roflumilast in this patient population as a treatment option.[2]

There is no evidence in the proposed positioning population which comprised approximately 15% of the population of the combined population of the REACT and RE^{2}SPOND studies. Neither of the studies achieved their primary outcome (reduction in rate of moderate or severe COPD exacerbations). In the REACT study, a 13% relative reduction in moderate or severe exacerbations with roflumilast compared with placebo did not reach statistical significance in the primary analysis.[3] Treatment with roflumilast, in comparison with placebo, led to a 24% reduction in severe exacerbations, however this did not result in reduced mortality.[3] In the RE^{2}SPOND study there was no significant benefit over placebo in rates of moderate to severe exacerbations or in severe exacerbations.[4] In both studies there was a higher dropout rate in patients receiving roflumilast than placebo: 28% versus 20% in REACT and 29% versus 22% in RE^{2}SPOND; the main reasons were adverse events or withdrawal of consent. There was no improvement in quality of life in either study.[3, 4]

A *post hoc* pooled analysis of the subgroup of patients in REACT and RE^{2}SPOND who had been hospitalised for COPD in the year before study entry and who were not necessarily receiving triple therapy, suggested that treatment with roflumilast versus placebo reduced the rate of moderate to severe COPD exacerbations and of severe exacerbations.[9]

The studies had a number of limitations. Although the submitting company considered that they were sufficiently similar to be pooled, there were substantial differences between the studies, including patient characteristics (disease severity and frequency of exacerbations) and concomitant medication (dose of inhaled steroids and proportions of patients on triple therapy [70% in REACT versus 47% in RE^{2}SPOND]). Another limitation is that some patients may have been treated sub-optimally as 65% of patients in the RE^{2}SPOND study were using fluticasone / salmeterol 250 / 50 twice daily. In the UK, the licensed dose of fluticasone / salmeterol for COPD is 500 / 50 twice daily.[10] It is unclear how many patients were stabilised on the higher dose prior to the study and had to down-titrate their dose of fluticasone on entry to the study. The use of LAMA was not tracked during either study; therefore, it is not known whether patients who began the study on LAMA continued this treatment throughout the study. In addition, the authors of the REACT study publication noted that mortality was not recorded between the completion of treatment and the end of the study, and that it was probably underestimated. Furthermore, the REACT study may not have had sufficient power to demonstrate a significant difference between treatment groups for the primary outcome, as it was powered to demonstrate a significant difference based on an assumed placebo-exacerbation rate that was higher than the one observed in the study (1.25 versus 0.93 per patient per year).[3] Different formulations of roflumilast were used in each study: tablets were film-coated (licensed formulation) in REACT and uncoated in RE^{2}SPOND, however bioequivalence has been demonstrated. Both studies excluded patients with asthma. [3, 4] There is an overlap population of patients who have both asthma and COPD.[2] The effect of treatment with roflumilast on these patients is not known. The duration of the studies was one year and no long-term evidence is available.

There are no relevant active comparators for the indication under review.

Clinical experts consulted by SMC considered that roflumilast is a minor therapeutic advancement as it may reduce the risk of severe exacerbations in the population under review. They considered that its place in therapy is in patients with at least one hospitalisation for a COPD exacerbation in the prior year despite triple therapy (ICS / LABA / LAMA).

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

Summary of comparative health economic evidence

The company provided a cost-utility analysis which compared roflumilast as an add-on to ICS / LABA / LAMA (roflumilast plus triple therapy) versus triple therapy in patients with severe to very severe COPD (FEV_1 % predicted <50%) and ≥2 moderate or severe COPD exacerbations within the previous year, one of which has been hospitalised. The LAMA and ICS / LABA combination products used in the analysis as part of triple therapy were tiotropium and budesonide / formoterol or fluticasone / salmeterol respectively.

The economic analysis used a Markov model with a 40 year time horizon, in order to evaluate the cost-effectiveness of roflumilast plus triple therapy against triple therapy. In terms of model structure, the model consisted of three health states: severe COPD, very severe COPD and death. Patients entered the model in the severe health state and patients could die in the analysis or transition to a worse health state. The threshold for severe COPD was defined as below 50% FEV_1 predicted and the threshold for very severe disease was below 30% FEV_1 predicted. Patients in the severe or very severe COPD health states were at risk of moderate or severe exacerbations.

Sources of the clinical data used in the model included a range of published studies which informed FEV_1 values for the general population, FEV_1 values for the population included in the economic model, the rate of disease progression, the transition probability from severe to very severe COPD, exacerbation related mortality and background mortality. It is worth noting that the same values for the above parameters were used for roflumilast plus triple therapy and triple therapy in the analysis. The exacerbation rates, which were treatment specific, were taken from an analysis of pooled REACT and RE^2SPOND data. The same source was also used to inform the adverse event rates used in the economic model.

The utility values were taken from a published study which collected EQ-5D data and estimates for severe and very severe COPD were 0.750 and 0.647 respectively. The base case analysis also included a disutility for exacerbations and adverse events, the latter being assumed equivalent to a severe exacerbation of COPD.

Medicines costs were included in the analysis as were costs associated with disease management, moderate exacerbations, severe exacerbations and adverse events.

The base case result indicated that the incremental cost-effectiveness ratio (ICER) for roflumilast plus triple therapy versus triple therapy was £9,914 per quality-adjusted life year (QALY). This result was based on an incremental cost of £2,230 and a QALY gain of 0.22. The base case analysis also generated a life year gain of 0.26 for roflumilast plus triple therapy versus triple therapy.

The results of key sensitivity analysis are as follows

Table 2: Selected sensitivity analyses

Analysis	ICER
Rate ratio severe exacerbations set to 0.86 from 0.64	£33,867
3 year time horizon	£31,757
5 year time horizon	£22,712
Alternative utility sources	£13,306
Transition probability from severe to very severe for triple therapy set to 0.0099 from 0.0124	£12,697

Remove any survival gain for roflumilast plus triple therapy from the economic model	£23,303
Remove any survival gain for roflumilast plus triple therapy from the economic model and use time horizon of 10 years	£27,833
Remove non-significant differences from the analysis	£10,423

The main weaknesses were

- Key clinical variables which informed the economic evaluation were rate ratios for severe and moderate exacerbations. However the rate ratios were derived from an unpublished post-hoc analysis of pooled data from two studies and neither study met their primary end point when considering the full study populations. The company has provided sensitivity analysis which increased the rate ratio for severe exacerbations to 0.86 and the results are presented in Table 2 above. Following discussions at the SMC, concerns were noted regarding the robustness of the post-hoc subgroup analysis which informed the relative efficacy of roflumilast plus triple therapy versus triple therapy in the economic model.
- In the economic analysis an important benefit for roflumilast as an add on to triple therapy versus triple therapy related to the reduced rate of exacerbations, particularly severe exacerbations. In addition, an exacerbation was associated with a loss of quality of life (i.e. disutility), a cost, and for severe exacerbations an impact on mortality; therefore avoiding exacerbations will improve the cost-effectiveness of roflumilast. However, there may be some uncertainty with the modelled benefit for roflumilast as data may not be available to support some of the assumptions used in the model. For example no data were presented which demonstrated that roflumilast was associated with a survival or quality of life advantage versus the comparator. The company has subsequently provided a sensitivity analysis which removed the survival gain for roflumilast plus triple therapy and the results are presented in Table 2 above.
- A time horizon of 40 years was used in the model which may be considered long for a cohort of patients with a baseline age of 65 years. In addition, the analysis assumed that the rate ratios which informed the rate of moderate and severe exacerbations did not vary over time, i.e. the analysis assumed a constant treatment effect. The company has provided sensitivity analyses which reduced the time horizon (see Table 2 above).

Due to the above uncertainties the economic case has not been demonstrated.

Summary of patient and carer involvement

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

- We received a patient group submission from Chest Heart & Stroke Scotland, which is a registered charity.
- Chest Heart & Stroke Scotland has not received any pharmaceutical company funding in the past two years.
- People living with COPD often describe: having a regular cough which can disturb sleep, feeling breathless when moving about and being very limited in how far they can walk.
- Feeling sad/depressed and anxious is common as people feel they are losing their "energy for life". The most common issue raised is the restrictions their condition places on things that are important to the person such as hobbies, going out, gardening etc and the fear of being a burden to others. People often need help for tasks that can make them breathless, such as shopping or housework.
- Inhaled medications are currently the main method of delivering medicine for COPD and in recent years there has been an increase in the range of devices that can be used. However many people

struggle to use their devices effectively and roflumilast as an oral medication offers a simple method of administration.
- Roflumilast offers an additional treatment option for those with advanced disease who are currently on optimal treatment providing more hope for patients.

Additional information: guidelines and protocols

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) published an updated 2017 version of their Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease.[2] In patients who continue to have exacerbations despite triple therapy (ICS / LABA / LAMA), GOLD recommends three options:

- Consideration of the addition of roflumilast in patients with FEV_1 <50% predicted, chronic bronchitis, and a hospitalisation for an exacerbation in the previous year.
- Consideration of the addition of a macrolide, with best available evidence supporting the use of azithromycin. (The guidance cautions that consideration should also be given to the development of resistant organisms when deciding if this is an appropriate treatment choice)
- Discontinuation of ICS. GOLD states that this recommendation is supported by evidence of a lack of efficacy, increased risk of AEs, and evidence demonstrating no harm associated with withdrawal of ICS.[2]

The National Institute for Health and Care Excellence (NICE) Clinical Guideline 101: Chronic obstructive pulmonary disease in over 16s: diagnosis and management[11] was last updated in 2010 and is currently under review. It is anticipated that a revised version of the guideline will be available in 2018. Current NICE guidance makes no recommendation and predates the licensing of roflumilast.

Additional information: comparators

There are no relevant comparators. Roflumilast would be added to existing therapy for COPD.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Roflumilast	**One 500 microgram tablet daily**	**458**

Costs from eVadis on 06 June 17.

Additional information: budget impact

The submitting company estimated there would be 3,004 patients eligible for treatment with roflumilast in year 1 rising to 3,527 patients in year 5 to which confidential uptake rates were applied.

The gross impact on the medicines budget was estimated to be £14k in year 1 rising to £162k in year 5. As no medicines were assumed to be displaced, the net medicines budget impact was equivalent to the gross medicines budget.

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

References

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6. AstraZeneca. Roflumilast in chronic obstructive pulmonary disease (COPD) patients treated with fixed combinations of long-acting β2-agonists (LABA) and inhaled glucocorticosteroid (ICS) (REACT) (NCT01329029). https://clinicaltrials.gov/ct2/show/NCT01329029

7. *Commercial in Confidence**

8. *Commercial in Confidence**

9. Conference abstract Martinez FJ, Rabe KF, Calverley P et al. Effect of Roflumilast on Exacerbations in Patients with Severe COPD and a History of Hospitalization Receiving Inhaled Combination Therapy: A Pooled Analysis of Two Randomized Phase 4 Studies American Journal of Respiratory and Critical Care Medicine 2017;195:A5724, presented at American Thoracic Society conference in Washington USA May 2017 http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A5724.

10. Salmeterol/fluticasone propionate (Seretide® 100, 250, 500 Accuhaler®) Summary of product characteristics. GlaxoSmithKline UK. Electronic Medicines Compendium https://www.medicines.org.uk/emc/medicine/2317 Last Updated on eMC 24-May-2017.

11. NICE, 2010. NICE clinical guideline 101: Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). Available at: https://www.nice.org.uk/guidance/cg101, accessed August 2016.

This assessment is based on data submitted by the applicant company up to and including 14 July 2017.

**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*

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.

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.