

# Roflumilast for treating chronic obstructive pulmonary disease

Technology appraisal guidance

Published: 26 July 2017

[www.nice.org.uk/guidance/ta461](http://www.nice.org.uk/guidance/ta461)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

## Contents

1 Recommendations .....	4
2 The technology .....	5
3 Evidence .....	6
4 Committee discussion .....	7
Clinical need of people with COPD .....	7
Clinical management of COPD.....	7
Comparators .....	8
Clinical effectiveness.....	8
Cost effectiveness .....	10
Pharmaceutical Price Regulation Scheme 2014 .....	13
Summary of appraisal committee's key conclusions.....	13
5 Implementation.....	19
6 Appraisal committee members and NICE project team.....	20
Appraisal committee members.....	20
NICE project team .....	20

This guidance replaces TA244.

## 1 Recommendations

- 1.1 Roflumilast, as an add-on to bronchodilator therapy, is recommended as an option for treating severe chronic obstructive pulmonary disease in adults with chronic bronchitis, only if:
- the disease is severe, defined as a forced expiratory volume in 1 second (FEV<sub>1</sub>) after a bronchodilator of less than 50% of predicted normal, and
  - the person has had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid.
- 1.2 Treatment with roflumilast should be started by a specialist in respiratory medicine.
- 1.3 These recommendations are not intended to affect treatment with roflumilast that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

## 2 The technology

<b>Description of the technology</b>	Roflumilast (Daxas, AstraZeneca) is an orally administered long-acting selective phosphodiesterase-4 enzyme inhibitor. It targets cells and mediators believed to be important in chronic obstructive pulmonary disease (COPD).
<b>Marketing authorisation</b>	Roflumilast has a marketing authorisation in the UK for maintenance treatment of severe COPD (forced expiratory volume in the first second [FEV <sub>1</sub> ] 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.
<b>Adverse reactions</b>	The most common adverse reactions associated with roflumilast include diarrhoea, weight loss, nausea, abdominal pain and headache. Roflumilast is subject to additional monitoring for weight loss. For full details of adverse reactions and contraindications, see the summary of product characteristics.
<b>Recommended dose and schedule</b>	The recommended dose is 500 micrograms (1 tablet) of roflumilast once daily.
<b>Price</b>	£37.71 for 30 tablets and £113.14 for 90 tablets (excluding VAT; 'British national formulary' [BNF] edition 72). Costs may vary in different settings because of negotiated procurement discounts.

### 3 Evidence

The appraisal committee ([section 6](#)) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

## 4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of roflumilast, having considered evidence on the nature of chronic obstructive pulmonary disease (COPD) and the value placed on the benefits of roflumilast by clinical experts. No evidence was submitted by patient groups and no patient experts attended the committee meetings. The committee also took into account the effective use of NHS resources.

### *Clinical need of people with COPD*

4.1 The committee heard that COPD is a chronic and progressive disease characterised by obstruction of the airways, breathlessness and cough. Airflow limitation becomes worse over time, with periodic acute exacerbations. The clinical expert advised that despite treatment with optimal inhaled therapy many people with severe COPD have several exacerbations each year, which is a huge burden on patients and the NHS. Exacerbations worsen a patient's health status, reduce their quality of life, accelerate decline in lung function, lead to hospitalisation and increase mortality. The committee was disappointed that no evidence was submitted by patient groups and that no patient experts attended the committee meeting. However, it recognised that a new treatment that reduced exacerbations in people with severe COPD would be highly valued by patients and their carers, and addresses an unmet need.

### *Clinical management of COPD*

4.2 The committee heard from the clinical expert that COPD is treated according to NICE's clinical guideline on [chronic obstructive pulmonary disease in over 16s: diagnosis and management](#). For severe COPD (defined as forced expiratory volume in the first second [FEV<sub>1</sub>] less than 50% predicted) the guideline recommends using either an inhaled long-acting muscarinic antagonist alone, a fixed combination of an inhaled corticosteroid and a long-acting beta-2 agonist (dual inhaled therapy), or a combination of all these treatments (triple inhaled therapy). The committee understood that triple inhaled therapy is the standard treatment for people who continue to have exacerbations despite treatment with monotherapy or dual therapy. It noted that the company was seeking a recommendation for the use of roflumilast as an add-on treatment to triple inhaled therapy but not for monotherapy or dual therapy, which were included in the NICE scope. The committee considered whether this was appropriate. It

heard from the clinical expert that the 2017 update of the [Global Initiative for Chronic Obstructive Lung Disease \(GOLD\)](#) report recommended roflumilast as an add-on therapy for people with severe COPD who continue to have exacerbations despite treatment with triple therapy, particularly if they had at least 1 hospitalisation for an exacerbation in the previous year. The committee also heard from the clinical expert that the company's proposed placement of roflumilast in the treatment pathway is consistent with clinical practice, and that around 90% of people having roflumilast will be on triple therapy. The committee concluded that the company's proposed positioning of roflumilast as an add-on to triple inhaled therapy is appropriate.

## Comparators

- 4.3 The committee understood that the comparators in the appraisal scope included monotherapy (a long-acting muscarinic or beta-2 agonist), dual therapy (the above treatments combined with each other or with inhaled corticosteroids), triple therapy (all of the above treatments) and theophylline in combination with inhaled maintenance bronchodilator treatment. The committee noted that the company did not consider monotherapy and dual therapy to be appropriate comparators because it intended to position roflumilast as an add-on treatment to triple inhaled therapy (see [section 4.2](#)). The committee accepted that this approach is appropriate. It also noted that the company does not consider theophylline to be an appropriate comparator. The committee heard from the clinical expert that theophylline is not generally used in clinical practice because of the high risk of toxicity, lack of evidence for clinical effectiveness, and associated side effects (such as seizures and cardiac arrhythmias). The committee accepted the company's rationale for excluding theophylline and concluded that triple inhaled therapy is the appropriate comparator for this appraisal.

## Clinical effectiveness

### Source of clinical evidence

- 4.4 The evidence for roflumilast submitted by the company came from REACT, a multicentre double-blind randomised controlled trial that included 1,935 patients with severe COPD, chronic bronchitis and 2 or more exacerbations in the previous year. It compared roflumilast plus inhaled



combination therapy (a long-acting beta-2 agonist plus inhaled corticosteroids, with or without a long-acting muscarinic antagonist) with placebo plus inhaled combination therapy. The committee noted that the evidence review group (ERG) presented a pooled analysis of REACT plus another multicentre double-blind trial of roflumilast that included 2,352 patients with severe COPD, chronic bronchitis and 2 or more exacerbations and/or hospitalisations in the previous year (RE<sup>2</sup>SPOND). It understood that the company did not include detailed information on RE<sup>2</sup>SPOND in its submission because it believed that the people in the trial do not accurately reflect the target population. The company stated that fewer than half of patients in RE<sup>2</sup>SPOND were on triple therapy (47% compared with 70% in REACT), 0.5% were from Western Europe (compared with 29.5% in REACT) and pre-treatment with inhaled therapies was for a minimum of 3 months rather than 12 months as in REACT. The committee heard from the clinical expert that the duration of background inhaled therapies is an important difference between the 2 trials. Patients in REACT were more likely to have well controlled COPD because they had optimal inhaled therapy for 12 months, whereas patients in RE<sup>2</sup>SPOND were not appropriately pre-treated with inhaled therapies. The clinical expert suggested that the population in RE<sup>2</sup>SPOND had a higher risk of exacerbations compared with the population in REACT. The committee also heard from the company that RE<sup>2</sup>SPOND did not reflect current clinical practice in the UK because it used lower doses of long-acting beta-2 agonists and inhaled corticosteroids and an alternative formulation of roflumilast. The committee discussed the characteristics of the people included in both trials and considered that there were many similarities between the trial populations. The committee also decided that any heterogeneity between the studies, including the difference in the duration of background inhaled therapy, is unlikely to have systematically biased the relative treatment estimates for roflumilast. The committee concluded that it had not heard adequate justification for not including RE<sup>2</sup>SPOND and therefore that both REACT and RE<sup>2</sup>SPOND are relevant for this appraisal.

## Clinical-effectiveness results

- 4.5 The committee noted that the company had presented clinical-effectiveness results for the subgroup of patients in REACT who were taking a concomitant long-acting muscarinic antagonist as part of their inhaled combination therapy (1,346 [70%] patients). It also noted that the ERG presented results for the same subgroup from RE<sup>2</sup>SPOND (1,094 [47%] patients) and had pooled the relative

effect of roflumilast from the 2 studies. The committee considered that it was reasonable to consider the results for this subgroup given the company's intention to position roflumilast as an add-on treatment to triple inhaled therapy (see [section 3](#)). It noted that the company's response to consultation presented pooled analyses from REACT and RE<sup>2</sup>SPOND based on individual patient-level data. The committee considered that these pooled analyses are appropriate and showed that roflumilast reduced the rate of moderate or severe exacerbations (the primary outcome in both trials) compared with placebo. The committee concluded that the company's pooled analyses provided sufficient evidence of the clinical efficacy of roflumilast compared with placebo in the subgroup of patients with severe COPD having exacerbations despite triple inhaled therapy.

## Adverse effects

- 4.6 The committee heard from the clinical expert that roflumilast is generally well tolerated but that weight loss and gastrointestinal adverse effects can lead to discontinuation of treatment in some people. It acknowledged that in its response to consultation, the company highlighted that there were more occurrences of weight loss, nausea and abdominal pain in patients taking roflumilast than patients taking placebo in the pooled individual patient-level data from REACT and RE<sup>2</sup>SPOND. The committee also heard from the clinical expert that there is virtually no clinical experience of using roflumilast in the UK. In addition, it was aware that roflumilast is subject to additional monitoring for weight loss and that patients are issued with a patient card for reporting side effects. The committee concluded that roflumilast appears to be generally well tolerated but that there is limited experience of using it in clinical practice in the UK.

## Cost effectiveness

- 4.7 The committee noted that the company had developed a Markov model with 3 health states (severe COPD, very severe COPD and death) and monthly cycles. The model was based on the rate of moderate and severe exacerbations for patients having roflumilast plus triple inhaled therapy, compared with triple therapy alone. The committee understood that exacerbations led to additional costs, a temporary decrease in quality of life and, in the case of a severe exacerbation, an increased risk of death. The committee agreed with the ERG

that the model structure excluded some important aspects of COPD progression. For example, health states were defined by FEV<sub>1</sub> values alone rather than incorporating other prognostic information. The model also assumed that exacerbations did not affect FEV<sub>1</sub>, previous exacerbations did not affect future risk of exacerbations and baseline characteristics such as smoking status did not affect disease progression and risk of exacerbation. The committee noted the limitations of the model but concluded that it is adequate for decision-making.

## Modelling rates of exacerbation

- 4.8 The committee noted that in each cycle of the model, patients were at risk of moderate or severe exacerbations and that these rates were incorporated separately in the model. It noted that in response to consultation the company presented a revised base-case model, using exacerbation rate ratios derived from individual patient-level data from the pooled intention-to-treat populations of REACT and RE<sup>2</sup>SPOND (see [section 4.5](#)). The committee considered that the company's approach was appropriate.

## Incorporation of health-related quality-of-life data in the model

- 4.9 The committee noted that in its original base case, the company derived the utility values in the model from 2 studies: Rutten van Molken (2006) for COPD severity and Rutten van Molken (2009) for disutilities for exacerbation. Rutten van Molken (2006) estimated utilities in 1,235 patients, including patients with COPD from the UK, using the UK tariff of the EQ-5D. Utility values from Rutten van Molken (2009) were from valuations of COPD health profiles (presented as vignettes) by the Dutch general public rather than EQ-5D. The committee noted that the ERG's analysis used disutilities for exacerbation from Hoogendoorn et al. (2011), because these were based on patient-reported EQ-5D values and used the UK tariff. The committee acknowledged that in its revised base case, the company incorporated disutilities for exacerbation from Hoogendoorn et al. (2011), which it considered appropriate. The committee recognised, however, that using a different data source for disutilities did not have a large impact on the incremental cost-effectiveness ratio (ICER).

## Incorporation of annual FEV<sub>1</sub> decline in the model

- 4.10 The committee noted that the company's revised base case incorporated an

annual FEV<sub>1</sub> decline of 52 ml based on a review by Tantucci and Modena (2012). The committee heard from the clinical expert that 52 ml is a reasonable estimate of FEV<sub>1</sub> decline, noting that the 2012 review identified studies reporting mean annual FEV<sub>1</sub> declines of 56 ml and 59 ml for people with severe COPD. The committee noted that changing the FEV<sub>1</sub> decline in the model did not have a large effect on the ICER and concluded that 52 ml was a reasonable estimate of annual FEV<sub>1</sub> decline in people with severe COPD.

## Incorporation of post-hospitalisation excess mortality in the model

- 4.11 The committee noted that the company's revised base case incorporated an increased post-discharge mortality risk associated with hospitalisation for a COPD exacerbation of 15.3% from Connolly et al. (2006). The committee was aware that the ERG considered a 12% increased risk to be more plausible, based on the UK National COPD Audit 2014. It heard from the clinical expert that it is difficult to be precise about the mortality rate because of variation each year. The committee concluded that the company's estimate was reasonable but also recognised that post-hospitalisation mortality was a key driver of the results.
- 4.12 The committee noted the ERG's comment that the company's method of incorporating post-hospitalisation mortality into the revised model causes double counting of deaths already accounted for while calculating standardised mortality ratios in the original model. The committee accepted that correcting this would slightly decrease the revised base-case ICER estimated by the company.

## Most plausible incremental cost-effectiveness ratio

- 4.13 Taking into account the amendments described in [section 4.8](#), and [sections 4.10–4.11](#), the company's revised base-case ICER was £24,976 per quality-adjusted life year (QALY) gained. The committee acknowledged that this incorporated the adjustments made by the ERG to the company's original model, which the committee agreed was appropriate. The committee noted that the company had done scenario analyses that varied the estimate for post-hospitalisation mortality, resulting in ICERs between £16,293 and £30,349 per QALY gained. It appreciated that the true ICER may be slightly lower because of the double counting of deaths highlighted by the ERG (see section 4.12). The committee concluded that the company's revised base-case ICER was a plausible estimate of the cost effectiveness of roflumilast as an add-on

treatment to triple inhaled therapy, and that the company's ICERs are within the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained).

- 4.14 The committee recalled that roflumilast is generally well tolerated but that there are potential adverse effects such as weight loss, for which people taking roflumilast should be monitored. It also recalled that there is a lack of clinical experience in using roflumilast in the UK. The committee concluded that roflumilast could be recommended for use in the NHS for adults with severe COPD, chronic bronchitis and frequent exacerbations (2 or more exacerbations in the previous 12 months) despite triple inhaled therapy, but that treatment should only be started by a specialist in respiratory medicine.

### *Pharmaceutical Price Regulation Scheme 2014*

- 4.15 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

### *Summary of appraisal committee's key conclusions*

TA461	Appraisal title: Roflumilast for treating chronic obstructive pulmonary disease	Section
Key conclusion		

<p>Roflumilast, as an add-on to bronchodilator therapy, is recommended as an option for treating severe chronic obstructive pulmonary disease in adults with chronic bronchitis, only if:</p> <ul style="list-style-type: none"> <li>the disease is severe, defined as a forced expiratory volume in 1 second (FEV<sub>1</sub>) after a bronchodilator of less than 50% of predicted normal, and</li> <li>the person has had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid.</li> </ul> <p>The committee concluded that there is sufficient evidence of the clinical efficacy of roflumilast compared with placebo in the subgroup of patients with severe COPD having exacerbations despite triple inhaled therapy.</p> <p>The committee concluded that the company's revised base-case incremental cost-effectiveness ratio (ICER) of £24,976 per quality-adjusted life year (QALY) gained is a plausible estimate of the cost effectiveness of roflumilast as an add-on treatment to triple inhaled therapy, and is within the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained).</p>		1.1, 4.5, 4.13
<b>Current practice</b>		
Clinical need of patients, including the availability of alternative treatments	The committee heard from the clinical expert that despite treatment with optimal inhaled therapy many people with severe COPD have several exacerbations each year, which is a huge burden on patients and the NHS. The committee was disappointed that no evidence had been submitted by patient groups and that no patient experts attended the committee meeting.	4.1
<b>The technology</b>		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee recognised that a new treatment that reduces exacerbations in people with severe COPD would be highly valued by patients and their carers and address an unmet need.	4.1

What is the position of the treatment in the pathway of care for the condition?	The committee understood that triple inhaled therapy is the standard treatment for people who continue to have exacerbations despite treatment with monotherapy or dual therapy. It concluded that the company's proposed positioning of roflumilast as an add-on to triple inhaled therapy is appropriate.	4.2
Adverse reactions	The committee concluded that roflumilast appears to be generally well tolerated but that there is limited experience of using it in clinical practice in the UK.	4.6
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The committee noted that the evidence for roflumilast submitted by the company came from REACT (a multicentre double-blind randomised controlled trial with 1,935 patients, comparing roflumilast plus inhaled combination therapy with placebo plus inhaled combination therapy) and RE <sup>2</sup> SPOND, another multicentre double-blind trial of roflumilast that included 2,352 patients.	4.4
Relevance to general clinical practice in the NHS	The committee concluded that both REACT and RE <sup>2</sup> SPOND are relevant for this appraisal.	4.4
Uncertainties generated by the evidence	The committee considered uncertainties in the clinical evidence and acknowledged the difference in duration of background inhaled therapies in REACT and RE <sup>2</sup> SPOND, but concluded that both trials are relevant for this appraisal.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee considered that it was reasonable to consider the results for the subgroup of patients who were taking a concomitant long-acting muscarinic antagonist as part of their inhaled combination therapy, given the company's intention to position roflumilast as an add-on treatment to triple inhaled therapy.	4.5

Estimate of the size of the clinical effectiveness including strength of supporting evidence	In the subgroup of patients who were taking a concomitant long-acting muscarinic antagonist as part of their inhaled combination therapy, the committee concluded that there was sufficient evidence of the clinical efficacy of roflumilast compared with placebo.	4.5
How has the new clinical evidence that has emerged since the original appraisal (TA244) influenced the current recommendations?	TA244 recommended that roflumilast should only be used as part of a clinical trial for adults with severe COPD. Since TA244 was published, 2 multicentre double-blind randomised controlled trials have been published and the results of both trials have informed the recommendations in this appraisal.	4.4
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The committee noted that the company had developed a Markov model that was based on the rate of moderate and severe exacerbations for patients having roflumilast plus triple inhaled therapy, compared with triple therapy alone. The committee noted some limitations in the model but concluded that it is adequate for decision-making.	4.7
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that there is uncertainty in the estimates used for annual decline in forced expiratory volume in the first second [FEV <sub>1</sub> ] and post-hospitalisation mortality, but concluded that the estimates used by the company were reasonable.	4.10, 4.11



<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee recognised that the data source for disutilities did not have a large impact on the ICER.</p>	<p>4.9</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The company presented cost-effectiveness results for the subgroup of people taking a concomitant long-acting muscarinic antagonist as part of their inhaled combination therapy. The committee considered this was appropriate given the company's intention to position roflumilast as an add-on treatment to triple inhaled therapy.</p>	<p>4.5, 4.7, 4.13</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee recognised that post-hospitalisation mortality was a key driver of the cost-effectiveness results.</p>	<p>4.11</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The committee concluded that the company's revised base-case estimate of £24,976 per QALY gained was a plausible estimate of the cost effectiveness of roflumilast.</p>	<p>4.13</p>
<p>How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA244) influenced the current recommendations?</p>	<p>The current appraisal used clinical evidence from 2 randomised controlled trials (REACT and RE<sup>2</sup>SPOND) to re-model the cost effectiveness of roflumilast and this has led to a change in the recommendations.</p>	<p>4.8</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>The company did not submit a patient access scheme.</p>	<p>–</p>

End-of-life considerations	Not applicable.	-
Equalities considerations and social value judgements	The committee did not note any specific equalities considerations.	-

## 5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has COPD and the doctor responsible for their care thinks that roflumilast is the right treatment, it should be available for use, in line with NICE's recommendations.

## 6 Appraisal committee members and NICE project team

### *Appraisal committee members*

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### *NICE project team*

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Abitha Senthinathan and Kirsty Pitt**

Technical Leads

**Zoe Charles**

Technical Adviser

**Liv Gualda and Marcia Miller**

Project Managers

ISBN: 978-1-4731-2609-1

## Accreditation

