Clinical Commissioning Policy: Riociguat for pulmonary arterial hypertension

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Clinical Commissioning Policy: Riociguat for pulmonary arterial hypertension

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Policy Statement

NHS England will routinely commission riociguat for additional categories of patients with pulmonary arterial hypertension in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About pulmonary arterial hypertension

Pulmonary hypertension (often shortened to PH) is a serious illness.

- In PH, the blood pressure in the vessels carrying blood from the heart to the lungs (called 'pulmonary arteries') is high.
- This causes damage to the heart and lungs - which gets worse over time.

Pulmonary arterial hypertension (PAH) is a type of PH that is caused by problems with the small branches of the pulmonary arteries.

In 2013/2014, 8,431 patients in the UK were treated for PH.

About the current treatments

There are many different treatments available for PH. These treatments can:

- improve the symptoms of PH - therefore improving quality of life
- slow the worsening (progression) of PH over time
- some can reverse damage to the heart and lungs.

Treatment for PH can be split into three categories:

- conventional therapy - such as ‘diuretics’ that lower blood pressure
- targeted therapy
- surgery

Many people with PH are treated with both conventional and targeted therapies, although this can be different for different people. Surgery is beneficial in some cases of PH but not PAH. How PAH is treated will depend on a number of things, for example how severe the PAH is or what type of PAH the patient has.

About the new treatment

NHS England has selected six centres to provide pulmonary hypertension services for adults and has a policy for targeted therapies. A medicine called ‘riociguat’ has been developed as a targeted therapy which can be used on its own or with some other therapies and was considered for inclusion in this policy to treat specific patients with PAH.

Conventional therapies help to manage the patient’s symptoms. However, targeted therapies act on the disease pathway itself. This means that they act on processes in the body that may be causing the symptoms,

- clinical improvement and better quality of life
- improvement to the blood flow in the organs and tissues (called ‘haemodynamic’ improvement).

What we have decided

NHS England has carefully reviewed the evidence to treat PAH with riogicuat. We have concluded that there is enough evidence to make the treatment available.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a policy to routinely commission riociguat for specific patients with pulmonary hypertension.

Pulmonary hypertension (PH) is a rare and debilitating chronic disease of the pulmonary vasculature, characterised by vascular proliferation and remodelling of the small pulmonary arteries. This results in a progressive increase in pulmonary vascular resistance (PVR) which can ultimately lead to right heart failure and premature death.

PH can be classified into five etiological subgroups including; idiopathic, heritable, drug and toxin induced, associated, and persistent pulmonary hypertension of the newborn. In addition, PH is typically scored on the basis of the severity of PH-specific symptoms into four different World Health Organisation (WHO) functional classes (FC). This system allows clinicians to make accurate differential diagnoses among diseases that demonstrate similarities in clinical presentation and pathophysiology, and helps to guide their decisions regarding appropriate treatment.

There is currently no cure for PH, other than lung transplantation.

The updated Classification of Pulmonary Hypertension is provided in the Definitions section 2 below

This policy considers the role of riociguat, in the treatment of patients with Functional Class III PH in the context of the existing published policies.

2 Definitions

PH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest (assessed by right heart catheterisation), a pulmonary wedge pressure of ≤15 mmHg and a pulmonary vascular resistance ≥3 Wood units.

PH can be classified based on the aetiology:

1. Pulmonary arterial hypertension
    1.1 Idiopathic PAH
    1.2 Heritable PAH 1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
        1.2.3 Unknown
    1.3 Drug and toxin induced
    1.4 Associated with:
        1.4.1 Connective tissue disease
        1.4.2 HIV infection
        1.4.3 Portal hypertension
        1.4.4 Congenital heart diseases
        1.4.5 Schistosomiasis 1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis′ 1" Persistent pulmonary hypertension of the newborn (PPHN).

2. Pulmonary hypertension due to left heart disease
    2.1 Left ventricular systolic dysfunction
    2.2 Left ventricular diastolic dysfunction
    2.3 Valvular disease
    2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies.

3. Pulmonary hypertension due to lung diseases and/or hypoxia
    3.1 Chronic obstructive pulmonary disease
    3.2 Interstitial lung disease
    3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
    3.4 Sleep-disordered breathing
    3.5 Alveolar hypoventilation disorders
    3.6 Chronic exposure to high altitude
    3.7 Developmental lung diseases.

4. Chronic thromboembolic pulmonary hypertension (CTEPH) - riociguat is already commissioned for this indication

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH.

The WHO provides a functional assessment grading for the severity of PH:
Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or syncope.
Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

This policy only concerns the use of riociguat for the above indications 1 - 1.4.5 and patients in WHO functional class III only.

3 Aims and Objectives

This policy considered NHS England's commissioning position on riociguat as a monotherapy or in combination with other PH therapies as part of the treatment pathway for adults with WHO functional class III PAH of aetiologies 1 - 1.4.5 (as per Section 2).

4 Epidemiology and Needs Assessment

The estimated annual incidence of diagnosed PAH in the general population ranges from 0.9 to 7.6 cases per million persons, while the prevalence of diagnosed PAH in the general population is between 6.6 and 26 cases per million persons (Frost et al., 2013, Peacock et al., 2007). Incidence and prevalence rates may be underestimated as a result of incorrectly and/or undiagnosed patients.

Between March 2013 and April 2014, 8,431 patients were treated by the UK pulmonary hypertension services, of which 45% (3,794) have the diagnosis of pulmonary arterial hypertension (diagnoses 1 - 1.4.5 in section 3). Over the same period, 49% (4,103) of patients received disease-targeted drug therapy, of which 81% (3,323) received sildenafil. This policy does not seek to commission riociguat as a competitor to sildenafil for these patients, rather as a substitute when already commissioned therapies are failing to achieve stasis in disease progression. Of the patients with pulmonary arterial hypertension started on monotherapy, 65% will experience failure of the monotherapy within two years (National Pulmonary Hypertension Audit, 2014).

Clinicians have estimated that there are approximately 300 patients expected to be suitable for riociguat therapy based upon the criteria for commissioning in Section 7. According to these criteria, there are three distinct groups of patients where riociguat therapy would be commissioned as a substitute to first line therapies.

(1) For patients in functional class III, as a monotherapy for those contraindicated or intolerant of a PDE5 inhibitor, c.20-30 patients.
(2) For patients in functional class III, as a third line therapy in combination with an ERA, c. 150-200 patients.
(3) For patients in functional class III, as a fourth line therapy in combination with a prostaglandin, where a PDE5 inhibitor is contraindicated or not tolerated, c.25-50 patients.

5 Evidence Base

NHS England has concluded that there is some evidence of effectiveness for the use of riociguat for pulmonary arterial hypertension. It should be noted that within this field, all major randomised trials are, and will continue, to be sponsored by the pharmaceutical industry. The largest trial to date concerning PAH involves 1,154 patients across three continents; the number of patients needed to carry out a non-inferiority study would be greater than three times this amount.

The search identified 154 articles of which 13 met the inclusion criteria for evidence review.

A large proportion of the papers related to in vitro studies considering cellular mechanisms of action, pharmacokinetic or animal studies. There were excluded as they were not directly relevant to the research questions.

A number of the studies related to patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH), as opposed to PAH. Relevant studies in a CTEPH population have been included with the aim to review evidence on safety or cost of riociguat.

The evidence is mostly characterised by studies graded as 1- (RCTs with a high risk of bias) or 2- (cohort studies with a high risk of bias). There are a number of randomised controlled trials (RCTs), but all are placebo controlled. The majority of the literature is sponsored by or linked to the drug manufacturer. It should be noted that the data available on currently commissioned treatments also arose from industry sponsored studies. The current body of evidence is lacking direct comparison of the risks and benefits of riociguat with currently established effective therapeutic agents for PAH, it remains difficult to conclude regarding comparative effectiveness and safety of the drug as a monotherapy or combination therapy.

Part 1: Clinical effectiveness of riociguat as a monotherapy compared with a PDE5 inhibitor or an ERA

PATENT1, a randomised double blind trial demonstrated a positive response to riociguat therapy (Ghofrani et al., 2013). This indicates that riociguat could be considered as first line therapy for patients. However, as none of the studies compared effectiveness and safety of riociguat to PDE5 inhibitor or an ERA the data is unable to provide information on comparative or superior effectiveness of riociguat. This this was a medium sized, commercially sponsored RCT, and is the study on which the European Medicines Agency (EMA) licence was granted. The patient population for this trial were group 1 PAH patients, of whom 42% were functional class II and 53% were functional class III. Patients were randomised to placebo, riociguat in individually adjusted doses of up to maximum 2.5 mg three times daily, or riociguat in individually adjusted doses up to maximum 1.5 mg three times daily. At week 12, the 6-minute walk distance had increased from baseline by a mean of 30m in the 2.5mg group and had decreased by a mean of 6m in the placebo group. There was improvement in the primary outcome across both groups in the first eight weeks followed by reduction in the 6 minute walking distance in the placebo group between weeks eight and twelve. The study reported primary outcome only for 2.5mg dosage group and not the 1.25mg group. There were significant improvements in the specified secondary endpoints, including pulmonary vascular resistance, NT proBNP levels, functional class and time to clinical worsening, and Borg Dyspnoea score when comparing patients in the 2.5mg riociguat group with the placebo group. Syncope, the most commonly occurring serious adverse event was higher in the placebo group (4%) compared to 1% in the riociguat group.

Of the total number of patients randomised (n=443), A total of 44% of the patients were receiving treatment with endothelin-receptor antagonists (primarily bosentan), and 6% were receiving prostanoid therapy (primarily inhaled iloprost); 50% were receiving no other treatment for pulmonary arterial hypertension. Patients who were receiving treatment with phosphodiesterase type 5 inhibitors or intravenous prostanoids were excluded. Further subgroup analysis showed that the functional benefits of riociguat therapy tended to be greater in patients who had previously

received prostanoids. The study demonstrated that the addition of riociguat to an ERA in combination was both safe and met the primary end point so there is clear evidence that the addition of riociguat to an ERA is effective.

There is limited value of comparative efficacy data with subgroups comprising of small numbers of patients and lack of information on the statistical tests used to ensure that perceived outcomes are not due to a random variation.

Zheng et al. (2014) reported a meta-analysis of a number of targeted therapies in the treatment of PAH. This study was excluded from the evidence review to avoid double counting of impact given the only paper relevant to this review that was included in the meta-analysis was Gofhrani et al. (2013). Analysis of data from 18 trials with a total of 4363 subjects by indicates that phosphodiesterase type 5 inhibitors were associated with a statically significant reduction in mortality (RR 0.22; 95% CI 0.07-0.71, p=0.011), while other drugs only showed a trend toward reducing mortality. Compared with placebo, endothelin receptor antagonists (ERAs), PDE-5Is and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased the 6-min walk distance.

Rosenkranz et al. (2015) reported an open label extension study to PATENT1 in a cohort of patients with PAH following repair of congenital heart disease. The authors conclude the drug is efficacious in this cohort compared to placebo and it is well tolerated. The authors note the exploratory nature of the study, given the small numbers and that the study is probably not appropriately powered to detect the differences reported. In addition, it should be noted the study is commercially sponsored.

Rubin et al. (2015) reported on the one year extension study for the PATENT1 cohort. This was an observational follow up of the PATENT1 cohort. The study concluded that long-term riociguat was well tolerated in patients with pulmonary arterial hypertension, and led to sustained improvements in exercise capacity and functional capacity for up to one year.

Langleben et al. (2015) aimed to investigate whether riociguat increased the proportion of patients achieving clinically relevant responder thresholds compared with placebo during PATENT1. In summary, the proportion of patients with a combination of response criteria (6MWD ≥ 380 m, WHO FC I/II, cardiac index ≥2.5 litre/min/m2, NT-proBNP < 1,800 pg/ml, and SvO2 ≥65%) was 15% and 13% at baseline in the riociguat group (n=193) and the placebo group (n=93), respectively. After 12 weeks of treatment, the proportion increased to 34% in the riociguat group, whereas it was largely unchanged in the placebo group (16%). Responders were reported to be younger (mean age 44 vs 53 years), be in a lower WHO FC (4/73/23/0% vs 4/34/60/1% in WHO FC I/II/III/IV, respectively) and have a lower BMI (24 vs. 27) compared with non-responders.

Bonderman et al. 2013 considered the efficacy of riociguat in a cohort with pulmonary hypertension caused by systolic left ventricular dysfunction. It was concluded that the primary end point of the study was not met but that riociguat was well tolerated in patients with pulmonary hypertension caused by systolic left ventricular dysfunction and improved cardiac index and pulmonary and systemic vascular resistance. This was a placebo controlled dose ranging study.

Bonderman et al. 2014 published a small (46 screened, 39 randomised) phase 2a study in a population of PH patients and low ejection fraction. With the highest dose, 2mg, there was no significant difference in the primary outcome, and some reported statistically significant differences in the secondary outcomes. The extent to which these differences are clinically relevant is uncertain.

Part 2: Cost-effectiveness of riociguat as a monotherapy compared with a PDE5 inhibitor or an ERA

There was no economic analysis of riociguat.

The National Institute for Health Research (NIHR) sponsored a health technology assessment (HTA) considering the clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension

(Chen et al., 2009). This reports incremental cost-effectiveness ratios for these treatments, all close to or above the threshold.

There were two papers that were excluded from the clinical evidence review giving some insight into quality of life (QoL) gain, Minai et al. (2015) – the CHEST study, and Mathai et al. (2015) – the PATENT study. They were excluded on account of them being conference abstracts.

Burudpakdee et al. (2014) reported the budgetary impact of adding riociguat to a hypothetical US population of 1 million for the treatment of patients with pulmonary arterial hypertension or CTEPH. The model estimated that 7 patients with PAH and 2 patients with CTEPH would be suitable for pharmacotherapy. Also the model estimated that the incremental per capita costs for coverage for riociguat were £0.18. This cost is for a Medicare insured population. As this was a US study some caution should be exercised in extrapolating this study to England.

Part 3: Clinical effectiveness of riociguat as a monotherapy compared with a PDE5 inhibitor and an ERA as dual therapy:

Almost all of the evidence did not adequately contextualise the treatment in a pathway of care, where distinctions were drawn between treatment naïve and prior treated, the numbers were too small to draw any meaningful conclusions.

Galie et al. (2015), reported a small (n=18) RCT and noted that combination of riociguat and sildenafil, compared to sildenafil alone did not make a difference to the primary outcome (max change in supine systolic blood pressure (SBP) within 4 hours post administration) and there were some unfavourable safety signals reported. The authors recommend that concomitant use of riociguat with phosphodiesterase-5 inhibitors (PDE5I) is contraindicated.

Part 4: Clinical effectiveness of riociguat and an ERA as dual therapy compared with a PDE5 inhibitor and an ERA as dual therapy:

Some of the studies provided information on potential dual therapies. For example, Ghofrani (2013) included patients both previously treated with background prostanoids or endothelin receptor agonists and patients not previously treated. Sub group analyses showed that riociguat improved the 6-minute walking distance (primary outcome) both in patients who were receiving no other treatment for the disease and in those who were receiving ERA (n=194) or prostanoids (n=28) was pre-specified (i.e. not post hoc). Hence, it would appear that addition of riociguat to an ERA in combination was safe and met the primary end point. Further evidence on the superiority of ERA and riociguat versus an ERA alone is not available due to absence of direct comparison groups.

Part 5: Clinical effectiveness of riociguat and a prostaglandin as dual therapy or riociguat, a prostaglandin and an ERA as triple therapy, compared with a PDE5 inhibitor and a prostaglandin as dual therapy, or a PDE5 inhibitor, a prostaglandin and an ERA as triple therapy:

There was insufficient data to draw a meaningful conclusion on riociguat as a dual therapy in combination with a prostaglandin or triple therapy with prostaglandin and an ERA. While 28 patients in PATENT1 trial received background prostanoids, the trial does not appear to be sufficiently powered for this sub group analysis due to the small number. It is noted use of riociguat as a triple therapy with a prostanoid and an ERA is outside of its licensed use in the UK.

6 Criteria for Commissioning

In addition to the patient population and disease-targeted treatments commissioned in the NHS England commissioning policy A11/P/a and A11/P/c, riociguat will be routinely commissioned for patients who meet the following criteria:

(1) Confirmed diagnosis of pulmonary arterial hypertension assessed to be in WHO functional class III

AND

(2) Belonging to one of the following clinical classifications:

1. Pulmonary arterial hypertension

1.1 Idiopathic PAH

1.2 Heritable PAH

1.3 Drug and toxin induced

1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis′

For these patients, riociguat will be commissioned as:

(1) An alternative monotherapy for functional class III patients where a PDE5 inhibitor is contraindicated (due to intolerance or adverse drug reaction), as an alternative to an ERA

(2) As a third line therapy for functional class III patients in combination with an ERA after failure to respond, or a sub-optimal response, to PDE5 inhibitor plus an ERA

(3) As a fourth line therapy for functional class III patients in combination with prostaglandin after failure to respond to, or, a suboptimal response to PDE5 inhibitor plus a prostaglandin

(4) As a fourth line therapy for functional class III patients who have been formally assessed by a transplant centre and accepted as a suitable candidate in accordance with Policy A11/P/c, after failure to respond, or a sub-optimal response to a PDE5 inhibitor plus an ERA plus a prostaglandin

(Note: an optimal response is reduced consequences of right heart failure (hospitalisation or death) with improved quality of life however measured)

Riociguat will not be routinely commissioned:

(1) For any patients outside of the described clinical classification

(2) For use in any other treatment combinations

(3) For use in patients receiving a PDE5 inhibitor or nitrate medications

(4) For use in patients who display adverse drug reactions to riociguat

7 Patient Pathway

All patients with PAH will receive structured care and follow up as recommended by the ERS/ESC guidelines. Patients are referred to PH service by a consultant physician (typically cardiology or respiratory but also from other services including haematology, rheumatology, infectious disease) where PAH is suspected as a cause of symptoms. A multi-disciplinary team (MDT) discuss and develop an individualised management plan, and a member of the MDT will be present with the patient when the final diagnosis is discussed.

Treatment:
If appropriate, disease-targeted therapy will only be initiated by the PH centre, which is responsible for monitoring and ensuring the safe, long-term prescribing of continuing treatments, where required.

Disease-targeted therapy is defined in Policy A11/P/c.
Specific elements of the pathway where riociguat may be used are:

Second-line monotherapy:
Patients who have failed to respond to a trial of therapy of adequate dose and duration (typically eight to twelve weeks), or patients who have failed to tolerate one of the oral first-line therapies will be switched to an ERA as alternative monotherapy. Riociguat will be considered for functional class III patients contraindicated to PDE5 inhibitor, or as an alternative to ERA.

Third-line combination therapy:
Patients in functional class III who have failed to respond to a PDE5 inhibitor and an ERA can be prescribed riociguat and an ERA.

Fourth line therapy:
Riociguat will be considered as a fourth line therapy for functional class III patients in combination with prostaglandin after failure to respond to, or, a sub-optimal response to a PDE5 inhibitor plus an ERA plus a prostaglandin.

Riociguat treatment will commence at an initial dose of 1mg, as per EMA license EMA/51814/2014, three times daily, and up-titrated by the patient (at home) using systemic blood pressure as the measure of effectiveness and in close communication with the PAH team. In addition, patients considered for riociguat therapy will be strongly encouraged to engage with smoking cessation programmes as the evidence demonstrates smoking to impair the benefit of riociguat.

The supportive care needs of all patients on the disease targeted therapy will be assessed, taking into account any requirements for home care delivery and support.

For those patients who are eligible for lung transplantation, referral will be sent, using the nationally agreed proforma, to the lung transplant centre within five working days of the clinician's decision.

Typically, any new therapy or change in regimen is reviewed at three months and then, every three to six months as an outpatient. Patients treated with disease targeted therapy will have lifelong follow up within the PH service. The PH centre will identify those patients suitable for shared care and ensure effective communication with shared care centres to plan patient reviews. These patients will be reviewed at least once each year by the visiting PH specialist or at the PH centre.

8 Governance Arrangements

Six centres are designated to provide pulmonary hypertension services for adults. The centres offer investigation and treatment of patients with idiopathic pulmonary hypertension, pulmonary hypertension complicating other diseases and assessment of response to treatment. The centres and staff also provide support for patients and their families.

Only the designated centres are able to initiate treatment with a disease-targeted medicine under this policy.

In some circumstances, explicit and formalised shared-care agreements may be made by the designated centres with other specialist centres to prescribe disease-

targeted therapies. However, non-specialist clinicians and general practitioners will not be asked to routinely prescribe these medicines since they are not able to submit information to the national database.

Where a patient is started on a disease-targeted therapy, their GP will be informed and alerted to any potential for unwanted effects, including interactions with other medicines.

A service specification for pulmonary hypertension has been published by NHS England including standards for the delivery of care.

9 Mechanism for Funding

All disease-targeted therapies (including riociguat) will be commissioned by NHS England through local specialised commissioning teams.

10 Audit requirements

Each centre will need to provide commissioners with a monthly monitoring statement covering the following fields:

- ID number
- Patient Initials
- NHS number
- PCT/SCG codes
- Drug and dose
- Notification of changes to drugs and dosage
- Discontinuation date
- Reason for discontinuation
- Monthly cost
- Annual cost
- Survival
- Quality of Life estimate (emphasis 10)
- Absolute 6 minute walk

The above data will need to be submitted to the National Pulmonary Hypertension Audit.

11 Documents which have informed this Policy

NHS England Clinical Commissioning Policy: Targeted Therapies for Pulmonary Hypertension Functional Class II (A11/P/a)

NHS England Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults (A11/P/c)

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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