



# **Clinical Commissioning Policy Proposition: Ziconotide (intrathecal delivery) for chronic refractory cancer pain**

**Reference: NHS England D08X03/01**

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# **Clinical Commissioning Policy Proposition: Ziconotide (intrathecal delivery) for chronic refractory cancer pain**

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Prepared by NHS England Specialised Services Clinical Reference Group for  
**Specialised Pain Services**

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## Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

## Plain Language Summary

Cancer is one of the leading causes of pain, and chronic cancer pain is pain of a moderate or severe nature that persists for longer than six to twelve months. It can be debilitating and severely affect both activities of daily living and quality of life.

Some people will achieve satisfactory pain relief using oral medications such as paracetamol or ibuprofen but others require more invasive approaches to pain management. Ziconotide is a licensed powerful analgesic drug for severe, chronic pain, which has to be delivered through a pump attached to the person, which delivers the medication into the fluid surrounding the spinal cord (intrathecal).

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission intrathecal ziconotide for chronic refractory cancer pain.

## 1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission intrathecal ziconotide for treatment of cancer pain.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether intrathecal ziconotide will be routinely commissioned for the treatment of cancer pain is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

## 2. The proposed intervention and clinical indication

Cancer pain is often very complex, and the most intractable pain is often neuropathic in origin, arising from tumour invasion of the meninges, spinal cord and dura, nerve roots, plexuses and peripheral nerves. Surgery, chemotherapy and radiotherapy are cancer treatments that can cause persistent pain in cancer survivors, up to 50% of whom may experience persistent pain that adversely affects their quality of life.

First line drug treatment includes analgesics (e.g. paracetamol, NSAIDs and opioids), or for neuropathic pain, specific antidepressants and anticonvulsants. However, clinicians estimate that 20% of patients on oral drug administration fail to achieve adequate and sustained pain relief, and this figure is similar for other systemic routes of drug administration (transdermal or parenteral). When pain relief is insufficient or side effects are intolerable from systemically administered analgesics, increasingly invasive strategies can be used. These advanced interventional approaches include nerve blocks, surgery or intrathecal injection of drugs such as morphine, hydromorphone, fentanyl, clonidine or local anaesthetics (bupivacaine), given alone or in combination.

A novel biological approach for pain management is the intrathecal infusion of ziconotide in chronic, intractable pain management for patients who are intolerant or whose pain is refractory to first line therapies including the more commonly used intrathecal drugs such as morphine. Ziconotide does not lead to the development of addiction and tolerance and therefore represents a beneficial treatment option in patient groups requiring long-term pain management. In addition, intrathecal ziconotide avoids the risk of granuloma formation (at site of delivery) and subsequent risk of neurological deficit.

Currently, NHS England routinely commissions intrathecal pumps (for intrathecal drug delivery) in severe cancer pain only and not chronic non-cancer pain. Additionally, the current commissioning position for severe cancer pain only commissions morphine (and other opioid-based medications) and baclofen, not ziconotide. This policy addresses the use of ziconotide for the treatment of chronic refractory cancer pain.

## 3. Definitions

Ziconotide is a potent synthetic neuroactive conopeptide derived from the venom of a marine snail (*Conus Magnus*) developed for the intrathecal treatment of patients with severe refractory chronic pain. Pain signals are transmitted to the brain via the spinal cord when a noxious stimulus triggers neurotransmitters (glutamate and neuropeptides) to be

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released across a synapse prompting the post-synaptic nerve cell to communicate the pain stimulus to the brain. Ziconotide is the first N type calcium channel blocker which binds onto calcium channels in the dorsal horn of the spinal cord blocking the influx of calcium and reducing the release of pain relevant neurotransmitters and relieving pain.

Intrathecal Drug Delivery (ITDD) systems are an advanced stage intervention and are only indicated where other conservative interventions have failed, are contraindicated and where the uncontrolled pain is causing a significant impact on physical and mental health. By positioning a catheter in the cerebrospinal fluid, ITDD ziconotide allows doses of drugs to be applied directly to the receptors of the central nervous system, achieving pain relief. Ziconotide has to be delivered intrathecally for safety reasons. Intrathecal administration in this context involves an injection into the fluid in the space around the spinal cord using either an internal or external infusion pump to control the rate of medication received.

Chronic pain is moderate to severe pain, lasting longer than six months, with associated functional impact, significant disability and impact on quality of life. Refractory pain is pain that is resistant or non-responsive to available treatment therapies or where current treatment options are resulting in significant and unacceptable side effects.

Cancer pain shares the same neuro-patho-physiological pathways as non-cancer pain. It is a mixed mechanism pain, rarely presenting as a pure neuropathic, visceral or somatic pain syndrome. Rather, it may involve inflammatory, neuropathic, ischaemic and comprehensive mechanisms at multiple sites. Development over time is complex and varied, depending on cancer type, treatment regimes and underlying concurrent morbidities.

Cancer pain is often very complex, but the most intractable pain is often neuropathic in origin, arising from tumour invasion of the meninges, spinal cord and dura, nerve roots, plexuses and peripheral nerves. Multimodal therapies are necessary and require a holistic approach combining psychological support, social support, rehabilitation and pain management.

### 4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on intrathecal ziconotide as part of the treatment pathway for adult patients with chronic refractory cancer pain that is not responding to already commissioned pain management options.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with chronic refractory cancer pain that is not responding to already commissioned pain management options.

### 5. Epidemiology and needs assessment

There are an estimated 2.5 million people in the UK in 2015 who have had a cancer diagnosis, the equates to approximately 4% of the UK population. This is an increase of almost half a million in the previous five years (Maddams et al., 2012). Of patients with

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cancer, 55% reported to have pain and 44% reported moderate to severe pain (VAS  $\geq 4$ ) (van den Beuken-van Everdingen et al., 2007).

Of all patients with chronic cancer pain, a number will never present and will manage their own symptoms. Patients who do present are first treated in primary care. Those who can not be managed in primary care are then referred to specialist pain management services. A small group of patients who cannot be managed in specialist care are then referred to a specialised pain centre. When pain relief is insufficient or side effects are intolerable from standard pain management strategies including systemically administered analgesics, increasingly invasive strategies can be used. These advanced interventional approaches include, nerve blocks, surgery or intrathecal injection of drugs such as morphine, hydromorphone, fentanyl, clonidine or local anaesthetics (bupivacaine), given alone or in combination.

A novel and biological approach is intrathecal ziconotide as an alternative to the above when they are either ineffective, contraindicated or limited by adverse effects. Only 1-2% of these patients will be considered for ITDD systems with only a small proportion being considered for ziconotide. All will have a multidisciplinary assessment as part of a specialised pain service assessment which will as part of it assess suitability prior to any trial of ziconotide and only if successful will longer term treatment be undertaken.

As described in the clinical commissioning policy for intrathecal drug pumps for treatment of severe chronic pain, approximately 100 new patients ITDD pumps for pain are implanted annually. Of these, approximately 50 will be for cancer pain.

Based on an estimate of current UK practice, use of ziconotide is very low, with only two centres using the drug. With no routine commissioning, limited experience and an estimated six patients currently on intrathecal ziconotide, expert clinical opinion estimates no more than 20 new cases per year across the country, of which 10 are estimated to be for cancer pain.

## 6. Evidence base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of intrathecal ziconotide for chronic refractory cancer pain.

The evidence fails to adequately evaluate the eligible sub-group population for whom intrathecal ziconotide is clinically effective. In addition, whilst the outcomes described in the following evidence show intrathecal ziconotide to have an overall improvement in visual analogue pain intensity scale (VASPI) the correlation to clinical improvements in patient outcomes, especially the improvement in functional disability caused by chronic pain needs further investigation. Furthermore, the benefits of ziconotide over opioid based medications with reference to tolerance and dependence needs further evaluation. The evidence has highlighted a wide range of adverse effects with intrathecal ziconotide use and further information is required regarding the safe dosage of ziconotide.

### Summary

There are over 30 publications reporting on the efficacy, or safety (or both) of intrathecal



ziconotide. Much of this evidence base comes from cohorts or case series, with patient numbers commonly ranging from around 15 to 80, although there are also three randomised controlled trials (RCTs) and some larger cohort studies. Patient selection criteria vary between the studies, with common groups included being those with chronic pain following failed back surgery and other neuropathic pain. There are a smaller numbers of studies looking at shorter term impact on patients with cancer-related pain. There are some well-designed studies, but much of the evidence is limited by small size of studies, heterogeneity of patients selected, or use of concurrent medications. In addition, as a range of tools are used to try to assess the measurement of pain, this provides a further challenge to the assimilation of evidence across disparate studies.

Overall, the evidence (reviewed in detail below) indicates that use of IT ziconotide has a positive impact on severe and refractory pain (particularly as measured by improvements in mean Visual Analogue Pain Intensity scale (VASPI) scores) in those who respond positively. However, the precise clinical significance of this change is hard to fully interpret. There are some data showing early responders to ziconotide can sustain this efficacy but good long-term efficacy data is limited, in large part due to a high discontinuation rate of ziconotide over time. Studies, almost invariably, show a high rate of adverse events (AEs), commonly neurologic or psychiatric (including dizziness, confusion, and memory impairment) or visual disturbances, urinary retention, nausea and vomiting.

### Detailed review

**Is ziconotide via intrathecal drug delivery clinically effective and safe to use in patients with severe chronic pain (malignant and non malignant pain) refractory to conventional management, compared with placebo or to alternative pain management strategies?**

Two RCTs looked at the short term impact (less than two weeks) of ziconotide among patients mainly with non-malignant (Wallace, 2006) or cancer and/or AIDs diagnoses (Staats, 2004). Wallace et al randomised patients with pain duration of over one year to IT ziconotide (169 patients) or placebo (86 patients), most of whom were on oral opioids at baseline. Patient eligibility for the study required a baseline VASPI score of at least 50, and the primary endpoint was set at a minimum 30% change in mean VASPI score after the initial titration period (6 days). The study results showed a 31.2% improvement in mean VASPI score from baseline in the ziconotide, which was significantly ( $p < 0.001$ ) different from the placebo group's mean change of 6.0%. Statistically significant improvements versus placebo were also seen in the ziconotide group in terms of secondary measures (e.g. Global McGill Pain Score (23% versus 9.2%)). However, the 95% confidence range for those with complete data ranged from 24.4-37.9%.

Although the authors conclude that ziconotide demonstrated efficacy, the wide confidence intervals raise questions. It seems that patients who did respond to ziconotide received an appreciable amount of pain relief (62% mean improvement in VASPI score), but this improvement was not consistent across the entire study population and is not generalisable. The dosing schedule was changed in response to high numbers of AEs and further limits this study. The most common SAEs in the ziconotide group were: dizziness, confusion, urinary retention, nausea and vomiting, amblyopia or visual abnormalities, abnormal gait, stupor or somnolence, ataxia or vestibular disorders, and encephalopathy.

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Overall, this study shows equivocal efficacy results and the potential for adverse events and the narrow therapeutic window with IT ziconotide. Major limitations of the study design include the change in dosing methodology mid-trial and the short duration of the trial, weakening the strength of evidence provided by this RCT.

Staats et al (2004) carried out a well powered (n=111, 96% power, 5% significance level, 30% change in VASPI scores between the two study groups), randomised, double-blind, controlled trial of IT ziconotide in cancer and AIDS patients with chronic, refractory pain (VASPI scores of at least 50 at baseline measurement). Primary endpoint results analysed for the "evaluable" population showed a significant difference between the ziconotide and placebo group in terms of mean VASPI improvement (ziconotide: 53.1% (95% CI 44-62.2%) versus placebo 18.1% (95% CI 4.8-31.4%)) with  $p < 0.001$  within the two weeks of the study. Additionally, moderate to complete pain relief was reported significantly more in the ziconotide group than in the placebo group (52.9% versus 17.5%,  $p < 0.001$ ). The ITT analysis also revealed a significant difference in mean VASPI score improvement between the ziconotide (51.4%) and placebo groups (18.1%) (95% CI 17.3-49.4%,  $p < 0.001$ ). A statistically significant difference in the percentage of patients responding (defined as a 30% improvement in VASPI score, without an increased dose or change in type of concomitant opioid) to the randomised treatment was seen, as well (ziconotide 50% versus 17.5% placebo,  $p = 0.001$ ).

Ziconotide responders then entered a maintenance phase (n = 48, change in VASPI scores of 69.2%) and seemed to sustain efficacy through that period (end phase change in VASPI scores of 69.4%). However, statistical significance was not reported. The study protocol was changed after the first 48 patients were evaluated for safety in order to decrease the ziconotide dosing (0.1 µg/h or less to start, dose increased once per 24 hours until pain control or 2.4 µg/h is reached). Compared with placebo, ziconotide was associated with a larger number of (typically dose-related) adverse events: abnormal gait, dizziness, nystagmus, confusion, somnolence, fever, postural hypotension, urinary retention, nausea, and vomiting.

The main limitations of this study are the short duration, and the protocol dosing change mid-trial. Overall, this is a RCT of significant power which reached its primary end point, but the study's limitations weaken the potential strength of the evidence.

Other studies have used longer follow-up periods. Rauck (2006) reported on 220 patients in a randomised, double-blind, placebo-controlled trial of IT ziconotide. The study was well powered (80%, 110 patients, 39.5% standard deviation, 5% level of significance) for a 15% change in the mean VASPI score at week 3 (versus baseline). Patients had chronic, severe, refractory pain that was mostly neuropathic in origin and 90% had prior IT morphine.

Although the primary end point was reached, the clinical significance of this is not as clear. The study's primary end point analysis demonstrated a significant ( $P = 0.036$ ) mean change in VASPI score from baseline with ziconotide treatment (14.7%) versus placebo (7.2%) at 3 weeks. However, the authors had pre-determined the definition of "responders" as patients showing a 30% change in VASPI score from baseline, and the mean VASPI change from baseline in the ziconotide group was only 14.7%. Results also revealed no statistically significant difference in other secondary measures (e.g. CPRS scores) or the

mean decrease in opioid use (23.7% Z vs 17.3% PI,  $p=0.44$ ).

During the treatment phase of the study, there was a significantly higher rate of AEs in the ziconotide group (92.9% Z vs 82.4% PI,  $p=0.023$ ), however most AEs were mild or moderate (83.6% Z, 83.8% PI). There was no significant difference in the SAEs reported during the treatment phase (11.6%, 19 SAEs Z vs 9.3%, 25 SAEs PI,  $p=0.57$ ), and only 1.8% (2/112) of patients in the ziconotide group had a treatment-related SAE (vs 1.9%, 2/108, in the placebo group). The study noted an AE profile that included chest pain, hypertension, ataxia, dizziness, and neuralgia.

Wallace (2010) carried out a qualitative systematic review of the published evidence relating to IT ziconotide in combination with other therapies (including morphine, clonidine and other agents). Due to the small size and heterogeneity of the source studies, no firm conclusions were drawn.

There have been two larger cohort studies: Ellis, 2008 (155 patients) and Wallace, 2008 (650 patients). Ellis (2008) was an open-label cohort study of 155 patients enrolled after responding to previous IT ziconotide in one of two study trials (both previous trials are reviewed separately in this evidence review, Staats 2004 and Wallace 2006). Efficacy outcomes revealed a 36.9% (SE 3.43) improvement in mean VASPI score from baseline until the last assessment ( $p<0.0001$ ,  $n=144$ ), and 45.8% (SE 6.8) mean change from baseline VASPI in the population remaining at 12 months ( $p<0.0001$ ,  $n=31$ ). Ziconotide-related AEs were experienced in 147 of 155 patients (usually mild or moderate in severity and reversible with dose decrease or discontinuation), and 31 patients had at least one SAE thought at least possibly related to ziconotide. No late-occurring AEs were noted. Limitations of the study include the open-label, non-randomised design, lack of control or direct comparison group, a high attrition rate, and selection bias introduced (patients had already been observed to be "responders" to ziconotide in one of two previous trials).

Wallace, 2008, reported on a large ( $n=644$ ), open-label cohort study which aimed to evaluate the safety of IT ziconotide. Results showed 99.7% of participants with an AE and a high discontinuation rate due to AEs (61%, with 48.9% permanently discontinuing ziconotide due to AEs). Only 18.5% (119 patients) had 360 days of ziconotide in this study (the study median duration was 67.5 days), with AE being the main reason for discontinuation (followed by lack of efficacy in 29.7% and transition into another trial in 10.6%). AEs included nausea (52.6%), dizziness (51.6%), headache (40.1%), confusion (35.1%), pain (32.0%), somnolence (29.3%) and memory impairment (27.8%). Most reported AEs were described as either mild (43.5%) or moderate (42.3%), and more than half (58.6%) were considered unrelated to ziconotide. Those AEs considered ziconotide-related with the highest incidence were dizziness, nausea, confusion, memory impairment, and nystagmus. In terms of efficacy, 32.7% of participants with a baseline VASPI score of 50 or more (85.2%) had at least a 30% improvement at month one. Improvement in pain impact on daily life scores was also seen in 35.1% at month 2 ( $P<0.001$ ). Study limitations include the relatively short duration for a comprehensive safety report, lack of comparator or control arm and the non-randomised, open-label design.

The rest of the main evidence derives from seven smaller cohort or case-control studies. Raffaelli (2011) undertook a retrospective cohort study of 104 patients enrolled in an Italian registry for IT ziconotide use of whom 51% had neuropathic pain and 53% of patients were

given ziconotide as their first-line IT therapy. The results showed a >30% improvement in pain intensity in 72 of the 104 patients, and 45 of these patients had maintained the study drug and efficacy for over six months. This sustained result was statistically significant ( $p < 0.01$ ) and no differences in the change in Visual Analogue Scores (VAS) were noted by diagnosis. Similar AE were seen as in previous studies. Key limitations of the study include the retrospective observational and non-controlled design, a lack of standardisation in treatment protocol and data collection, and missing data.

Ver Donck (2008) led an open-label cohort study of 71 patients for which IT ziconotide was initially titrated. The duration of the titration phase was altered twice from the initial study methodology plans, first to accommodate local practice, then in response to a high rate of meningitis diagnoses. The authors also note that the study was initially designed for a larger population, but enrolment rates were not able to fulfil the initial set criteria. Approximately 90% of patients experienced AEs (363 AEs), with 33.8% of severe intensity and two AEs reported in 10% or more of patients (dizziness 31% and nausea 14%). 26.8% of patients had an SAE, with 1 SAE being ziconotide-related (asthenia/leg weakness). Despite 52% with "moderate to complete pain relief" (per CPRS) and "good to excellent pain control" in 53.6% (per the CGI), only 10% reported complete satisfaction (per CGI), and only 62.3% were "at least somewhat satisfied." Median percent change in opioid dose was unchanged from baseline at week 4. The median percent change in VASPI scores showed significant improvement at weeks 1-4 (week 1: 11%, week 2: 32.6%, week 3: 31%, week 4: 23.5).

Webster (2009) reported on an open-label, long-term (133.4 patient-years), cohort extension study of IT ziconotide in 78 patients who had completed one of two prior studies (Wallace 2008, Ellis 2008, both independently reviewed in this evidence review), where only 43% completed the study with others transferring to another trial, withdrawing consent or otherwise discontinuing. 71 of 78 patients had new AEs, with 37 (52%) considered ziconotide-related and 50 (70.4%) considered severe in intensity. Efficacy results showed no significant loss of pain control (per change in mean VASPI scores) over time, however there were only two points (days 600 and 960) where a >30% improvement in mean VASPI scores from the baseline in the study of origin were noted (a >10% mean improvement was noted otherwise, except for the Day 60 time point). This study is mainly limited by its post-trial, open-label, non-randomised, uncontrolled, non-comparative study design.

Dupoiron (2012) carried out a non-randomised, observational study of 77 patients assessing the safety of combined IT ziconotide, morphine, ropivacaine, and clonidine in patients with chronic cancer pain. There two major limitations to this study are the non-randomised, observational study design, and the use of four study medications together limiting the ability to determine a causal effect between outcomes and any one of the four new medications. Additionally, the patients had various forms of cancer (though a notable 19.5% had pancreatic cancer), and the percentage of patients with neuropathic versus other forms of pain was not reported.

The study results showed a significant improvement in pain intensity (numerical scale) from baseline after 15, 30, 60, and 90 days of IT therapy. However, the study does not definitively provide cause-effect evidence for ziconotide outcomes given the concomitant dosing of four other new IT medications, nor is there any evidence reported regarding use of ziconotide in first line presented in the publication.

Backryd (2015), Mohammed (2013), and Alicino (2012) are three smaller cohort studies enrolling 23, 20 and 20 patients respectively. They do not add additional information to that summarised above but were reviewed as part of this rapid evidence review.

Overall, there is some evidence supporting the efficacy of IT ziconotide in severe, refractory chronic pain. However, the evidence derives from studies with considerable methodological challenges, thus limiting its generalisability. It is clear that many patients experience adverse effects and for a substantial proportion, this is significant enough for them to cease treatment. However, the evidence implies there may be un-defined subgroups who derive much greater benefit.

### **Is Ziconotide via intrathecal drug delivery cost effective in patients with severe chronic pain (malignant and non malignant pain) refractory to conventional management, compared with placebo or to alternative pain management strategies?**

There is one publication reporting on the cost-effectiveness of ziconotide use for the severe, refractory chronic pain population (Dewilde, 2009). This article discussed the results of a cost-effectiveness model for IT ziconotide versus "best supportive care," from a UK NHS perspective. The simulation model used three studies from which to base the clinical assumptions for ziconotide (Rauck 2006, Webster 2008 and Wallace 2006, all of which are reviewed independently in this evidence review). The authors report a base case incremental cost-effectiveness ratio (ICER) of £27,443 per QALY with a 95% CI between £18,304 and £38,504. A probabilistic sensitivity analysis was performed and the authors concluded that the model was robust to most assumptions, noting the most sensitivity to the dosage of ziconotide and discount rates. The sensitivity analysis showed variability in the ICER due to ziconotide dosing assumption changes, ranging from a low of £15,500 (95% CI £8,206–£25,405) with 0.15mg/hour to a high of £44,700 (95% CI £30,541–£62,670) with 0.45mg/hour dosing (from a base case rate of 0.26mg/hr).

This cost-effectiveness model is limited by the reliance on several different sources of data as the basis for assumptions, the lack of long-term data from which to base model assumptions (the authors note a 3-year maximum to reference data), and the use of expert opinion as the basis for some assumptions. The potential for bias therefore, limits the strength of the results.

### **Does any evidence exist on how to minimise the complications of using Ziconotide including the monitoring and dosing of patients?**

There is some evidence to suggest that adverse events can be decreased using lower doses and slower titrations of ziconotide, particularly Dupoirion (2012), Staats (2004), Rauck, (2006), and Alicino (2012). Usual best practices for avoiding complications with IT devices or pumps were not reviewed.

## **7. Documents which have informed this policy proposition**

D08/S/a, NHS Standard Contract for Specialised Pain, (Publications Gateway Reference 01722), 2013.

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D08/P/a, Intrathecal pumps for treatment of severe chronic pain, (Publications Gateway Reference 03738), 2015.

### 8. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016)