



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Brachytherapy of the Coronary Arteries

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Hyperlink to Related Coverage Policies

Drug-Eluting Stents for Ischemic Heart Disease

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers coronary artery brachytherapy as medically necessary when used as an adjunct to percutaneous coronary intervention (PCI) for treatment of in-stent restenosis in a native coronary artery or saphenous vein graft.

CIGNA does not cover coronary artery brachytherapy for any other indication because it is considered experimental, investigational or unproven.

General Background

Revascularization of obstructed arteries due to coronary artery disease may be accomplished by percutaneous coronary intervention (PCI) with balloon angioplasty, a minimally-invasive procedure in which a catheter with an inflatable balloon at the tip is inserted into the lumen of the artery and inflated, dilating the area of blockage. Coronary stents are implanted in most patients during PCI, resulting in lower rates of restenosis compared to balloon angioplasty alone. Several drug-eluting stents have been developed to minimize the incidence of restenosis, and represent approximately 60–70% of stent implantations. The choice of stent (bare metal vs. drug-eluting) depends on various factors, including lesion location and morphology, patient characteristics, and the patient's ability to adhere to the extended period of dual antiplatelet therapy required for drug-eluting stents. In-stent restenosis continues to be a significant problem, and is thought to be caused by neointimal hyperplasia within the stent. Brachytherapy was introduced as a method to treat in-stent restenosis by the delivery of

gamma or beta radiotherapy via a catheter-based system. Brachytherapy affects the proliferation of smooth muscle cells that are responsible for restenosis, and may be used to treat in-stent restenosis of native coronary arteries and saphenous vein grafts (SVGs). Drug-eluting stents have also emerged as an option for treatment of in-stent restenosis in bare metal stents, and several trials compare these two approaches.

U.S. Food and Drug Administration (FDA)

Three brachytherapy devices have received U.S. Food and Drug Administration (FDA) premarket approval (PMA). The Novoste™ Beta-Cath™ System (Novoste Corp., Norcross, GA) and the GALILEO™ Intravascular Radiotherapy System (Guidant Corp., Houston, TX) deliver beta radiation, while the Cordis Checkmate™ System (Cordis Corp., Miami, FL) delivers gamma radiation. Each operates in a similar fashion. A delivery catheter is placed in the coronary artery at the site of in-stent restenosis and a transfer device is connected to the catheter, delivering the radioactive seeds to administer radiation to the artery. After a specified period of time, the radioactive seeds are returned to the transfer device and removed.

Literature Review

In-Stent Restenosis of Native Coronary Arteries and Saphenous Vein Grafts: Several early multicenter trials of brachytherapy demonstrated the treatment benefits of intracoronary radiation for the treatment of in-stent restenosis (Initial Hyperplasia Inhibition with Beta In-stent Trial [INHIBIT], Waksman et al., 2002; STents And Radiation Therapy [START], Popma et al., 2002; GAMMA-1 trial, Leon, et al., 2001; Coronary Radiation to Inhibit Proliferation Post Stenting [SCRIPPS], Teirstein, et al., 1997, Washington Radiation for In-Stent Restenosis Trial [WRIST], Ajani et al., 2002).

Ellis et al., for the TAXUS V ISR Investigators, conducted a randomized study to evaluate two-year outcomes of treatment with a paclitaxel-eluting stent (PES) (n=195) or brachytherapy (n=201) in patients referred for PCI for bare metal stent in-stent restenosis. Between 9 and 24 months, ischemia-driven target lesion revascularization (TLR) tended to be required less in the PES group compared to the brachytherapy group (5.3. vs. 10.3%, p=.07). At 24 months, ischemia-driven TLR and ischemia-driven target vessel revascularization (TVR) were significantly reduced in the PES group compared to the brachytherapy group (10.1 vs.21.6%, p=0.003, and 18.1 vs. 27.5%, p=.03, respectively). There were no significant differences between the two groups in death, myocardial infarction, or target vessel thrombosis between 12 and 24 months, or cumulative to 24 months.

Holmes et al. for the SISR Investigators (2008) conducted a randomized trial to evaluate the safety and efficacy of sirolimus-eluting stents (SES) (n=259) compared to vascular brachytherapy (n=125) for treatment of in-stent restenosis in a bare metal stent. At three years, survival free from TLR or TVR was significantly improved with SES; freedom from TLR was 81.0% for SES vs. 71.6% for brachytherapy, p=0.018; TVR was 78.2% for SES vs. 68.8% for brachytherapy, p=0.022. Target vessel failure and major adverse cardiac events (MACE) were improved with SES but did not reach statistical significance. There was no statistically significant difference in definite or probable stent thrombosis between the two groups.

Drug-eluting stents were compared to beta-radiation for the treatment of in-stent restenosis in a case series conducted by Zavalloni et al. (2006). The first 68 patients (group I) were treated with brachytherapy using the Novoste Beta-Cath system. The latter 73 patients (group II) were treated with a Cypher sirolimus-eluting stent or a Taxus paclitaxel-eluting stent. Nine months following treatment, restenosis rates were 37.8% (28/74) for patients in group I and 14.9% (11/74) for patients in group II (p=.0028). A diffuse pattern of recurrence was more frequently seen after brachytherapy (20/74 vs. 6/74, p=.005). The "edge effect" following brachytherapy was associated with worse outcomes and accounted for most failures. Recurrence within the original restenotic stent was similar in both groups (12.9% vs. 14.9%, p=.8). Patients treated with drug-eluting stents for diffuse in-stent restenosis experienced more favorable clinical and angiographic outcomes compared to a similar cohort of patients treated with beta-brachytherapy.

The three devices described above received FDA approval for in-stent restenosis in native coronary arteries, and most published studies have focused on this indication. Brachytherapy has also been used to successfully treat in-stent restenosis in saphenous vein grafts. The SVG-WRIST trial (Waksman, et al., 2002), a randomized, double-blind, placebo-controlled trial, evaluated the effect of intravascular gamma radiation in 120 patients with in-stent restenosis in saphenous vein grafts. Patients underwent balloon angioplasty, atherectomy, additional stenting or a combination of these procedures. If the intervention was successful, patients were randomly assigned in a double-blind fashion to intravascular treatment with a ribbon containing iridium-192 (n=60) or nonradioactive seeds (n=60). Revascularization and radiation therapy were successful in all patients. At six

months, the restenosis rate was lower in the iridium-192 group (21%) than in the placebo group (44%). At 12 months, revascularization of the target lesion was lower in the iridium-192 group (17%) than in the placebo group (57%). The rate of major cardiac events at 12 months was also lower in the iridium-192 group (32%) than the placebo group (63%).

Rha et al. (2005) published a follow-up to the SVG-WRIST trial to determine whether the safety and efficacy of brachytherapy is durable. At 36 months, target lesion revascularization (TLR), repeat percutaneous transluminal coronary angioplasty (PTCA) and TLR-major adverse cardiac events (MACE) remained significantly lower in the irradiated group, although TVR and TVR-MACE did not. The beneficial effect and efficacy of irradiation declined with time and manifested with late recurrences. The authors stated that saphenous vein grafts are known to degenerate over time, and when PCI is required, the clinical outcome of these patients is markedly impaired. The outcomes of patients in the SVG-WRIST trial are therefore driven by the restenotic process, with a high likelihood that graft failure was a result of progression of degenerative disease within the graft or within the native coronary arteries distal to the graft. The authors concluded that patients in the SVG-WRIST trial treated with brachytherapy had a marked reduction in the need for repeat TLR at 36 months, with sustained clinical benefit at three years despite late recurrences which were more pronounced in the irradiated group.

Meta-Analyses

Oliver et al. (2008) conducted a meta-analysis of randomized trials assessing the outcome of brachytherapy or drug-eluting stents for the treatment of in-stent restenosis. The analysis included 14 studies/3103 patients. Neither treatment had any effect on mortality or rate of myocardial infarction. At intermediate follow-up, brachytherapy reduced the rate of revascularization, binary restenosis, and late loss compared to balloon angioplasty and selective bare metal stents alone. MACE rates were lower in patients treated with brachytherapy at both intermediate and long-term follow-up. Drug-eluting stents reduced the rate of revascularization, MACE, and binary restenosis compared to brachytherapy, but follow-up was limited to nine months. The authors concluded that vascular brachytherapy improves the long-term outcome of angioplasty compared with bare metal stents alone in the treatment of in-stent restenosis, and drug-eluting stents appear to provide similar results during short-term follow-up.

Uchida et al. (2006) conducted a meta-analysis of randomized controlled trials comparing intracoronary gamma- and beta-radiation therapy to placebo for in-stent restenosis. The authors assessed the effectiveness of brachytherapy and of the two radiation sources, and also evaluated the performance of the procedure in native coronary arteries and SVG. Five randomized controlled trials that compared brachytherapy to placebo in 1310 patients were reviewed. There was considerable between-study variance, and diabetes was found to be a significant factor in this variance. In multivariate meta-regression analyses adjusted for diabetes and lesion length, neither gamma radiation source nor SVG was a significant factor for the between-study variance ($p=0.675$ and 0.433 , respectively). Neither procedure in SVG (gamma radiation) nor difference in radiation source (beta or gamma) in native coronary arteries was a significant factor in brachytherapy effectiveness compared to placebo. Intracoronary brachytherapy was effective compared to placebo at mid-term follow-up.

Additional Indications: Intracoronary brachytherapy has been proposed as a treatment for new stenosis of native coronary arteries and SVG, as well as restenosis of native coronary arteries and SVG at the unstented site of a previous PCI. Brachytherapy has also been evaluated as a method of primary prevention of restenosis after stent implantation for de novo lesions.

In the BetAce randomized trial, Ribichini et al. (2006) evaluated brachytherapy for prevention of in-stent restenosis after angioplasty of de novo lesions in patients with high plasma angiotensin converting enzyme (ACE). Elevated plasma ACE levels have been proposed to increase the risk of in-stent restenosis. Thirty-one patients (33 stenoses) were randomized to stent implantation (control group), and 30 patients (31 stenoses) were randomized to brachytherapy and stented angioplasty. Following angioplasty, in-stent minimal lumen diameter (MLD) was similar in both groups. At six months, MLD had decreased in the control group to 1.74 ± 0.8 mm, compared to 2.25 ± 1.05 mm in the brachytherapy group. The mean in-stent diameter was 2.3 ± 0.8 in the control group vs. 2.9 ± 1.05 in the brachytherapy group, and the restenosis rate was 37.5% in the control group vs. 17.9% in the brachytherapy group. At six months, a higher need for TVR was seen in the control group (35.5%) than in the brachytherapy group (13.3%). The authors concluded that this study confirms that patients with high plasma ACE levels are exposed to an increased risk for in-stent restenosis and that the preventive use of brachytherapy in these patients reduced neointimal formation and increased MLD.

Ferrero et al. (2007) reported five-year follow-up of the BetAce trial, analyzing the incidence of death, myocardial infarction (MI), and ischemia-driven target vessel revascularization (TVR). The incidence of stent thrombosis was slightly higher in the brachytherapy group (10%) than in the control group (6.5%). This difference was not statistically significant. Although there was a significantly higher need for TVR in the control group at six months, the difference lost its significance at 12 months and five years because of a late catch-up phenomenon in the brachytherapy group, with a higher incidence of edge stenosis and stent occlusion. Five-year event-free survival rank for death, MI and TVR was 43% in the brachytherapy group compared to 45% in the control group ($p=.95$). The occurrence of additional ischemic events in both groups equalized the long-term clinical outcomes. The authors stated that intracoronary beta radiation at the time of stent implantation only transiently prevents excessive neointimal proliferation that leads to stenosis recurrence in the first year after treatment. The late catch-up phenomenon, along with the natural progression of the atherosclerotic disease in other segments, is responsible for the loss of the clinical benefit of brachytherapy in the long term.

Syeda et al. (2006) conducted a double-blind, randomized trial of beta brachytherapy for prevention of restenosis after stent implantation in native coronary de novo lesions. Eighty-nine diabetic patients (106 lesions) were randomly assigned to treatment with beta radiation or placebo treatment. Angiographic analysis at nine months demonstrated a late lumen loss of 0.7 ± 0.9 mm in the brachytherapy group vs. 1.2 ± 0.8 mm in the control group at the injured segment, 0.9 ± 1.0 vs. 1.3 ± 0.7 mm at the radiated segment, and 0.9 ± 1.0 vs. 1.3 ± 0.7 mm at the target segment. Binary restenosis rates were significantly lower in the brachytherapy group in all subsegments. TVR for restenosis was necessary in nine lesions (17.6%) in the brachytherapy group vs. 18 (34%) in the placebo group. Late thrombosis occurred in four brachytherapy patients after premature discontinuation of antiplatelet therapy, resulting in a MACE rate of 37.2%, compared to 38.6% in the placebo group. The authors concluded that, in diabetic patients with de novo coronary lesions, intracoronary radiation after stent implantation significantly reduced restenosis. This clinical benefit was reduced, however, by the frequent occurrence of new thrombosis.

Professional Societies/Organizations

A guideline update for PCI published by the American College of Cardiology (ACC), American Heart Association (AHA) and the Society for Cardiovascular Angiography and Interventions (SCAI) states that vascular brachytherapy has been successful in treating restenosis occurring within stents, while other adjunctive therapies, such as the cutting balloon, rotary ablation, excimer laser and restenting have shown mixed results. The ACC/AHA/SCAI guideline ranks brachytherapy for the treatment of in-stent restenosis as a Class IIa recommendation, which indicates that there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment but that the weight of evidence is in favor of usefulness/efficacy (Smith, et al., 2005).

Guidelines for PCI issued by the European Society of Cardiology (ESC) state that brachytherapy proved to be the only evidence-based nonsurgical treatment for in-stent restenosis. The guideline also states that a prolonged intake of clopidogrel for one year after radiation is necessary. The ESC guideline recommends brachytherapy for the treatment of in-stent restenosis in native coronary arteries as a Class 1A recommendation. Brachytherapy for treatment of in-stent restenosis of a saphenous vein bypass graft is considered as a Class 1B recommendation. Class I indicates evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective. Level of evidence A indicates that data is derived from multiple randomized clinical trials or meta-analyses, while level of evidence B indicates data is derived from a single randomized clinical trial or large non-randomized studies (Silber, et al., 2005).

Summary

In-stent restenosis following percutaneous coronary intervention (PCI) is a significant clinical problem, frequently resulting in the need for repeat revascularization procedures. Intracoronary brachytherapy has been shown to be an effective treatment for in-stent restenosis of native coronary arteries or saphenous vein grafts. There is insufficient evidence in the published medical literature to demonstrate the safety and efficacy of brachytherapy for expanded indications, however, including treatment for new stenosis of native coronary arteries and SVGs; restenosis of native coronary arteries and SVGs at the unstented site of a previous PCI; or as primary prevention of restenosis after stent implantation for de novo lesions.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
77785	Remote afterloading high dose rate radionuclide brachytherapy 1 channel
77786	Remote afterloading high dose rate radionuclide brachytherapy; 2-12 channels
77787	Remote afterloading high dose rate radionuclide brachytherapy; over 12 channels
92974	Transcatheter placement of radiation delivery device for subsequent coronary intravascular brachytherapy (List separately in addition to code for primary procedure)
92980	Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method, single vessel
92982	Percutaneous transluminal coronary balloon angioplasty, single vessel
92995	Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty, single vessel
93508	Catheter placement in coronary artery(s), arterial coronary conduit(s), and/or venous coronary bypass grafts for coronary angiography without concomitant left heart catheterization

ICD-9-CM Diagnosis Codes	Description
414.00	Coronary atherosclerosis of unspecified type of vessel, native or graft
414.01	Coronary atherosclerosis of native coronary artery
414.02	Coronary atherosclerosis of autologous vein bypass graft
414.03	Coronary atherosclerosis of nonautologous biological bypass graft
414.04	Coronary atherosclerosis of artery bypass graft
414.05	Coronary atherosclerosis of unspecified type of bypass graft

*Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	11/15/2007	0228	Brachytherapy of the Coronary Arteries

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