



# 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**

**Effective Date ..... 11/15/2008**  
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## Hyperlink to Related Coverage Policies

[Drug-Eluting Stents for Ischemic Heart Disease](#)

### INSTRUCTIONS FOR USE

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## 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

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the United States. Revascularization of obstructed arteries of patients with CAD may be accomplished by percutaneous coronary intervention (PCI) with balloon angioplasty. Balloon angioplasty is 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. PCI was developed as a less invasive alternative to coronary artery bypass graft (CABG) surgery. Prior to the advent of coronary stents, however, restenosis rates following PCI were high, occurring in approximately 35–45% of patients. Currently, coronary stents are implanted at the time of the procedure in most patients. Although stents have reduced the restenosis rate, approximately 15–20% of stented arteries will restenose, primarily due to neointimal hyperplasia within the stent, and repeat revascularization procedures must be performed. Drug-eluting stents were developed to address the problem of restenosis. These stents,

which emit (elute) paclitaxel, sirolimus, or zotarolimus, are more effective in preventing in-stent stenosis than bare metal stents. Insertion of drug-eluting stents, however, is limited to patients without contraindications and with lesions of native coronary arteries of a specific size and type. Many patients, therefore, are not candidates for drug-eluting stents and still receive bare metal stents.

Brachytherapy was introduced as a method to prevent or reduce the rate of 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).

### **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.

FDA approval of the Novoste Beta-Cath system on November 6, 2000, was based primarily on the STents And Radiation Therapy (START) trial, a randomized, placebo-controlled trial (Popma, et al., 2002) involving 476 patients at 50 centers. All patients had diffuse in-stent restenosis and were randomized to receive an active Beta-Cath System (n=244) or a placebo Beta-Cath system (n=232). The primary endpoint of clinically-driven target vessel repeat revascularization by eight months was seen in 56 (26.8%) patients assigned to the placebo system and only 39 (17%) patients assigned to the radiation system. In-stent restenosis was 45.2% in the placebo group and 28.8% in the radiation group. The START investigators concluded that <sup>90</sup>Sr/<sup>90</sup>Y beta radiation is safe and effective for preventing recurrence in patients with in-stent restenosis. The Beta-Cath system was approved for treatment of in-stent restenosis in native coronary arteries with discrete lesions in a reference vessel diameter of 2.7–4.0 mm.

The GALILEO system received FDA approval on November 2, 2001, based on three multicenter studies. The largest of these was the INitial Hyperplasia Inhibition with Beta In-stent Trial (INHIBIT), a randomized, placebo-controlled trial with 332 patients enrolled at 24 sites in the U.S., Europe, Asia, and Australia (Waksman, et al., 2002). This trial compared the effect of intracoronary beta radiation with that of placebo in patients with diffuse in-stent restenosis, with the primary endpoint being angiographic restenosis rates within the nine-month follow-up period. The angiographic restenosis rate was 25% lower in the radiated group (14) than in the placebo group (37). The researchers concluded that localized intracoronary beta radiation can be used to reduce overall revascularization in patients undergoing treatment for in-stent restenosis. The GALILEO system was approved to deliver beta radiation to the site of successful PCI for the treatment of in-stent restenosis in native coronary arteries with discrete lesions ≤ 47 mm in a reference vessel diameter 2.4–3.7 mm.

The Cordis Checkmate system received FDA approval on November 6, 2000, based on the results of the GAMMA-1 trial, the Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) trial, and the Washington Radiation for In-Stent Restenosis Trial (WRIST). The GAMMA-1 trial (Leon, et al., 2001) was a multicenter, prospective, randomized, double-blind trial (n=252) that demonstrated a significant treatment effect for diffuse in-stent restenosis patients who received brachytherapy, with a 41% reduction compared to the placebo group in the recurrence of obstruction requiring revascularization of the target lesion. A reduction in major adverse cardiac events (MACE) was also seen. Late thrombosis was seen at 18 months in 5.3% of the patients receiving brachytherapy compared to 0.8% in the placebo group. Late thrombosis occurred in irradiated patients only after oral anti-platelet therapy was discontinued and only in patients who had received new stents at the time of radiation treatment.

### **Literature Review**

**In-Stent Restenosis of Native Coronary Arteries and Saphenous Vein Grafts:** The SCRIPPS (Teirstein, et al., 1997) and WRIST (Ajani, et al., 2002) trials demonstrated similar treatment benefits for intracoronary radiation in patients with restenosis, and provided additional information on the extended use of antiplatelet medication. Patients in both studies received anti-platelet therapy for at least six months. New stents were inserted in 25% of patients in the SCRIPPS trial and 29% in the WRIST trial. In the combined population,

thrombosis-free survival was 99%. The FDA's marketing approval included a requirement that the product labeling explicitly advise avoidance of the placement of new stents and maintenance of antiplatelet therapy for at least six months after brachytherapy and for a year if a new stent was implanted. The warning for avoidance of new stents was also included in the Beta-Cath labeling. The Checkmate system was approved for treatment of native coronary arteries with in-stent restenosis using current interventional techniques, and is for use in vessels 2.75mm–4.0mm in diameter and for lesions up to and including 45 mm in length. Published five-year follow-ups of the WRIST study (Waksman, et al., 2003) and the SCRIPPS study (Grise, et al., 2002) demonstrated that the clinical benefit of brachytherapy continued at five years, with reduction in target lesion revascularization (TLR) and an improvement in event-free survival, although there was some mitigation of efficacy over time.

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, however, 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%).

Castagna et al. (2002) published results of intravascular ultrasound (IVUS) volumetric analysis of 45 participants in the SVG-WRIST trial. In this substudy, of the 45 patients for whom IVUS imaging was available, 26 had been treated with placebo and 19 with iridium-192. IVUS was performed immediately after treatment and at six-month follow-up. Patients treated with iridium-192 had significantly smaller changes in intrastent lumen and intimal hyperplasia cross-sectional area (CSA) and volume compared to patients who received placebo. In addition, patients treated with iridium-192 showed no significant decrease in minimum lumen CSA, while those treated with placebo showed a significant decrease. The reduction in six-month intimal hyperplasia reaccumulation was associated with a reduction in target vessel revascularization (TVR) at six months from 77% to 26% and at 12 months from 85% to 37%. The authors concluded that brachytherapy with iridium-192 effectively reduces intimal hyperplasia reaccumulation in vein graft in-stent restenosis with no deleterious effect on reference segments within six months.

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-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.

As stated earlier, FDA approval of the Novoste Beta-Cath system was based in large part on the randomized, placebo-controlled START Trial. Two year clinical follow-up of the START Trial was published in 2006 (Silber, et al. for the START Investigators). Two-year outcomes of patients receiving brachytherapy were based on 196 of 244 original patients (79.9%) and in the placebo arm were based on 183 of 232 original patients (78.9%). The primary endpoint, TVR, was reduced by 25%, from 36.6% in the placebo group to 27.5% in the brachytherapy group. TLR was also significantly reduced by 28%, from 32.8% in the placebo group to 23.4% in the brachytherapy group. The authors concluded that the initially beneficial outcome effects of brachytherapy with beta radiation for in-stent restenosis are maintained during a two-year follow-up period, and brachytherapy can significantly reduce clinical need for reintervention (TVR) and MACE after two years.

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.

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. Risk differences for MACE, TVR, TLR, and angiographic binary restenosis at 6–12 months were calculated, and a meta-regression analysis of MACE was performed. The risk difference for MACE was 0.19, ( $p=0.00$ ). There was considerable between-study variance, and diabetes was found to be a significant factor in this variance ( $p=0.00$ ). 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.

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.

**Additional Indications:** Intracoronary brachytherapy has been proposed as a treatment for new stenosis of native coronary arteries and SVGs, as well as restenosis of native coronary arteries and SVG's 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.

The Beta-Radiation Investigation with Direct stenting and Galileo in Europe (BRIDGE) Trial (Serruys, et al., 2004) assessed the efficacy of vascular brachytherapy combined with stenting for the primary prevention of restenosis. In this multicenter, randomized controlled trial, 112 patients with de novo lesions were randomized to receive stenting with brachytherapy ( $n=54$ ) or without brachytherapy ( $n=58$ ). At six months, intra-stent loss was 0.43 and 0.84 mm in the irradiated and control groups, respectively. In the irradiated group, however, there were six late occlusions and eight restenoses outside the stented and peri-stented area at the fall-off dose edges of the irradiated area. The TVR rate at one year was higher in the brachytherapy group (20.4%) than in the control group (12.1%), and the MACE and cerebrovascular event rate was also higher in the brachytherapy group (25.9%) than in the control group (17.2%). The authors concluded that despite the optimization of pre-, peri-, and post-procedural factors, and despite the relative efficacy of brachytherapy for the prevention of intra-stent neo-intimal hyperplasia, the clinical outcome of the irradiated group was less favorable than that of the control group.

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  $1.74 \pm 0.8$  mm, compared to  $2.25 \pm 1.05$  mm in the brachytherapy group. The mean in-stent diameter was  $2.3 \pm 0.8$  in the control group vs.  $2.9 \pm 1.05$  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 TVR for all patients alive at that time point. Long-term follow-up was obtained via clinical evaluation or telephone contact at an average of  $62 \pm 7$  months for the 58 patients who were alive 23 months after treatment. Between one and five years, two deaths occurred in the brachytherapy group—one due to heart failure and one due to unknown cause. In the control group, one noncardiac death and one nonfatal MI occurred at 21 and 48 months, respectively. Both groups experienced similar progression of atherosclerotic disease in the non-target vessels. 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  $0.7 \pm 0.9$  mm in the brachytherapy group vs.  $1.2 \pm 0.8$  mm in the control group at the injured segment,  $0.9 \pm 1.0$  vs.  $1.3 \pm 0.7$  mm at the radiated segment, and  $0.9 \pm 1.0$  vs.  $1.3 \pm 0.7$  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. The ultimate role of irradiation in the treatment of coronary disease has not been defined. Additional well- designed clinical trials that evaluate long-term efficacy and safety are needed before brachytherapy is expanded beyond the treatment of in-stent restenosis in native coronary arteries or saphenous vein grafts.

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## Coding/Billing Information

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

**Covered when medically necessary:**

CPT®* Codes	Description
77781	Remote afterloading high intensity brachytherapy; 1-4 source positions or catheters (Code deleted 12/31/08; Replaced by 77785-77787)
77782	Remote afterloading high intensity brachytherapy; 5-8 source positions or catheters (Code deleted 12/31/08; Replaced by 77785-77787)
77783	Remote afterloading high intensity brachytherapy; 9-12 source positions or catheters (Code deleted 12/31/08; Replaced by 77785-77787)
77784	Remote afterloading high intensity brachytherapy; over 12 source positions or catheters (Code deleted 12/31/08; Replaced by 77785-77787)
77785	Remote afterloading high dose rate radionuclide brachytherapy 1 channel (New code effective 1/1/09)
77786	Remote afterloading high dose rate radionuclide brachytherapy; 2-12 channels (New code effective 1/1/09)
77787	Remote afterloading high dose rate radionuclide brachytherapy; over 12 channels (New code effective 1/1/09)
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
	Multiple/varied

**\*Current Procedural Terminology (CPT®) ©2007 American Medical Association: Chicago, IL.**

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## Policy History

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

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